7th EDITION

BURNS' Pediatric Primary Care

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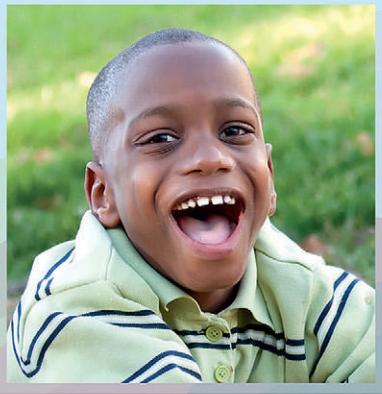

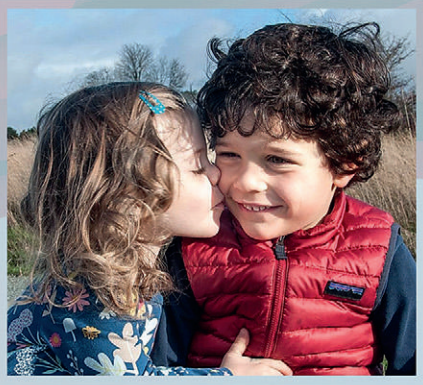

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SEVENTH EDITION

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This edition is dedicated to the timeless leadership, professional expertise dedication, and hard work of the three emeriti authors who have nurtured this project through the years. Mentors to dozens, role models to thousands, and tireless advocates for millions of children and their families, these pediatric nurse practitioners helped to shape pediatric focused advanced practice and set the standards for best pediatric care. We are honored to be their friends and colleagues, and we are better pediatric nurse practitioners because of our association with them. We hope this edition celebrates their renowned legacy while continuing to honor their purpose and passion. With deepest thanks and sincere admiration to:

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Preface

We are delighted to introduce the seventh edition and updated title of *Burns' Pediatric Primary Care*. With the retirement of three of the initial authors of this book, the team believed it was time to alter the title to call it what it is commonly referred to by those who love it and use it. Changes to this edition were made to ensure the contemporary relevance of topics and to support the educational needs of those in pediatric primary care. The editorial team consists of actively practicing pediatric nurse practitioners who understand the contemporary challenges and complexity of the primary care health care system. Each of the contributing authors of the chapters are experts in their fields. As always, every chapter has been thoroughly updated.

This book was initially developed more than 20 years ago as a resource for advanced practice nurses who were providing primary health care to infants, children, and adolescents. Currently, pediatric nurse practitioners (PNPs) and family nurse practitioners (FNPs) are the primary audience. However, physicians, physician assistants, and nurses who care for children in a variety of settings also find this book to be a valuable resource. This is the only nurse practitioner (NP) editorial team and NP-focused pediatric primary care text on the market.

*Burns' Pediatric Primary C*are emphasizes health promotion, disease prevention, and problem management from the primary care provider's point of view. Each chapter introduces key concepts, provides an evidence-based and theoretical care foundation, and includes a discussion of the identification and management of symptoms or conditions of specific disease entities. Experienced clinicians can simply jump to the topic or diagnosis in question while the novice can read the chapter for immersion into the topic. Additional resources for each chapter include websites to access organizations and printed materials that may be useful for clinicians and their patients and families.

Special Features of the Seventh Edition

Some features of the seventh edition about which we are particularly excited include the following:

- **NEW!** This edition includes a significant content reorganization. We made this change to reflect current understanding of the continuum of health and illness and to ensure that the flow and classification of information is intuitive to students and providers.
- **NEW!** Because of the evolving clarity of the primary care versus acute care roles, this edition now solely focuses on primary care management and the role of referral and consultation for acute care issues.
- **NEW!** Pediatric primary care providers see patients with a wide range of issues and health complexities. In order to reflect the depth and breadth of this role, nine new chapters were created. These include: a chapter on unique issues in pediatrics (Chapter 1), an overview of genetic and genomic concepts (Chapter 3), environmental issues that impact health (Chapter 4), children with special healthcare needs (Chapter 7), developmental management of newborns (Chapter 9), immunizations (Chapter 22), injury prevention and child maltreatment (Chapter 24), perinatal disorders (Chapter 19), and developmental, behavioral, and mental health promotion (Chapter 30).
- Unit 3 was redesigned to include typical developmental health issues and to emphasize health promotion and health protection. The first section includes developmental, behavioral, and mental health promotion. The second section covers the biophysical domains of nutrition, breastfeeding, elimination, physical activity and sports, sleep, and sexuality. The final section focuses on health protection in the areas of dental health, injury and child maltreatment prevention, and immunizations.
- Unit 4 was redesigned to include management of common diseases and disorders. This section no longer includes developmentally typical conditions and instead focuses on health restoration. Developmentally typical conditions and issues were relocated to Unit 3. The initial chapter in this unit details principles of pediatric disease management common to all ages.
- All other chapters have been updated and redesigned to reflect the highest level of contemporary evidence including *Healthy People 2020* (Healthy People, 2019) and the new edition of *Bright Futures* (Hagan et al., 2017).
- We expanded the use of algorithms to streamline the decision making for clinicians.

Organization of the Book

Children are a special population. Pediatric healthcare requires unique perspective grounded in a fundamental understandings of the complexities of child development, unique epidemiologic health influences, varied social determinants and environmental influences of health, and each child's unique genetic influences. These themes are carried throughout this book.

The book is organized into four major sections—Pediatric Primary Care Foundations, Management of Development, Pediatric Health Promotion and Protection, and Disease Management. Each chapter follows the same format. Standards and guidelines for care are highlighted, relevant child development is described, the physiologic and assessment parameters are discussed, management strategies are identified, and management of common problems is presented in a problem-oriented format. The scope of practice of the primary care provider is always emphasized with appropriate referral and consultation points identified.

It is our hope that this book continues in the tradition of the prior editions by supporting the primary care provider with the highest quality, evidence-based care strategies to foster improved health and wellness of children and their families.

Acknowledgments

A book of this size and complexity cannot be completed without considerable help—the work of the chapter authors who researched, wrote, and revised content; the consultation and review of experts in various specialties who critiqued drafts and provided important perspectives and guidance; and the essential technical support from those who managed the production of the manuscript and the final product. We are particularly grateful to Laura Goodrich, Sharon Corell, and Sandra Clark at Elsevier for their tireless support and advocacy during the development of this book.

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- Aloha and mahalo to my Jon, Jonah, and AnnaMei. I am ever grateful for the joy you bring to my life as well as your support of my time with "the book." Likewise, I am ever thankful for Denise and my APA colleagues who give me the flexibility and challenge to work hand in hand to provide model pediatric care. *Nancy Barber Starr*
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- To my parents who first loved, supported, and encouraged me. To my husband, Mark, who loved me second and continues to love, support, and encourage me in all my professional endeavors. To my children, Curtis and Leah, who make life fun and will continue to do so with their own children. *Nan Gaylord*
- To my children and their children and their children who, along with children everywhere, are the living messages we send to a time we will not see. Here's hoping we have done well by them. *Martha Driessnack*
- The health of our nation's children is our most important resource. My hope is that this edition will contribute to that critical mission of improving the health and well-being of our children and families. Further, to my ever-patient husband who has sustained and bolstered me through the work on this edition! *Karen Duderstadt*
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1 Health Status of Children: Global and National Perspectives

KAREN G. DUDERSTADT

The health of all children is interconnected worldwide, and the health status of all children must be viewed with a global lens. Whether considering pandemic infectious diseases or global migration, inequities in the health status of children globally and nationally are largely determined by common biosocial factors affecting health. Biosocial circumstances, or social determinants of child health, are shaped by economics, social policies, and politics in each region and country. There is a social gradient in health that runs from the top to bottom of the socioeconomic spectrum globally. Therefore the social gradient in health means that health inequities affect low-, middle-, and high-income countries (World Health Organization [WHO], 2018). Significant progress has been made in reducing childhood morbidity and mortality. However, a sustained effort is required globally and nationally to build better health systems to continue to positively impact child health outcomes. The framework of the United Nations Millennium Development Goals (United Nations Development Program [UNDP], 2015) and Healthy People 2020 (U.S. Department of Health and Human Services [HHS] Office of Disease Prevention and Health Promotion [ODPHP], 2018) goals set the mark for improving child health status.

This chapter presents an overview of the global health status of children, current health inequities, the progress achieved in the Millennium Development Goals and Healthy People 2020 targets, and the factors currently affecting the health of children in the United States, including food and housing insecurity. The chapter also discusses the important role pediatric healthcare providers have in advocating for polices that foster health equity and access to quality healthcare services for all children and families.

Global Health Status of Children

Thirty-one million children younger than 20 years old are part of the international migration of populations across continents (United Nations International Children's Emergency Fund [UNICEF], 2017). Among the world's refugees are an estimated 10 million children, who have been forcibly displaced from their home country, and 17 million more who have been displaced due to conflict and violence (UNICEF, 2017). Immigrant children have increased health and educational needs that impact the health and well-being of communities; many of these communities have fragile healthcare systems. The United Nations Convention on the Rights of Children (UNCRC) charter was established 25 years ago and declares the minimum entitlements and freedoms for children globally, including the right to the best possible health (UNICEF, 2017a). The charter is founded on the principle of respect for the dignity and worth of each individual, regardless of race, color, gender, language, religion, opinions, origins, wealth, birth status, or ability. Immigrant children have the right to be protected under this charter (Box 1.1).

Health equity is the absence of unfair or remediable differences in health services and health outcomes among populations (WHO, 2016). Addressing health equity globally requires bold goals, political will with broad fiscal support, and a commitment within low-resource countries to prioritize the health of children and families as a primary goal.

Progress on the Millennium Development Goals

The United Nations (UN) Millennium Development Goals, adopted in 2000 with a deadline of 2015, produced the most successful movement in history by the UN to reduce child poverty globally (UNDP, 2015). The achievements are the result of the collaborations between governments, international communities, civil societies, and private corporations. Although the UNDP acknowledges shortfalls that remain, significant progress has been made globally in the 30 developing countries targeted. Although the rate of child mortality globally remains high, the global under-5 mortality rate declined by more than half, from 90 deaths per 1000 live births in 1990 to 43 deaths per 1000 births in 2015 (UNDP, 2015). The neonatal mortality rate fell to 19 per 1000 live births in 2016 from 37 per 1000 births in 1990. The highest rates of infant mortality occurred in two countries—39% of newborn deaths occurred in southern Asia and 38% in sub-Saharan Africa. Half of all newborn deaths occurred in just five

• BOX 1.1 UNICEF[a] Summary of the United Nations Convention on the Rights of Children

The UNICEF conventions include 42 articles that are summarized in the following list. They represent the worldwide standards for the rights of children. The conventions apply to *all* children younger than 18 years old. The best interests of children must be a top priority in all actions concerning children.

- Every child has the right to:
  - Life and best possible health
  - Time for relaxation, play, and opportunities for a variety of cultural and artistic activities
  - A legally registered name and nationality
  - Knowledge of and care by his or her parents, as far as possible, and prompt efforts to restore the child-parent relationship if they have been separated
  - Protection from dangerous work
  - Protection from use of dangerous drugs
  - Protection from sale and social abuse, exploitation, physical and sexual abuse, and neglect and special care to help them recover their health if they have experienced such toxic life events
  - No incarceration with adults and opportunities to maintain contact with parents
  - Care with respect for religion, culture, and language if not provided by the parents
  - A full and decent life in conditions that promote dignity, independence, and an active role in the community, even if disabled
  - Access to reliable information from mass media, television, radio, and newspapers, as well as protection from information that might harm them
- Governments must do all that they can to fulfill the rights of children as listed here.

[a]UNICEF stands for the full name United Nations International Children's Emergency Fund. In 1953, its name was shortened to the United Nations Children's Fund. However, the original acronym was retained.

countries: India, Pakistan, Nigeria, the Democratic Republic of the Congo, and Ethiopia (United Nations Inter-agency Group for Mortality Estimates [UN IGME], 2017).

Pneumonia, diarrhea, and malaria remain the leading causes of death globally in children younger than 5 years (UN IGME, 2017). The highest proportion of deaths due to these conditions are in children younger than 2 years old. *Rotavirus* is the most common cause of diarrhea globally, and *Streptococcus pneumoniae* is the leading cause of pneumonia—both are vaccine-preventable infectious diseases. Successful vaccination programs have markedly reduced the mortality caused by some infectious diseases, particularly measles and tetanus. Approximately 84% of children worldwide received at least one dose of a measles- containing vaccine in 2013, up from 73% in 2000 (UNDP, 2015). Other UNDP achievements include:

- More than 6.2 million malaria deaths have been averted between 2000 and 2015, primarily of children younger than 5 years in sub-Saharan Africa.
- More than 900 million insecticide-treated mosquito nets were delivered to malaria-endemic countries in sub-Saharan Africa between 2004 and 2014.
- The primary school net enrollment rate in the developing regions has reached 91% in 2015, up from 83% in 2000.
- More than 71% of births were assisted by skilled health personnel globally in 2014, an increase from 59% in 1990.

Undernutrition, low rates of breastfeeding, and zinc deficiency contribute significantly to the childhood mortality rates globally. As a micronutrient, zinc is essential for protein supplementation, cell growth, immune function, and intestinal transport of water and electrolytes, and it reduces the duration and severity of diarrhea and likelihood of reinfections (Khan and Sellen, 2015).

Sustainable Development Goals

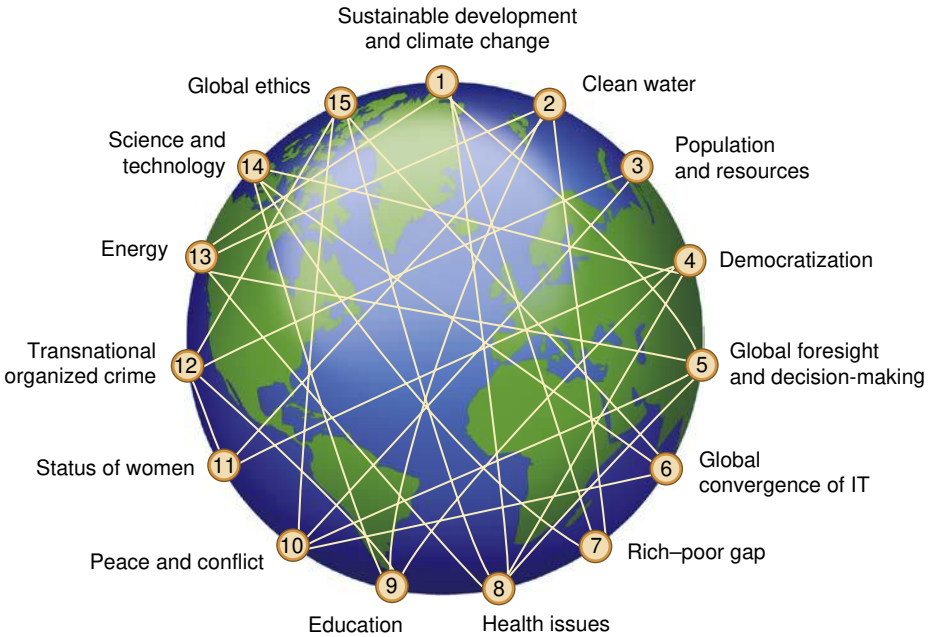
Building on the successes of the UNDP, the Sustainable Development Goals (SDGs) came into effect in 2016 and will continue through 2030. The SDGs include 17 expanded goals, including climate change, economic inequality, innovation in industry and infrastructure, sustainable consumption, peace and justice, and a universal call to action to end poverty and to protect the planet and ensure that all people enjoy peace and prosperity (Fig 1.1) (UNDG, 2016). The UNDG initiatives include work in 170 countries and territories and provide support to governments to integrate the SDGs into their national development plans and policies. The plan focuses on key areas including poverty alleviation, democratic governance and peacebuilding, climate change and disaster risk, and economic inequality. Increased resources are needed to meet the data demand for the new development agenda. Global standards and an integrated information technology (IT) system are also needed for effective monitoring. If every country achieves the SDGs target by 2030, an additional 10 million lives of children younger than 5 years will be saved throughout the period 2017–30 (UNDG, 2016). Fig 1.2 illustrates 15 global challenges in countries collaborating to address the issue of health equity from a global perspective (The Millennium Project, 2014).

Health Status of Children in the United States

Child poverty rates in the United States remain higher than in other economically developed nations, and there are significant inequalities in race and ethnicity. In 2016, 19% of children—one in five children or 14.1 million—were living in poverty, with children comprising 32.6% of all people in poverty (Annie E. Casey Foundation, 2018). Mississippi and New Mexico have the highest rate of child poverty, at 30%. The rate of household poverty is 34% in African-American and Native American children and 28% in Latino children. In addition, 35% of children live in single-parent families, which often have fewer resources.

Despite having the highest health expenditure per capita in the world, infant mortality in the United States remains higher than other high-income countries; however, there has been a decline in infant mortality over the past decade largely due to a decline in sudden infant death syndrome (SIDS) from 50 per 100,000 in 2002 to 13 per 100,000 in 2015 (Khan et al., 2018). Inequality in infant mortality rates remain, and African-American infants have the highest mortality rate, at 1128 per 100,000 infants compared with 498/100,000 in non-Hispanic white infants and 466/100,000 in Latino infants (Khan et al., 2018). For children 1 to 19 years of age, mortality rates have declined over the past decade due to the decline in unintentional injury deaths. However, the rate of suicide mortality has increased slightly in children 10 to 19 years of age over the past decade, with the highest rate among non-Hispanic white youth in early and late adolescence. Rising suicide rates resulted in approximately 1400 additional deaths in 2015. Suicide by firearms increased in white youth 15 to 24 years of age, and intentional drug poisonings increased in African-American and Latino youth (Khan et al., 2018).

• **Fig 1.1** United Nations Development Program (UNDP) Sustainable Development Goals for 2030. (United Nations Development Program: the millennium development goals report 2015. UNDP. http://www.undp.org/content/undp/en/home/librarypage/mdg/the-millennium-development-goals-report-2015.html. Accessed September 10, 2018.)



• **Fig 1.2 Fifteen Global Challenges Facing Humanity.** *IT,* Information technology. (From http://107.22.164.43/millennium/challeng.html.)

Most concerning among the child health indicators is the percentage of overweight and obese children. Seventeen percent of children 2 to 19 years of age are *obese,* defined as a body mass index (BMI) greater than the 95th percentile for age on the BMI age- and gender-specific growth charts. The rate of obesity among adolescent males and females 12 to 19 years of age is currently 20.5% and has continued to rise over the past decade. Although rates of obesity among children and youth in the United States

remain the highest among the high-income countries, surveillance studies show that the rate of overweight and obesity has stabilized among 2 to 5 year olds at 8.9% and the prevalence is less than the Healthy People 2020 goal of 9.4% in early childhood (Ogden et al., 2015). Obese and overweight children and youth are more at risk for developing adult health problems, including heart disease, type 2 diabetes, metabolic syndrome, stroke, and osteoarthritis. Of all the child health indicators, overweight and obesity significantly affect the cost of providing healthcare services in the United States.

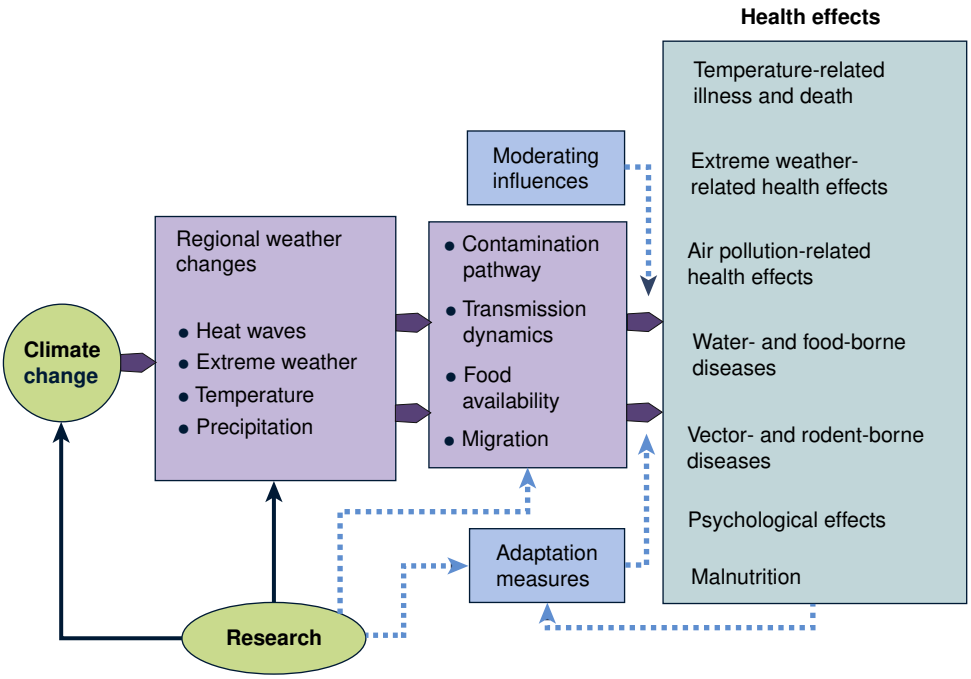
Food and Housing Insecurity and Effect on Children's Health

Hunger and undernutrition are often associated with *food insecurity,* which exists when populations do not have physical and economic access to sufficient, safe, nutritious, and culturally acceptable food to meet nutritional needs. Food insecurity occurs in impoverished populations in developing countries and in industrialized nations, particularly among migrant populations. Children affected by migration and family separation are at risk for food insecurity and are vulnerable to further health consequences, including exposure to exploitation and child trafficking. Growing evidence about climate change indicates the dramatic effect on food crops that has led to food distribution issues globally, which is one of the primary contributors to the migration patterns and food insecurity (Fig 1.3). Globally, undernutrition is an important determinant of maternal and child health and accounts for 45% of all child deaths in children younger than 5 years of age (UN, 2015). Low rates of breastfeeding remain a problem in developed and developing nations. Children who are exclusively breastfed for the first 6 months of life are 14 times more likely to survive than nonbreastfed infants.

Despite many government food assistance programs in the United States, nearly one in five children in the United States lives in a food-insecure household. Children who are food insecure are more likely to have poorer general health, higher rates of hospitalization, and increased incidence of overweight, asthma, and anemia and to experience more behavioral problems. Factors other than income impact whether a household is food insecure. Maternal education, single-parent households, intimate partner violence, and parental substance abuse also contribute to food insecurity. Children living in households where the mother is moderately to severely depressed have a 50% to 80% increased risk of food insecurity (Gundersen and Ziliak, 2015).

Three-quarters of children spend some portion of the preschool years being cared for outside of the home. Depending on child care arrangements, the care can contribute to or ameliorate the effects of food insecurity for children. Young children who attend a preschool or child care center have lower food insecurity, whereas children cared for at home by an unrelated adult are at higher risk for food insecurity (Gundersen and Ziliak, 2015). The Supplemental Nutritional Assistance Program (SNAP), the Special Supplemental Nutrition Program for Women, Infants, and Children (WIC), and the School Breakfast Program (SBP) are federally funded programs with the purpose to combat childhood hunger. The average monthly WIC benefit for families is $43. Recent WIC data indicate the proportion of infant-prescribed formula declined over the past decade. This may reflect the trend of increased rates of breastfeeding in the United States reported in 2016 (Patlan and Mendelson, 2018).

Children living in poverty are also significantly affected by the affordable and adequate housing crisis in the United States, particularly immigrant children and families living in large metropolitan areas. Approximately 21% of persons experiencing homelessness in the United States are children (OHCHR, 2017). Although many children are reportedly experiencing sheltered homelessness, this lack of family financial stability, the



• **Fig 1.3** Health Effects of Climate Change.

limited housing supply in inner cities, and the high eviction rates negatively impact the education and physical and mental health of children.

Addressing Children's Health in the United States

Healthy People 2020

The Healthy People 2020 goals for children include foci specific to early and middle childhood and adolescents, social determinants of health in childhood, health-related quality of life for children, and specific disparities in child health to improve healthcare services and health outcomes. With increased proportions of children with developmental delays, Healthy People 2020 focuses on objectives to increase the percentage of children younger than 2 years old who receive early intervention services for developmental disabilities and to increase the proportion of children entering kindergarten with school readiness in all five domains of healthy development—physical health and well-being; social emotional development; approaches to learning; language development and communication; and cognitive development. The objectives set benchmarks to increase the percentage of young children who are screened for autism and other developmental delays at 18 and 24 months of age (National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention [CDC], 2015).

Reports indicate Healthy People 2020 objectives have been achieved in many areas. The United States surpassed the overall goal of a 10% reduction in infant and youth mortality in almost all age groups, averting 1200 child deaths in 2015 (Kahn et al., 2018). Infectious diseases among children in the United States—*Haemophilus influenzae* B, hepatitis B, group B streptococcal and pneumococcal infections, and meningococcal disease—declined, meeting or exceeding the Healthy People 2020 targets and indicating movement toward the 2020 objectives for completion of the vaccine series across age groups (National Center for Health Statistics [NCHS], 2016).

Healthy People 2020 objectives also address the need for increasing the proportion of practicing primary care providers, including nurse practitioners, to improve access to quality healthcare services. An integrated workforce can provide appropriate evidence-based clinical preventive services to reduce overall health care costs, as well as improve access and facilitate communication and continuity of care for children and families. Approaches to health care must be interprofessional and must consider the biosocial factors in the delivery of health care to achieve child health outcomes beyond those of the biomedical dynamics of disease (Holmes et al., 2014). The ODPHP advisory committee is building the Healthy People 2030 objectives on the foundational principles, mission, and overarching goals of the Healthy People 2020 framework.

Social Determinants of Health and Health Equity

The social determinants of health result in unequal and unavoidable differences in health status within communities and between communities. Individuals are affected by economic, social, and environmental factors in their communities. Social determinants of health recognize that home, school, workplace, neighborhoods, and access to health care are significant contributors to child health outcomes. Many of the Healthy People 2020 leading health indicators address social determinants of health. However, the targets often fall significantly below what is required to decrease the economic inequalities between communities and neighborhoods.

Some communities are addressing social determinants of health through connecting community safety and healthy child development and advocating for system, policy, and practice change (Prevention Institute, 2017). Exposure to neighborhood violence impacts children, and safer communities can promote social-emotional development for young children. Safe communities offer public places for children to play and community safety promotes economic development. Policies of community safety and early childhood development intersect and impact determinants of the sociocultural environment, physical/built environment, and educational/economic environment (Prevention Institute, 2017). Fig 1.4 illustrates a framework to help communities better understand and address the inequities that contribute to violence and how early experiences influence development over the life course.

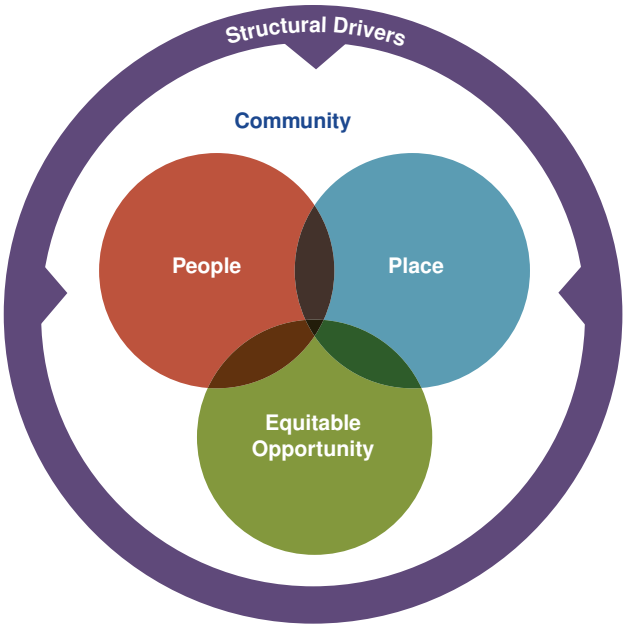
Adverse Childhood Events and Impact on Child Health Outcomes

There is growing evidence about the disruptive impact of toxic stress on biologic mechanisms that impact childhood development. Early adverse stress is linked to later impairments in learning, behavior, and physical and mental well-being (American Academy of Pediatrics [AAP], 2014; Shonkoff et al, 2012). Toxic stress results from strong or frequent and prolonged activation of the body's stress response systems in the absence of the protection of a supportive, adult relationship (Shonkoff et al, 2012). The adversity can occur as single, acute, or chronic event in the child's environment, such as emotional or physical abuse or neglect, intimate partner violence, war, maternal depression, parental separation or divorce, and parental incarceration (Box 1.2). Adverse childhood events (ACEs) occur across all income groups, but 58% of children with ACEs live in homes with incomes less than 200% of the federal poverty level (FPL). African-American children are disproportionately affected by ACEs—6 out of 10 African-American children have experienced ACEs and represent 17.4% of all children in the United States with ACEs (Bethell et al., 2017). Emotional abuse is the most commonly reported ACE, followed by parental separation or divorce, and household substance abuse (Merrick et al., 2018).

Toxic stress in childhood has implications that carry over into adulthood. Evidence suggests that the results of the prolonged and altered biologic mechanisms lead to increased risk of chronic health conditions in adulthood, including obesity, heart disease, alcoholism, and substance abuse (Shonkoff et al., 2012). A child who has experienced ACEs is also more likely to engage in high-risk behavior, such as the initiation of early sexual activity and adolescent pregnancy. Limiting the impact of ACEs through effective interventions that strengthen communities and families and protect young children from the disruptive effects of toxic stress is critical to improve health outcomes throughout the life course for future generations (Merrick et al., 2018).

Child Health and Access to Care

Child heath is fundamental to overall child development, and children with health insurance are more likely to have a regular source of care and access to preventive healthcare services. Nationally, there has been significant progress over the past decade on



People
- Social networks & trust
- Participation & willingness to act for the common good
- Norms & culture

Place
- What's sold & how it is promoted
- Look, feel & safety
- Parks & open space
- Getting around
- Housing
- Air, water, soil
- Arts & cultural expression

Equitable Opportunity
- Education
- Living wages & local wealth

• **Fig 1.4 Tool for Health and Resilience in Vulnerable Environments (THRIVE) Clusters and Factors Impacting Early Child Development.** (Prevention Institute & Center for Study of Social Policy; Cradle to community: a focus on community safety and health child development; 2017:1–47. http://preventioninstitute.org/sites/default/files/publications/PI_Cradle to Community_121317_0.pdf. Accessed October 12, 2018.)

• BOX 1.2 Adverse Childhood Events

- Emotional abuse or neglect
- Physical abuse or neglect
- Sexual abuse
- Mother treated violently
- Household substance abuse
- Household mental illness
- Parental separation or divorce
- Incarcerated household member

expanding public insurance for children. In 2016, 4% of children lacked health insurance, which is half the uninsured rate in 2010 (Annie E. Casey Foundation, 2018). Alaska has the highest rate of uninsured children, at 5%, whereas just 1% of children in Massachusetts are uninsured. Inequalities remain among racial and ethnic populations as 7% of Latino and 12% of Native American children remain uninsured.

Thirty million children are currently covered by public insurance programs in the United States (Bettenhausen et al., 2018). The expansion of Medicaid and the Children's Health Insurance Program (CHIP) expanded healthcare access to primary care services for many low-and middle-income families and decreased avoidable hospitalizations and child mortality. States are dependent on federal financial support for Medicaid and CHIP, and the federal share of public costs exceeds 70% in some states (Bettenhausen et al., 2018). The public insurance eligibility rates vary across states, from 150% to 405% of the FPL income. A decrease in federal funding levels would limit access to public insurance enrollment and therefore access to preventive and acute care services. Hospitalizations represent the highest healthcare costs. Reductions in public insurance eligibility decreases access to primary care and preventative services which shifts costs to hospitals and families. Sustained federal funding at current levels is needed to maintain access to vital healthcare services and improve child health outcomes.

Role of Primary Care Providers for Improving Child Health

Pediatric primary card providers (PCPs) have a key role in advocating for child health locally, nationally, and globally. Advanced Practice Registered Nurses (APRNs) provide continuity of care in the ambulatory care setting for underserved children with health conditions such as asthma, pneumonia, and vaccine-preventable conditions that might otherwise lead to greater use of costly emergency departments and hospitalizations. Increasing access to APRNs who deliver primary care services reduces healthcare costs, improves health outcomes, and produces health care savings—all steps that would allow the United States to lead rather than trail the other economically developed countries in child health indicators. In addition, APRNs are able to advocate for children and potentially influence economic and political decisions to ameliorate health disparities and increase health equality among populations and communities to build a healthier generation of adults.

Health Promotion and Evidence-Based Clinical Preventive Services

Many children are not receiving the recommended preventive services and developmental surveillance required for health promotion. There are many barriers to effective well-child care, including time constraints; low levels of reimbursement for preventive care

and developmental screening services; lack of provider education in current strategies to identify child development, emotional, and behavioral problems; and lack of community referral sources to assist children, adolescents, and families. These issues have led to inconsistent quality of preventive healthcare services affecting children and families.

Much of the basis for primary care practice is not yet evidence based. Primary care would benefit from stronger scientific clinical research that could strengthen primary care principles and prevention. Lack of funding and infrastructure to support such primary care clinical research stands in sharp contrast to the organized commitment and emphasis on advancing knowledge in disease entities and treatment options. This gap provides an area of research open to pediatric nurse researchers and other pediatric healthcare providers trained in clinical research. Increased evidence in the primary healthcare domain would help to move the public dialogue toward a greater focus on primary prevention and away from a disease-focused healthcare system.

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2

Unique Issues in Pediatrics

MARTHA DRIESSNACK

This chapter focuses on some of the unique issues that inform pediatric primary care, beginning with the inherent challenges of providing patient-centered care when the focus of care is a two-generation or dual patient. This introduction is followed by a brief discussion of contemporary contexts and theories that influence how we view children, as well as how the continued use of a developmental lens, although important, creates challenges. Also highlighted is the importance of early investment in lifelong health, with a particular focus on a child's first 1000 days, adverse childhood experiences (ACEs), and household and health literacy. The final section is a reminder that transitioning from a pediatric to an adult primary care system is critical for all children, but especially for adolescents and young adults with chronic physical and medical conditions.

Two-Generation or Dual Patient

One of the unique challenges in pediatrics is the two-generation or dual patient. Although the primary focus in pediatrics is the child, each child and/or adolescent comes with at least one parent or caregiver, if not three or four, and cannot be seen or cared for without this context. Taking time to understand and work with parents is paramount in pediatric primary care, but it is distinct from patient- and family-centered care (PFCC). In PFCC, providers acknowledge the patient's ultimate control over health-related decisions, while acknowledging that these decisions are contextualized within each patient's broader life experiences and family. The challenge of using a pure PFCC model in pediatric primary care is that there is not one patient, but two, and while the child is the focus, the parent is considered the authority in terms of decisions (Eichner, 2012).

For pediatric providers, one of the greatest challenges is how to access, acknowledge, and include the child's voice, which is often lost and/or overridden in healthcare. This tendency to lose track of and/or override children's voices is rooted in the long-standing tradition of seeing children using deficit-based or developmental lenses. Using these lenses there is a presumption of decisional incapacity in the patient and therefore deference to parental authority. This view is contrasted to how the patient is seen in adult healthcare, where there is a presumption of decisional capacity in the patient, with familial insight serving as adjunctive.

All health care providers are obligated to provide beneficial care to the patient. For adults this means the patient's needs and wishes take priority. In pediatrics, balancing the needs and wishes within the context of the dual patient continues to give rise to some of the most difficult and challenging care decisions, especially as children's cognitive and executive function matures. Parents are clearly authorities and caregivers, but they are not surrogates. Pediatric providers need to seek out children's voices and encourage children's participation in care and health-related decisions over time.

Looking Through a Developmental Lens

How children are viewed influences how primary care providers (PCPs) interact with them. If children are seen only as works in progress using a deficit-based, developmental lens, they are regarded as human *becomings*, rather than as human *beings* (Driessnack, 2005). Children are not seen as agents in their own right, human beings who are capable of influencing their learning and others. Instead, our understanding of children and childhood is left to reports from adult surrogates. Although pediatric PCPs embrace the concept that every child is considered within the context of family, it does not mean that parents' perspectives are preferred or take precedence over the child's when health-related decision-making and plans of care are being considered.

Past dominance of deficit-based, stage theories as the lens through which children are primarily viewed is being challenged, replaced with a call for a more balanced understanding. This shift in understanding parallels the emerging emphasis on patient-centered care and shared decision-making. Although being patient-centered has some inherent challenges in pediatrics, it is a reminder to advocate for the voices of children, which too often are absent from health-related decision-making and plans of care. New tools and approaches are needed that access children's voices based on children's cognitive strengths and abilities. In the past, clinicians and researchers have relied on adult-developed and adult-centered tools and approaches, which have been *adapted* for use with children by adding pictures and/or simpler language. There is increasing realization that data from adapted, adult-centered tools have not adequately captured the voices and/or experiences of children, giving rise to national movements, such as *No More Hand-Me-Down Research* and *Nothing About Me Without Me*.

Understanding how children develop from conception through adolescence is foundational in pediatric primary care. Although a number of major theories have informed the study of child development over the past century, there are a few that have been resurrected, or borrowed from other disciplines, to examine the impact of modern societal contexts, rapid advances in science, and expanding worlds of media and technology (Table 2.1).

TABLE 2.1 Theories of Child Development

Type of Theory	Major Theorists	Focus
Psychoanalytic	Freud Erikson	Personality formation through conflict resolution
Cognitive	Constructivist Piaget Vygotsky Information processing Siegler	How children think
Learning	Pavlov Watson Skinner Bandura	How experience affects children's learning and behavior
Ethologic	Bowlby Lorenz	Biology and the role of early experiences during specific developmental periods
System	Bronfenbrenner Gottllieb Lerner Sameroff	How environmental and biologic systems interact and shape development

Among these theorists, Vygotsky and Siegler are highlighted here because they both provide pediatric primary care with a new understanding or alternative lens through which to view children and childhood.

Vygotsky's cognitive theory is not new. In fact, he was a contemporary of Piaget, whose stage theory of cognitive development remains a curriculum constant in many introductory psychology classes. Although contemporaries, they differed in how they viewed development. For Piaget, development precedes learning; for Vygotsky, learning precedes development. This is a subtle but important shift of focus. Piaget's cognitive theory, as with all other stage theories, uses a deficit-based lens, pointing out what children are not yet able to do at each stage, rather than what they can do. Vygotsky's theory, in contrast, uses a strength-based lens, looking at what children can do.

One group of theories that has emerged in this call for a more balanced understanding of development is information processing theory. This group of theorists (e.g., Siegler) has borrowed concepts from computer science, focusing on how information is received, processed, and stored, as well as how it then produces output. Like Vygotsky, information processing theory centers on the continuity of development; change occurs smoothly, gradually, and predictably over time. This view is in contrast to stage theories (e.g., Piaget), which center on discontinuity, the idea that development proceeds through a series of distinct stages over time with each stage qualitatively different from the last. The focus is less on whether children can solve a problem or complete a task correctly and more on how problems are solved or tasks approached.

Parents, Families, and Behavioral Economics

Parents clearly play an integral role as active agents on behalf of their children. Yet, in pediatrics, best practices are determined based on children's needs, not on the behaviors of their parents or the mental models, cultural influences, and worldviews that inform and guide parents in meeting those needs (Gennetian, Darling, and Aber, 2016). *Behavioral economics* is a relatively new field that combines insights from psychology, judgment, and decision-making with conventional economic theory to understand human behavior, especially in terms of individual influences on decision-making.

The introduction of behavioral economics represents a paradigm shift that is already making an impact, as policy makers embrace its approach to understanding a wide range of high-impact social issues, including obesity and poverty. Of particular interest in pediatric primary care is the role of cognitive load, which refers to an individual's current capacity to focus on and digest information. A parent's cognitive load can have far-reaching implications in pediatrics because any one individual can attend to only certain phenomena at any given point in time. Behavioral economics focuses on developing interventions that temporarily manipulate the salience of different cues, which can have large effects on decision-making. This shift to focus on salience created a new behavioral science term, *nudge,* and the teams examining such efforts are often called nudge units (Thaler, 2016; Thaler and Sunstein, 2009).

In this era of PFCC, pediatric PCPs can integrate the concept of nudging and nudge units, because there are many opportunities to nudge children's and parents' behaviors by making subtle changes to the context in which they make decisions. The shift in focus, drawing attention to the ways in which an individual's family, community, and cultural contexts affect people's real-world, in-the-moment decision-making, is at the heart of behavioral economics (Gennetian, Darling, and Aber, 2016). In addition to providing a new lens for considering individual and parent decision-making, behavioral economics and its focus on cognitive load and creating salience present an alternative lens for understanding larger social issues, such as poverty.

Early Investment in Lifelong Health

Early experiences shape the architecture of the developing brain and lay a foundation for long-term health. Health in the earliest years strengthens the systems that enable children to thrive and grow to be healthy adults. Ensuring that children have safe, secure environments, families, and communities in which to grow and learn creates a strong foundation for their futures and a thriving, prosperous society. New frameworks focus their attention not only on programs but also policies that support the foundations of children's health (Hoagwood et al., 2018). These new frameworks ask providers to work toward enhancing community efforts to change *social environments*, expanding their horizons beyond focusing their efforts solely on *people*.

Science shows that early exposure to adverse experiences can disrupt healthy development and have lifelong consequences. This new awareness is fueling a new way of looking at life, not as disconnected stages but as an integrated process across time—a *life course perspective* (Russ et al., 2014). At the forefront of this new perspective is the emergence of evidence surrounding adverse childhood experiences (ACEs) and their lifelong consequences. There are many other parallel bodies of evidence that all point to shifting attention upstream to early childhood, not only locally, but globally. Historically, early childhood interventions have focused on children of preschool age, but we currently know that interventions encompassing the period before conception through the first 2 years of life can greatly reduce adverse growth and health outcomes.

Clearly, what children experience in their earliest days and years of life shapes and defines their future. One of the best resources is Harvard's Center for the Developing Child. The World Health Organization (WHO), World Bank, and the United Nations International Children's Emergency Fund (UNICEF) have all drawn attention to the First 1000 Days of Life—from conception to birth (270 days), to a child's first birthday (+365 days), through to the second birthday (+365 days)—as a unique period where the foundations of health, growth, and neurodevelopment across the life span are established. All three global organizations contributed to and offered guidance to the pivotal series entitled Advancing Early Childhood Development: from Science to Scale (Lancet, 2016). Furthermore, a major focus of the United Nations' 2030 Sustainable Development Goals (SDGs) is on early childhood health and development to ensure that every child achieves her/his potential (United Nations, 2015). Accordingly, curricula offerings for parents and providers around the world have been developed (e.g., *ReachUpandLearn* and *Care for Child Development* [CCD]).

Equally intriguing is the science behind *Developmental Origins of Health and Disease* (DOHaD). This field examines models of causality and/or mechanisms that can trace the origin of many noncommunicable conditions or chronic diseases (e.g., hypertension, metabolic syndrome) to environmental influences during early development. The link between early life environmental factors and later life diseases was originally called the Barker hypothesis, because Barker showed that poor nutrition during organ development could lead to increased risk for chronic disease later in life. His work highlighting the influences of adverse events that occur during early phases of human development on the pattern of an individual's health and disease throughout life provided the foundation for the more recent study of adverse childhood experiences.

ACEs are currently linked to risky health behaviors (e.g., smoking, alcoholism, drug use), chronic health conditions (e.g., obesity, diabetes, depression, heart disease, cancer stroke, COPD), low life potential (graduation rates, academic achievement, lost time from work), and early death (https://www.cdc.gov/violenceprevention/acestudy/index.html). Of note is that as the number of ACEs increases, so does the risk for these outcomes, which highlights the call for all pediatric PCPs to screen for and identify adverse events early in life. The research on ACEs continues to be tracked by the Centers for Disease Control and Prevention (CDC). The CDC and American Academy of Pediatrics (AAP) also provide toolkits and practice and provider resources. The AAP's resources and tools are housed within *The Resilience Project*.

Health Literacy

Health literacy is most often defined as the degree to which an individual is capable of obtaining, processing, and applying basic health information. In addition to general literacy and numeracy skills, health literacy requires knowledge of health topics. When individuals have limited health literacy, they lack knowledge or have misinformation about the body, the nature and causes of disease, disease risk, and the relationship between lifestyle factors, such as diet and exercise, and health outcomes. In pediatric primary care, parents' health literacy levels not only affect their children's but also affect their children's care. What parents learned about health or biology during their own education may currently be outdated or incomplete. According to the AAP, only 12% of adults have proficient levels of health literacy (Winkelman et al., 2016). This is extremely important in pediatrics because health literacy is one of the strongest predictors of health. In pediatrics, PCPs need to assess parental health literacy levels up front, so that additional time may be added to encounters as needed. Furthermore, it is important for providers to remember that even parents with advanced literacy skills can be easily overwhelmed by health information, especially during stressful or hurried interactions.

Limited health literacy in adults has been linked to poor disease management skills, medication treatment errors, difficulties navigating the health care system, and poorer health care comes for themselves and their families (Orkan et al., 2018). In the past few years, attention has shifted upstream because the roots of health literacy are formed early in childhood as children are developing their health behaviors (Winkelman et al., 2016). Accordingly, childhood and schools are the newest population for targeted health literacy interventions. The *National Health Education Standards* (NHES) emphasize student comprehension of health promotion and disease prevention, offering unique opportunities for partnering with a growing number of school-based health centers (American Cancer Society, 2007).

Pediatric practices and PCPs are increasingly involved in these efforts as they support childhood literacy, the key precursor to learning. Office-based programs, such as *ReachOutAndRead*, ensure that children receive age-appropriate books and literacy-development instructions from their providers beginning with the first well-child visit. One of the simplest household literacy screening tools is the single-question query about the number of children's books in the home. The presence of 10 children's books is associated with adequate household literacy (Driessnack et al, 2014). The commitment to ensuring the presence of children's books in every child's home may well be one of the most impactful child health interventions undertaken in primary care. Enhancing both literacy and health literacy holds the potential to improve the health of children and to provide them with tools to be more informed and capable consumers in adulthood.

Transitioning to Adult Care

Transitioning from pediatrics to an adult primary care system is critical for all children but especially for adolescents and young adults with congenital and/or chronic physical and medical conditions (e.g., corrected congenital heart disease). Although advances in neonatal and pediatric medicine continue to improve the prognosis for children, care transition is increasingly identified as a critical process in health care management. Well-timed, -planned, and -executed transition plans enable all youth to maximize lifelong functioning and well-being and optimize their ability to assume adult roles and activities, regardless of their health care needs. Such transitions require interprofessional teams from both systems to work collaboratively with youth and their families, anticipating the unique medical, psychosocial, and educational needs as they move from child- to adult-centered care. Accordingly, the AAP and the National Center for Medical Home Implementation created a health care transition planning algorithm that specifies the protocol for managing the transition process (AAP, 2011). The guidelines highlight specific activities and decision points and provide a clear timeline suggesting transition plans begin by age 12. All PCPs are encouraged to adopt and adapt these materials for their practice.

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3

Genetics and Genomics: The Basics for Child Health

SANDRA DAACK-HIRSCH AND MARTHA DRIESSNACK

The future is not in front of us, but inside us.

Joanna Macy

Knowledge of the human genome continues to evolve, transforming not only the field of genetics, but also prior understanding of human embryology, physiology, and disease processes. In short, it is changing the way health care providers approach the diagnosis, treatment, and prevention of human diseases. The study of single genes and their role in inheritance has expanded to include the interaction of genes across the genome, as well as how these interactions are influenced by the environment, random events, and epigenetic factors and impact subsequent phenotypic changes. Very few diseases are entirely genetic and inherited, and health care providers should no longer characterize disorders as genetic or nongenetic. Rather, the astute clinician should consider to what extent genomics influences an individual's susceptibility to disease and, for that matter, an individual's potential/actual response to treatment (Fig 3.1).

At the same time, with the current emphasis on patient-centered care and patient engagement, children and families are becoming active participants in both their care and health care decisions. Of equal importance is the impact of the Internet, which delivers all forms of information in real time, accompanied by instant commentary and interpretation by anyone willing to weigh in. While healthcare is being transformed by the sheer volume of knowledge and technologies, it is also being transformed by its consumers. Today's children are right in the mix, growing up at the intersection of the genome era and information age (Driessnack, 2009).

A basic understanding of genomics is essential for all primary care providers (PCPs) to provide the best care. The medical home model of care identifies PCPs as holding a crucial role in the management of patients who have the potential for or have been diagnosed with an inherited or congenital disorder. Core competencies in genetics for nurses at all levels of practice have already been established, as communicated in *The Essentials of Baccalaureate Education for Professional Nursing Practice* (American Association of Colleges of Nursing [AACN], 2008), *The Essentials of Masters Education in Nursing* (2011), *The Essentials of Doctoral Education for Advanced Nursing Practice* (AACN, 2006), and the *Core Competencies in Genetics for Health Professionals* (National Coalition for Health Professional Education in Genetics [NCHPEG], 2007). In addition, there are specific resources available for PCPs through the American Academy of Pediatrics (AAP) *Genetics in Primary Care* website (Table 3.1: American Academy of Pediatrics [AAP] Genetics in Primary Care).

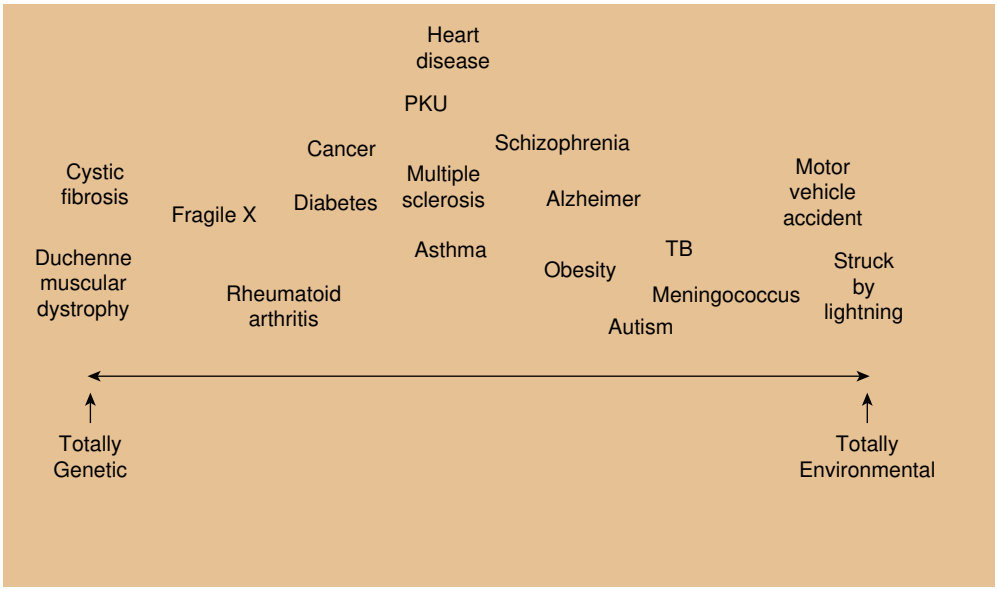
This chapter provides a brief review of basic genetic and genomic concepts and terminology, genetic contribution to disorders, and patterns of inheritance, along with insights into obtaining a family history and conducting a pediatric assessment using a genetics lens. The concept of epigenetics, types of genomic testing, and some of the ethical challenges that can arise are introduced.

Basic Principles of Genetics

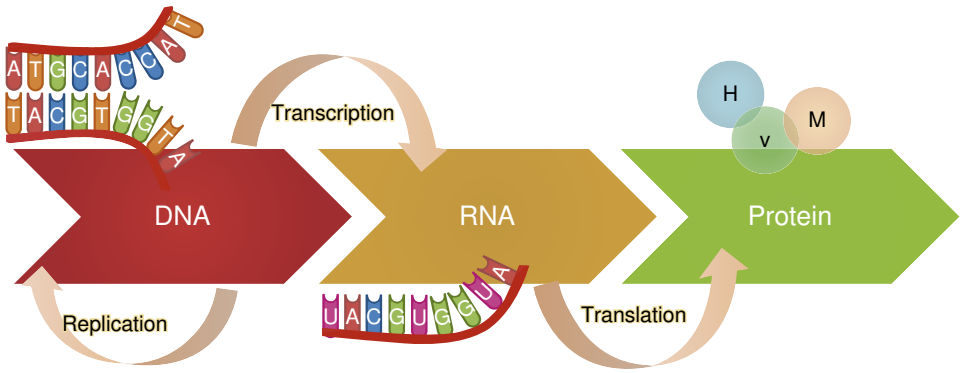
Each human is unique, established by the joining of one egg and one sperm, each of which provided a unique deoxyribonucleic acid (DNA) package. An individual's total DNA package is called a *genome.* Within each cell, genetic information flows from DNA to ribonucleic acid (RNA) to protein, with each gene coding for up to 20 different proteins. In other words, the information carried within the DNA dictates the end product (protein) that will be synthesized. This is known as the central dogma of biology (Fig 3.2). An individual's genome and the encoded protein products, in turn, interact with the individual's internal and external environment in very complex ways.

Deoxyribonucleic Acid

DNA is a molecule that contains genetic instructions for the structure and function of all living organisms. DNA is made up of a string of nucleotides, and each nucleotide consists of deoxyribose, a phosphate group, and one of four bases, called *adenine (A)*, *cytosine (C)*, *guanine (G)*, and *thymine (T).* The two backbones of the DNA helix are formed by the deoxyribose and phosphate groups, whereas the rungs that hold them together are formed by complementary pairing (A-T and C-G) of the bases. The DNA helix is coiled tightly encircling histone proteins. Uncoiled, each DNA strand is approximately 6 feet long. Although each person has a unique DNA package that reflects one in several million possible combinations from the four grandparents' genetic material; the base sequences of any two human genomes are thought to be 99.9% identical. In short, people's DNA structure is more alike than different. Yet, the slightest alteration in an individual's DNA sequence can have devastating health consequences.



• **Fig 3.1 Spectrum of Disease Causation** *PKU,* Phenylketonuria; *TB,* tuberculosis. (From HealthKnowledge [website]; 2017. https://www.healthknowledge.org.uk/public-health-textbook/disease-causation-diagnostic/2d-genetics. Accessed February 14, 2018.)



• **Fig 3.2** Central Dogma of Biology (From Genius [website]; 2018. https://genius.com/Biology-genius-the-central-dogma-annotated. Accessed February 14, 2018.)

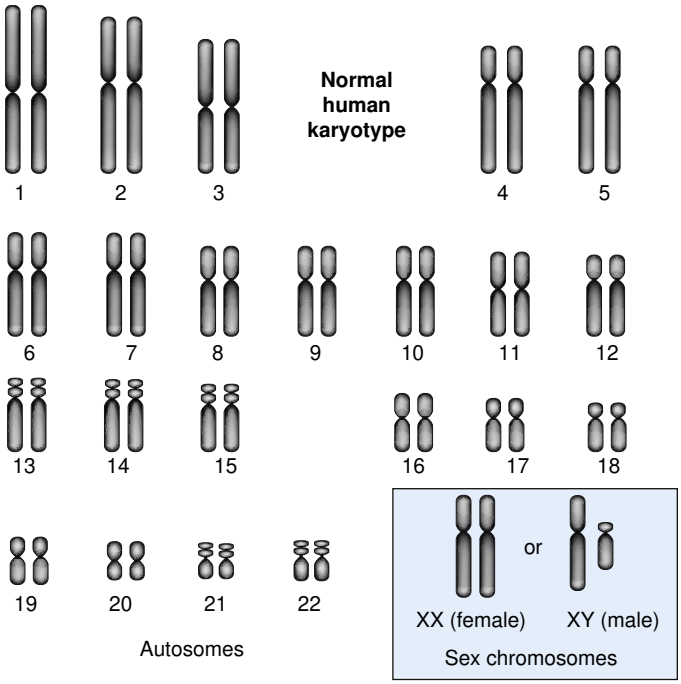
For example, virtually every case of sickle cell anemia is caused by the smallest of genetic changes—a substitution of a single nucleotide (A→T). On the other hand, some DNA alterations have no known effect on an individual, whereas still others appear to provide a benefit or protective action. The same single nucleotide alteration that is responsible for sickle cell anemia can confer a survival advantage to unaffected carriers challenged with the malaria pathogen (Withrock, Anderson, Jefferson, McCormack, Mlynarczk et al., 2015). This is why sickle cell alterations, including both the trait and disease, persist in populations where malaria is endemic.

Chromosomes

Cytogenetics is the study of genetics at the chromosome level, where most of our genetic information is located. Each chromosome is a strand of DNA. In the nucleus of all normal human cells, with the exception of gametes, are 46 chromosomes arranged in 23 pairs. Twenty-two of the pairs are called *autosomes*; they look the same in females and males. The remaining pair, the sex chromosomes, differs between females and males, with two X chromosomes in females (XX) and one X and one Y chromosome (XY) in males. The 22 autosomes are numbered by size—from largest (1) to smallest (22). The picture of human chromosomes lined up in pairs is called a *karyotype* (Fig 3.3).

Human somatic cells are *diploid*, containing 23 paired chromosomes. Diploid cells are replicated through the process of *mitosis*, which creates two identical daughter cells. In contrast, gametes, or germline cells (egg and sperm), are *haploid* cells, each containing only 23 chromosomes. Gametes are produced in the ovary or testicle during *meiosis*, where there is an exchange of genetic material, through crossing over and recombination, resulting in a random assortment of maternally and paternally derived genetic material in the daughter cells. Fusion at fertilization restores the 46-chromosome (23-pair) complement, with one of each chromosome pair from each gamete, creating a unique human being.

A chromosome has a long arm (q) and a short arm (p). Geneticists often use a diagram, or *ideogram*, which shows a chromosome's size and banding pattern. The bands are used to further describe the location of genes on each chromosome. For example, the cytogenetic location of the *CFTR* gene (cystic fibrosis) is



• **Fig 3.3** Normal Human Karyotype (From Genetics Home Reference. Normal human karyotype. http://ghr.nlm.nih.gov/handbook/illustrations/normalkaryotype. Accessed November 16, 2015.)

7q31.2, which means the *CFTR* gene is located on the long arm (q) of chromosome 7, band 3, sub-band 1, and sub-sub-band 2. Other common symbols include *del,* for deletion; *dup,* for duplication; and + indicating an increased or – indicating a decrease in number. For example, 47, XY+21 indicates a male with three copies of chromosome 21 (Down syndrome), whereas 46, XX,8q– denotes a female with a deletion on the long arm of chromosome 8 (Genetics Home Reference, 2018).

At the ends of each chromosome are protective caps, or *telomeres.* Telomeres, specific repetitive sequences of noncoding DNA, contain and protect the genetic information on the chromosome. The telomeres shorten each time a cell divides, losing their protective function over time until cells can no longer replicate and divide, and therefore die. This shortening process is the focus of ongoing research related to aging and cancer. Emerging research now suggests that growing up in a stressful environment can also leave lasting marks on young chromosomes. In particular, children from poor and/or unstable homes have been shown to have shorter telomeres than their unaffected peers (Madhusoodanan, 2014). This line of research parallels the work of the adverse childhood experiences (ACE) study, whose findings suggest that as the number of stressors during childhood increase, the risk for adult health problems also increases in a strong and graded fashion (see Table 3.1: Centers for Disease Control and Prevention [CDC]a).

Genes

A gene is a specific *coding* sequence of DNA organized in small blocks of three letters (e.g., GGC, ATG), known as a *codon.* There are 64 different codons in the genetic code. To early geneticists, a gene was an abstract entity whose existence was only known through its reflected *phenotype*, or physical expression transmitted between generations. Later, genes on chromosomes were thought to be like beads on a string, each coding for one protein; however, it is now known that one gene codes for an average of three proteins. Today, genes are increasingly viewed through informational science and computational biology lenses, resulting in the infusion of information processing and systems language (e.g., upstream regulation). *Genotype* refers to an individual's collection of genes. The *phenotype* is the manifestation of the individual's genotype; however, more precisely, the phenotype is the result of gene expression, which is regulated by molecular mechanisms and modified by environmental factors. Phenotype includes an individual's physical and cognitive features, organ structure, and biochemical and physiologic nature.

Each human inherits two copies of each gene—one copy, or *allele,* from each parent. Alleles are forms of the same gene with differences in their DNA sequence. These differences contribute to each person's unique features. If the two alleles at any given location (locus) are similar, the individual is *homozygous*; if the

TABLE 3.1 Online Resources

Resource	URL (Accessed February 21, 2018)
American College of Medical Genetics and Genomics (ACMG) ACT Sheets and Confirmatory Algorithms	http://www.ncbi.nlm.nih.gov/books/NBK55827
American Academy of Pediatrics (AAP) Genetics in Primary Care	https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/pages/Genetics-in-Primary-Care-Institute.aspx
Autism Speaks	https://www.autismspeaks.org/science/initiatives/autism-genome-project
Baby's First Test	http://www.babysfirsttest.org/
Centers for Disease Control and Prevention (CDCa)—ACE Study	https://www.cdc.gov/violenceprevention/acestudy/index.html
Clinical Pharmacogenomics Implementation Consortium (CPIC)	https://cpicpgx.org/
Centers for Disease Control and Prevention (CDCb)—Folic Acid	https://www.cdc.gov/ncbddd/folicacid/index.html
Genetic Testing Registry (GTR)	https://www.ncbi.nlm.nih.gov/gtr/
Genes In Life	http://www.genesinlife.org/
Genetic Alliance	http://www.geneticalliance.org/
MotherToBaby	https://mothertobaby.org/
NCHPEG National Coalition for Health Professional Education in Genetics Family History Collection and Risk Assessment	https://www.jax.org/education-and-learning/clinical-and-continuing-education/family-history
Online Mendelian Inheritance in Man, Neural tube defects, susceptibility to; NTD	http://omim.org/entry/182940
Positive Exposure	http://positiveexposure.org/
Recommended Uniform Screening Panel RUSP	https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html

alleles are different, the individual is *heterozygous.* For example, a child with cystic fibrosis may have identical CFTR gene sequences (e.g., mutation F508del) in both alleles, and as such would be called *homozygous* for that mutation, whereas this child's parents are heterozygous in their CFTR gene sequence, each with only one copy of the mutation allele and one copy of a normal allele.

In humans, genes can vary in size from 200 to more than 2 million DNA bases. Humans are thought to have between 20,000 and 25,000 different genes. Although every human cell contains every gene, not all genes are active at once; certain mechanisms activate them, turning them on or off at various developmental points or at various locations within the body. Each gene also has coding sequences (exons), separated by noncoding sequences (introns), and occupies a specific location (locus) on a chromosome. It was previously believed that differences in noncoding DNA sequences did not have relevance to human health and development. However, it is now known that some of these differences are associated with increased risk for common diseases, such as diabetes, heart disease, and cancer (Genetics Home Reference, 2018). In addition, a small number of genes are located in the mitochondria.

Mutations

An allele is typically regarded as a *mutation* when its genetic variation is found in less than 1% of the population or a *polymorphism* when it is found in greater than 1% of a population; however, the cutoff of at least 1% prevalence is somewhat arbitrary (Genetics Home Reference, 2018). The term *mutation* is usually used to mean a disease-causing variation, whereas a *polymorphism* is used to refer to a normal variation, or one that does not *directly* cause disease. But really the key difference between the classification of mutation and polymorphism is the frequency that each occurs.

One type of polymorphism is known as *single nucleotide polymorphisms,* or *SNP* (pronounced "snip"). SNPs are used to study the genetic contribution to multifactorial disorders, such as cleft lip and cleft palate, diabetes, heart disease, and cancer, as well as individual response to drugs (pharmacogenomics). A SNP is a single base pair alteration that is common in a given population. On average, SNPs are found every 300 to 2000 nucleotides in the human genome (Genetics Home Reference, 2018). Typically, SNPs are not directly disease-causing mutations; however, they are biologically relevant because they help identify individuals at increased risk for multifactorial disease. They also are used in pharmacogenomic testing to identify individuals at increased risk for adverse response to medications.

Mutations that directly cause disorders are further subclassified as *point mutations, nucleotide repeat expansions, copy number variants,* or *chromosome mutations.* It is important to remember that although these types of mutations can have a large effect on individual human health and development, human evolutionary changes are more likely to result from the accumulation over time of many mutations with small effects.

Point Mutations

Point mutations are single base pair changes (i.e., substitutions, deletions, or insertions), occurring at the level of the nucleotide, yet capable of changing the function of a gene or gene product. They are responsible for many single-gene disorders, including sickle cell anemia and cystic fibrosis. Point mutations should not be confused with SNPs. Although both are single nucleotide differences in a DNA sequence, a SNP, by definition, is present in at least 1% of the general population.

Deletions are mutations in which a section of DNA is lost or deleted. The number of base pairs deleted can range from one to thousands. Examples some syndromes cause by deletion mutations include 22q11.2 deletions syndrome, Duchenne muscular dystrophy, and neurofibromatosis type I.

Insertions are mutations in which extra base pairs are inserted into a new place in the DNA, making it longer than it should be. Like deletions, the number of base pairs involved ranges from one to thousands. Examples of some syndromes caused by an insertion include Duchenne muscular dystrophy and Charcot-Marie-Tooth Type 1A. Note that Duchenne muscular dystrophy was presented as an example for both insertion and deletion mutations. Many inherited and congenital syndromes are associated with more than one type of mutation; however, these different types of mutations involving the same gene result in the same syndrome.

Insertions and deletions are often collectively referred to as *INDELS*. Protein coding DNA is divided into codons. Insertions and deletions in the codons can totally change the gene message so that it cannot be coded or it cannot be coded correctly. This specific type of INDEL is called a *frameshift mutation*. Tay-Sachs, many types of cancers, and Crohn disease are some examples of disorders associated with frameshift mutations.

Nucleotide Repeat Expansions

A repeat expansion is a special type of insertion mutation that increases the number of times a short DNA sequence is normally repeated. When the number of repeats increases beyond the normally tolerated limit, the mutation (i.e., repeat expansion) results in a disorder that could be inherited. For example, almost all cases of fragile X syndrome are caused by an expansion of a trinucleotide (three-base-pair) repeat sequence (CGG) in the *FMR1* gene (Xq27.3) from a normal 5 to 40 times to over 200 times. The expansion makes the gene unstable, resulting in little or no protein output with an outcome of signs and symptoms of fragile X syndrome.

Copy Number Variations

A copy number variation (CNV) involves larger areas of chromosomes, beyond point mutations and repeat expansions. During egg and sperm production, unequal crossover events occur throughout the genome. When this happens, children may have lost (deletion) or gained (duplication) copies of genetic information that were present in either of their parents' chromosomes. Unlike other types of mutations that have been inherited for countless generations, geneticists now recognize that CNVs have a more recent origin. The study of CNVs has already enriched current understanding of autism and other neuropsychiatric diseases, such as mental retardation and schizophrenia (Yoo, 2015; see Table 3.1: Autism Speaks).

Chromosome Mutations

Chromosome mutations occur when even larger segments of a chromosome (involving many bands) are deleted, duplicated, rearranged, or translocated in such a way that there is a resulting alteration of the DNA sequence, a modification of the gene dosage, or a complete absence of a gene or several genes. For example, cri-du-chat syndrome (5p–) is caused by the deletion of the entire end of the short (p) arm of chromosome, whereas Down syndrome is caused by the addition of an entire chromosome. Chromosome mutations usually result in multiorgan, large effects, such as in Down syndrome, in which the individual can have neurologic, eye, ear, orthopedic, cardiac, and other abnormalities.

Genetics and Diseases

The term "genetic disorder" is in some ways an antiquated term. Nearly all diseases are now thought to have a genetic component, in that diseases are caused in whole, or in part, by changes in DNA sequence or gene expression (see Fig 3.1). Traditionally, disease and the respective genetic contribution are grouped under one of four categories: (1) single-gene disorders, (2) chromosome disorders, (3) multifactorial disorders, or (4) mitochondrial disorders. The genotype associated with a particular disease can be inherited, arise spontaneously, or be acquired over a lifetime. For example, some diseases are caused by inherited mutations; diseases can also be caused by spontaneous mutations that occur during the development of the gametes or in early human development (de novo), whereas most forms of cancers are the result of acquired mutations in a gene or group of genes that occur during a person's life. Mutations that are acquired during a person's life happen at the somatic level and occur either randomly or due to a random event or environmental exposure.

Single Gene Disorders

Single gene disorders (also referred to as *monogenetic disorders*) occur when the mutation affects one gene. The mutation may be present on one or both chromosomes, associated with one of three different *Mendelian* patterns of inheritance—dominant, recessive, or X-linked. Dominant disorders are caused by the presence of the gene mutation on just one of the two inherited parental alleles; recessive diseases require the presence of the gene mutation on both of the inherited alleles; X-linked diseases are monogenic disorders confined to the X chromosome. They can be dominant or recessive. Some examples of monogenic disorders that should be familiar to PCPs are sickle cell disease, thalassemia, neurofibromatosis, hemophilia, Duchene muscular dystrophy, cystic fibrosis, fragile X syndrome, polycystic kidney disease, Marfan syndrome, and Tay-Sachs disease.

Chromosome Disorders

Chromosome disorders occur with changes in the number or structure of an entire chromosome, or large segments of it. For example, Down syndrome (trisomy 21) is caused by an extra copy of chromosome 21, Prader-Willi syndrome is caused by the absence of a group of genes on chromosome 15, and chronic myeloid leukemia (CML) results from a translocation in which portions of chromosomes 9 and 22 are exchanged, resulting in a new, abnormal gene (Genetics Home Reference, 2018). Other examples of chromosomal disorders that should be familiar to providers in primary care are cri-du-chat syndrome (5p–), Williams syndrome, and DiGeorge syndrome, also referred to as *velocardiofacial* or *22q11 deletion syndrome.*

Chromosome disorders can also involve sex chromosomes, such as Klinefelter syndrome (XXY), which is caused by an extra X chromosome, and Turner syndrome (XO), which is caused by the absence of an X chromosome.

Another type of chromosomal disorder is called *mosaicism*, which occurs when an altered chromosomal arrangement occurs in some cells but not in others within the same individual. The clinical symptoms are usually milder, and the prognosis improves with fewer numbers of cells involved.

When taking a family history, PCPs should remember there is a high frequency of chromosomal disorders in spontaneous abortions and stillbirths. Further, the prevalence of chromosomal disorders due to nondisjunction increases with advancing maternal age.

Multifactorial Disorders

Multifactorial disorders result from a combination of genetic and environmental factors. Recurrence risks are based on empirical statistics—observations based on data collected from thousands of family histories transformed into probabilities. These disorders can cluster in families; the exact recurrence risk is difficult to predict because the individuals' or couples' precise genetic and environmental risks are usually not known. Therefore a population-based recurrence risk rather than a personal recurrence risk is given. One example of a multifactorial disorder includes neural tube defects (NTD), such as spina bifida or anencephaly. NTDs appear in females more often than in males, and once a child is born with an NTD, the chance for those parents to have another child with an NTD in a future pregnancy increases (see Table 3.1: Online Mendelian Inheritance in Man [OMIM]). The rate of NTDs decreases with sufficient maternal folic acid supplementation. Therefore the CDC recommends that all women of childbearing age consume 0.4 mg (400 μg) of folic acid daily (see Table 3.1: Centers for Disease Control and Prevention [CDC] b). In contrast, the rate of NTDs increases when mothers have uncontrolled diabetes or take certain medications (e.g., valproic acid). The specific combination of genetic factors or how they interact with each other or other environmental factors is unknown. Other examples of multifactorial disorders that should be familiar to PCPs are congenital heart defect, club foot, cleft lip/palate, pyloric stenosis, Hirschsprung disease, hip dysplasia, and asthma.

Teratogens

A *teratogen* is any agent that results in, or increases the incidence of, a congenital malformation. Although teratogens have traditionally been considered as environmental toxins altering critical embryonic and fetal development events, it appears that genomic factors can have significant modifying effects to the teratogen. The same teratogenic exposure can induce a severe malformation in one embryo, while failing to do so in another, even though the timing and dose of the exposure were similar (Wlodarczyk et al., 2011). A teratogen may also affect the embryo at one developmental point but not at a different one. The Organization of Teratology Information Specialists (OTIS) provides both health care providers and the public with evidence-based information about exposures during pregnancy and while breastfeeding (see Table 3.1: MotherToBaby). The world's most notorious teratogen is probably thalidomide; however, clinicians today are probably more familiar with fetal alcohol spectrum disorder (FASD), which results from prenatal exposure to alcohol. Teratogenic exposures can also include viruses, such as rubella, cytomegalovirus, and toxoplasmosis; medications, such as warfarin, lithium, tetracycline, and phenytoin; and maternal conditions such as type 2 diabetes and phenylketonuria (PKU).

Mitochondrial Disorders

Although the majority of an individual's DNA is found in chromosomes within the nucleus of a cell, a small amount of genetic material is found in the mitochondria located in the cytoplasm, outside the nucleus. This genetic material is known as

mitochondrial DNA (mtDNA) and contains only 37 genes. Each cell contains hundreds to thousands of mitochondria, which also means there are more opportunities for mutations. Mitochondrial disorders are caused by mutations in mtDNA (i.e., nonchromosomal DNA) and are typically progressive disorders affecting the brain and muscles. Mitochondrial disorders are characterized by exclusively maternal (matrilinear) transmission. When many normal mitochondria are present, the effects from the aberrant mtDNA may be minimal. Some examples of mitochondrial disorders that should be familiar to PCPs are Leber hereditary optic neuropathy (LHON), Leigh syndrome, nonsyndromic deafness, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS). Of note, mtDNA also provides individuals with genealogic information about their female ancestral line.

Patterns of Inheritance

Terminology

One of the important outcomes of taking a family history is the ability to recognize basic inheritance patterns; however, it is important to understand that there can be variable phenotypes, making some patterns of inheritance harder to detect. There are a few terms that clinicians need to understand, including penetrance, expressivity, pleiotropy, variable age of onset, and anticipation (Table 3.2).

Mendelian Inheritance Patterns

Disorders caused by mutations in a single gene are usually inherited in one of several patterns, commonly referred to as *Mendelian* (after Gregor Mendel, known as the father of genetics) patterns of inheritance. They include autosomal dominant (AD), autosomal recessive (AR), X-linked dominant, and X-linked recessive, as well as maternal or mitochondrial inheritance. In contrast, most chromosomal disorders are not passed from one generation to the next.

Autosomal Dominant

This type of single gene disorder is characterized by the inheritance of a single copy of a mutated gene located on one of the autosomal chromosomes (chromosome 1-22). The gene mutation is passed on from only one parent but results in an inherited disorder. The paired gene from the other parent is normal. The parent passing on the gene mutation typically has the disorder. For the offspring, the risk of inheriting the mutation from an affected parent is 50%, regardless of sex and independent of having an affected sibling (Fig 3.4). Children without the abnormal gene will neither develop the disorder nor pass it on. Examples of disorders with an AD inheritance pattern include Huntington disease, Noonan syndrome, and neurofibromatosis type 1.

The clinician reviewing a child's family history should consider AD inheritance when a specific phenotype appears in a family generation after generation, both sexes appear equally affected, and male-to-male transmission occurs. However, penetrance, expressivity, pleiotropy, variable age of onset, and anticipation can interfere with one's ability to recognize AD inheritance. Further, some AD disorders, such as achondroplasia, have a high rate of de novo (new) mutations, making it highly likely that a pedigree will not reveal additionally affected relatives.

Autosomal Recessive

This type of single gene disorder requires inheritance of two copies of a mutated gene (one from each parent) located on one of the autosomal chromosomes (chromosome 1-22). Offspring who inherit only one abnormal gene in the pair are considered *carriers*; they can pass that gene to their children but are typically unaffected.

TABLE 3.2 Definitions of Gene Expression Variables

Term	Definition	Examples
Penetrance—complete or incomplete	Proportion (%) of individuals with a specific genotype that exhibit the corresponding disease phenotype. Complete: Everyone with a specific disease genotype (100%) manifests the corresponding phenotype Incomplete: Some (varying %) of the affected individuals manifest the phenotype	Complete: Huntington disease Incomplete: Breast cancer from BRCA1 or BRCA2 mutation
Expressivity (variable expressivity)	Degree to which a phenotype is expressed. Can vary by compilation and/or severity, even within families.	Van der Woude syndrome: Children can have a cleft lip, cleft palate, or both. Children can have pits near the center of the lower lip; mounds, and/or missing teeth.
Pleiotropy	One genotype results in multiple, seemingly unrelated phenotypes	Marfan syndrome: From joint hypermobility and limb elongation to aortic and heart disease, vision problems, caused by a dislocated lens in either one or both eyes, as well as varying severity, timing of onset, and rate of progression
Variable age of onset	Phenotypic expression does not emerge until later in life	Alzheimer or Parkinson disease
Anticipation	Some phenotypes become more severe and/or appear at an earlier age as a disorder is passed from one generation to the next	Myotonic dystrophy, fragile X syndrome, Huntington disease

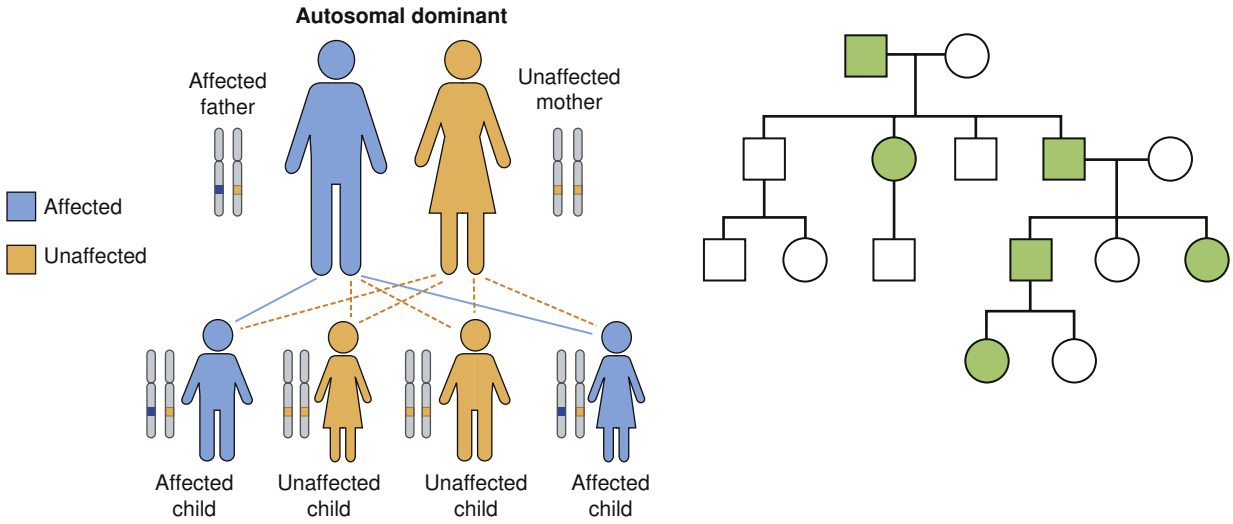
For offspring of parents who both carry an AR mutation, there is a 25% chance of inheriting the mutation from both parents, thus developing the associated disorder, a 50% chance of inheriting one copy and becoming a carrier, and a 25% chance of not inheriting either mutation (Fig 3.5). Examples of AR disorders include cystic fibrosis, albinism, PKU, thalassemia, and sickle cell anemia.

The clinician reviewing a child's family history should consider AR inheritance when a specific phenotype affects multiple siblings and both sexes are affected. The phenotype is often not present in a family generation after generation. However, a family's geographic ancestry and ethnic background, as well as consanguinity, can influence the likelihood of AR disorders, making it more likely that the family will have affected family members in several generations. Examples of geographic ancestry increasing risk for AR disorders include (1) gene mutations associated with cystic fibrosis occur most frequently in populations of European descent and (2) gene mutations associated with sickle cell anemia occur more frequently throughout sub-Saharan Africa, the Middle East, and the Indian subcontinent (Williams and Weatherall, 2012).

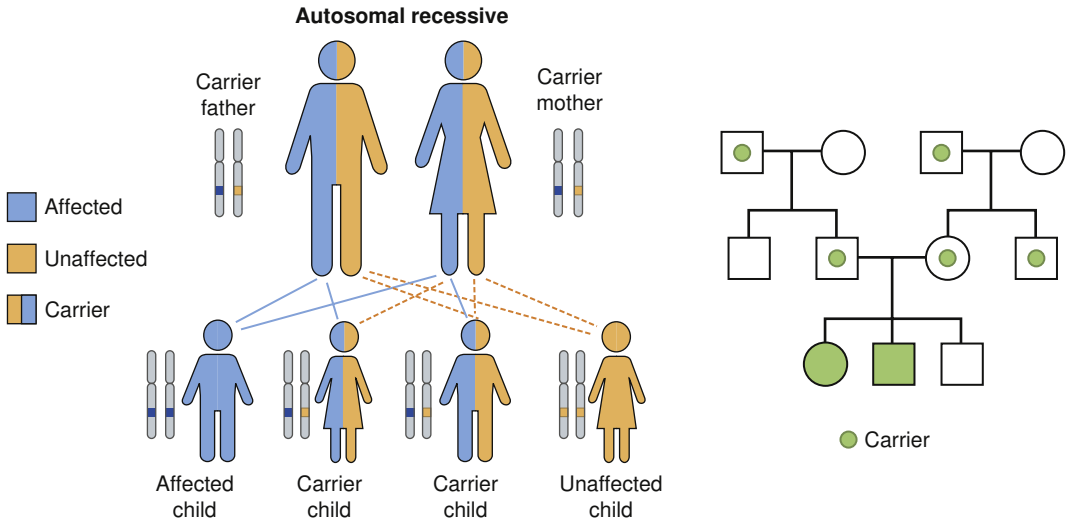
X-Linked Inheritance

Although X-linked inheritance patterns have traditionally been separated into subcategories of X-linked dominant or recessive, there is a move toward collapsing these categories, considering X-linked inheritance patterns across a spectrum. However, for the purposes of this chapter, they will be presented separately.

X-Linked Dominant. When a disorder is classified as *X-linked dominant*, it means that a single abnormal gene on the X chromosome gives rise to the disease (Fig 3.6). If the father is affected (abnormal gene on his X chromosome) and the mother is not, all of his female offspring will inherit the disease-causing allele, but none of his male offspring, because daughters always inherit their father's X-chromosome, whereas sons inherit their father's Y-chromosome. If the mother is affected (one abnormal gene on an X chromosome)



• **Fig 3.4** Autosomal Dominant Inheritance (From Genetics Home Reference. Autosomal dominant. http://ghr.nlm.nih.gov/handbook/illustrations/autodominant. Accessed November 16, 2015.)

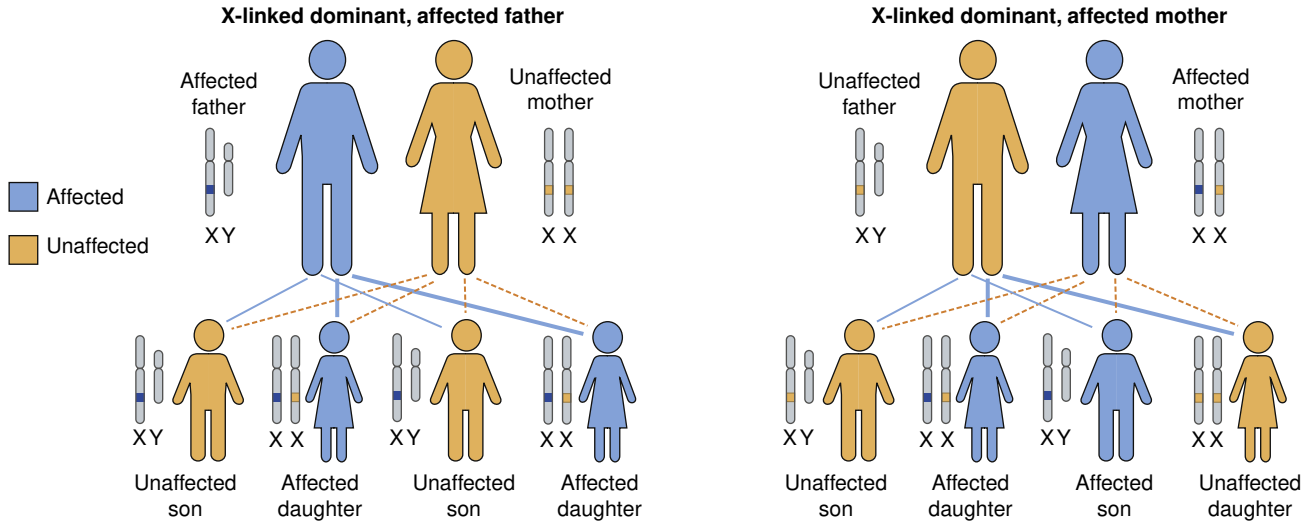


• **Fig 3.5** Autosomal Recessive Inheritance (From Genetics Home Reference. Autosomal recessive. http://ghr.nlm.nih.gov/handbook/illustrations/patterns?show=autorecessive. Accessed November 16, 2015.)

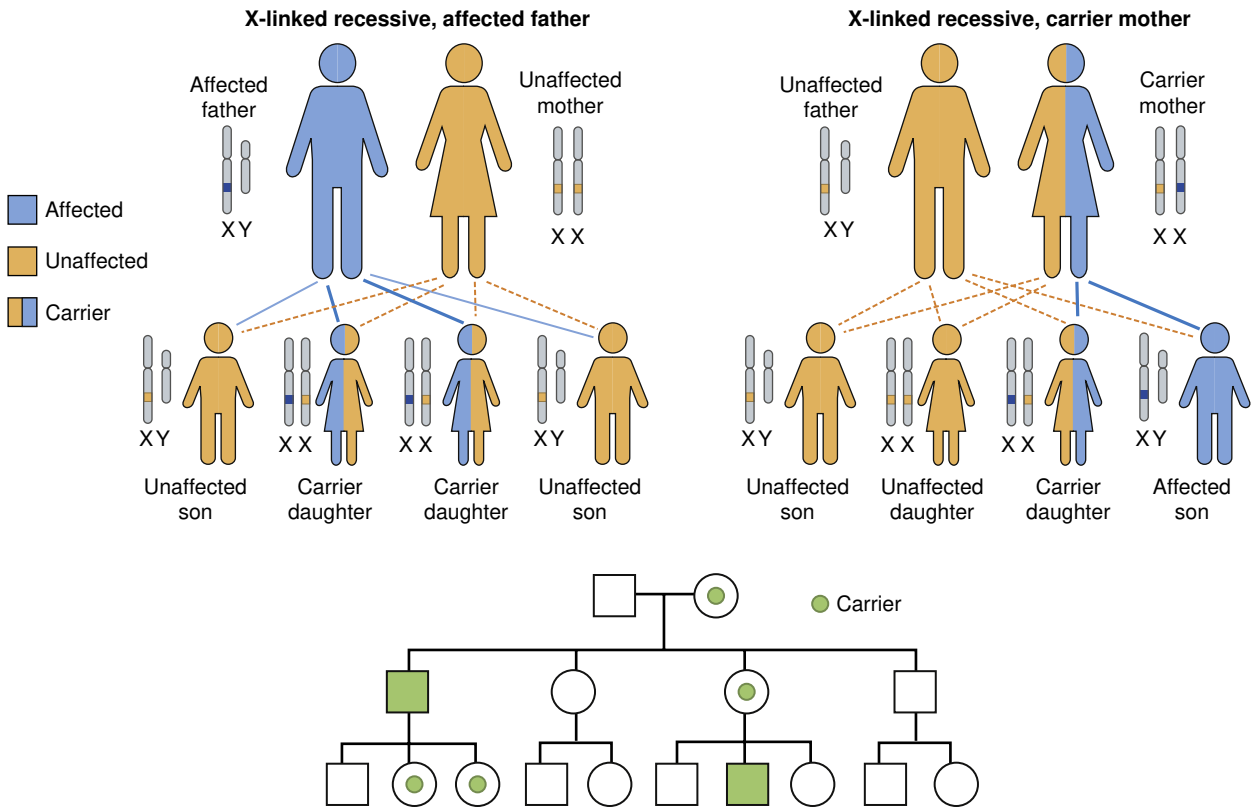
and the father is not, there is only a 50% chance that each daughter or son will inherit the disease-causing allele and manifest the disorder, because mothers have two X chromosomes to pass on.

The clinician reviewing a child's family history should consider X-linked dominant inheritance when a specific phenotype affects both sexes in each generation, with slightly more females (X-linked dominant conditions are often lethal in males) and the absence of male-to-male transmission. Examples of disorders with X-linked dominant inheritance include Rett syndrome and vitamin D–resistant rickets.

X-Linked Recessive. When a disorder is classified as *X-linked recessive*, it usually occurs in males (Fig 3.7). This pattern is seen



• **Fig 3.6** X-Linked Inheritance—Dominant (From Genetics Home Reference. Inheritance patterns. http://ghr.nlm.nih.gov/handbook/illustrations/patterns?show=xlinkdominantfather; and http://ghr.nlm.nih.gov/handbook/illustrations/patterns?show=xlinkdominantmother. Accessed November 16, 2015.)



• **Fig 3.7** X-Linked Inheritance—Recessive (From Genetics Home Reference. Inheritance patterns. http://ghr.nlm.nih.gov/handbook/illustrations/patterns?show=xlinkrecessivefather; and http://ghr.nlm.nih.gov/handbook/illustrations/patterns?show=xlinkrecessivemother. Accessed November 16, 2015.)

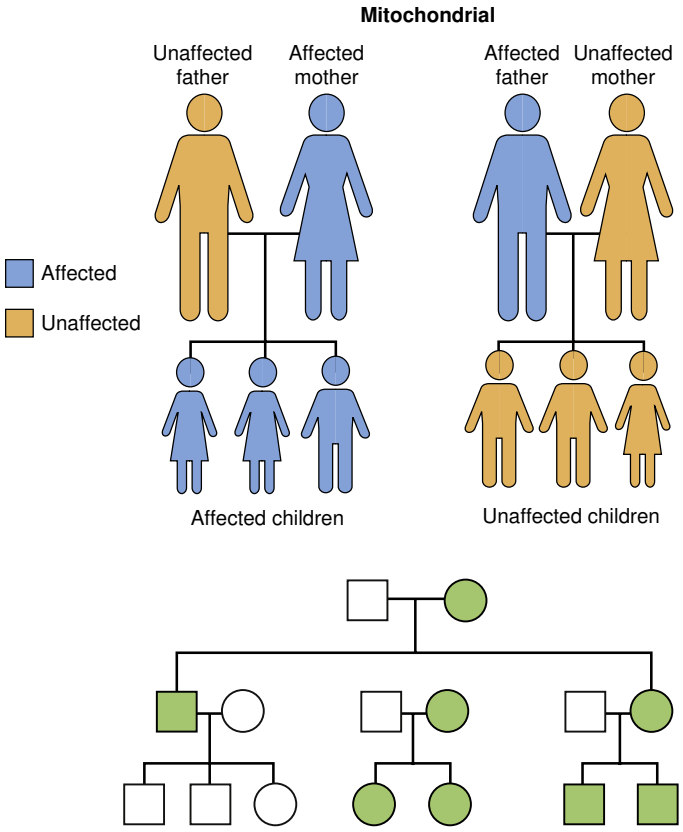
because males have only one X chromosome, so a single, abnormal, recessive allele on that X chromosome is enough to cause the disease. When the father is affected, none of his sons will be affected, and all of his daughters will be *carriers.* If the mother is a carrier (one abnormal gene on one of her X chromosomes), there is a 50% chance that each son will be affected. Daughters have a 50% chance of being a carrier like their mothers. Although females can have an X-linked recessive disorder, it is rare.

When reviewing a child's family history, one should consider X-linked recessive inheritance when a specific phenotype is noted in males more often or more severely than females. Examples of X-linked recessive disorders include Fabry disease, hemophilia A and B, G6PD deficiency, and Duchene muscular dystrophy. As with AD inheritance, some disorders (e.g., Duchene muscular dystrophy) have high rates of de novo (new) mutations, thus rendering the past family history negative.

Nontraditional Inheritance Patterns

Mitochondrial Inheritance

Another inheritance pattern arises from the mtDNA, which accordingly is called *mitochondrial inheritance* (Fig 3.8). Mothers alone pass on mtDNA (i.e., matrilinear or maternal inheritance) because only egg cells contribute mitochondria to the developing embryo. Disorders that arise from mutations in mtDNA can appear in every generation, affecting both sexes. On average, males are more severely affected compared with females. Examples of disorders with maternal (mitochondrial) inheritance include LHON, myoclonic epilepsy with ragged red fibers (MERRF), and MELAS.



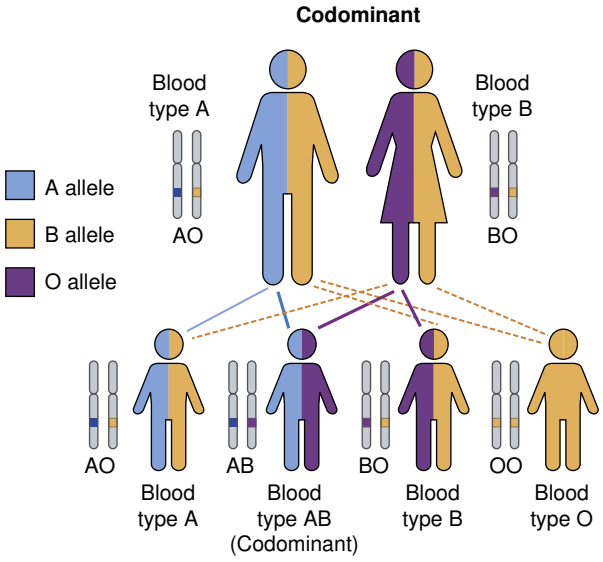
• **Fig 3.8** Mitochondrial Inheritance (From Genetics Home Reference. Inheritance patterns. http://ghr.nlm.nih.gov/handbook/illustrations/patterns?show=mitochondrial. Accessed November 16, 2015.)

Codominant Inheritance

A disorder is categorized as having a *codominant inheritance* when two different alleles for a gene can be expressed and different combinations result in slightly different proteins (Fig 3.9). There are a few genes with established codominant inheritance patterns; however, some disorders do not follow established patterns and are considered multifactorial in origin. Sometimes the specific gene(s) remain partially or fully unidentified. The best example of this type of inheritance is reflected in blood type (ABO blood group) determination.

Genomic Imprinting

Children typically inherit two copies of genes, one from their mother and one from their father, and both copies are active (i.e., turned on) in the cells together; however, in some cases only one copy needs to be expressed, and therefore the other copy is turned off or silenced during embryogenesis. The decision as to which gene remains working and which is silenced depends on the parent of origin. Only a small number of genes go through genomic imprinting, which occurs when the origin of the gene (maternal vs. paternal) is marked (imprinted) on the gene during the formation of egg or sperm cells through methylation. Imprinted genes tend to cluster together in the same regions of certain chromosomes (Genetics Home Reference, 2018). Improper imprinting can result in a child having two active copies or two inactive copies. Two major clusters of imprinted genes have been identified in humans, on chromosomes 11 and 15. Prader-Willi syndrome occurs when the paternally derived genes located in a specific chromosome 15 region are either improperly imprinted or deleted, whereas Angelman syndrome occurs when the maternally derived genes in the same area are either improperly imprinted or deleted. Thus the developing embryo does not detect a paternal or maternal copy of chromosome 15, producing one syndrome or the other. Beckwith-Wiedemann and Russell-Silver syndromes are other examples of disorders influenced by genomic imprinting.



• **Fig 3.9** Codominant Inheritance (From Genetics Home Reference. Inheritance patterns. http://ghr.nlm.nih.gov/handbook/illustrations/patterns?show=codominant. Accessed November 16, 2015.)

Uniparental Disomy

When a child receives two copies of one chromosome, or a part of a chromosome, from one parent and none from the other parent, it results in uniparental disomy (UPD). The child will be homozygous for every gene located on that chromosome, which increases the possibility of inheriting an AR disorder. UPD can occur as a random event during the formation of egg or sperm cells, or may happen in early fetal development.

In many cases, UPD has no effect on a child's health or development, because most genes are not imprinted. Thus it does not matter if a child inherits both copies from one parent or one copy from each parent. However, in some cases, maternal or paternal inheritance of a specific gene is important. Examples of disorders that can arise from UPD include Prader-Willi and Angelman syndromes, which were also noted under genomic imprinting. Prader-Willi syndrome (caused by UPD) happens when the fetus inherits two maternal chromosome 15 (she or he is missing a paternally derived chromosome 15). Angelman syndrome (caused by UPD) happens when the fetus inherits two paternal chromosome 15 (she or he is missing a maternally derived chromosome 15).

Epigenetics

Epigenetics is the study of changes in gene expression that occur without a change in DNA sequence (Genetics Home Reference, 2018). Epigenetics regulates which genes get turned on and off. Its study is increasingly important in the identification and treatment of childhood diseases and developmental disorders. Unlike the genome, the epigenome is modifiable. The epigenome consists of molecular compounds that "mark" the genome and modify genetic expression by telling a gene or several genes what to do, when to do it, and where to do it. DNA methylation, histone modification, and/or microRNA (miRNA) are examples of three types of epigenetic modifications. *DNA methylation* involves the addition of a methyl (CH_3) group to the DNA, which modifies gene expression by turning the gene(s) off. *Histone modification* involves adding or subtracting molecules that in turn change how tightly coiled a segment of DNA is around its corresponding histone. DNA that is tightly coiled is closed to transcription, and therefore local genes cannot be expressed, whereas loosely coiled DNA is open to transcription and subsequent expression. *miRNA* regulate expression of target genes through posttranscription gene silencing. Different experiences or exposures may influence the epigenetic profile, including chemical exposures, diet, endocrine disruptive compounds, hypoxia, maternal physical state and age, placenta size, smoking, stress, and trauma. Many common adult disorders are now believed to be caused by epigenetic changes that occurred during that individual's embryonic development or in early childhood, such as obesity, heart disease, hypertension, diabetes, and obesity (Puumala and Hoyme, 2015).

Integration of Basic Genetics and Genomics into Pediatric Primary Care

Assessment

Family health history and the recognition of genetic red flags provide the foundation from which care evolves. Emphasis is on understanding genetic screening, working with children and families to understand the implications of a genetic workup and diagnosis, and coordinating care with genetic specialists. A complete head-to-toe physical and developmental assessment, combined with a comprehensive family health history, is important in identifying inherited and congenital disorders.

Family Health History and Pedigree

In primary care practice, taking the time to collect a child's family health history and pedigree can be just as important as information from a laboratory test, yet this is often underused or absent in today's increasingly time-constrained well child visits. Individual and family involvement in family health history got a boost in 2004, when the U.S. Surgeon General declared Thanksgiving as the ideal day to investigate and/or update one's family health history. An individual's family history should be updated annually.

Three-Generation Pedigree. The pedigree is a valuable visual record of genetic links and health-related information. It should include at least three generations and is much more helpful in visual form, rather than in lists or narrative formats. It is important to remember that most disorders have some genetic component, and the strength or pattern of traits or diseases may become apparent based on the number or pattern of individuals in a family who are affected. Table 3.3 suggests specific questions to use when conducting a comprehensive family health history. Insights about families are gained, not only because families share genes, but also because they also often share environments, behaviors, and culture—all of which contribute to shared health problems. See Figs 3.4 to 3.9 for the exemplars of pedigrees highlighting different patterns of inheritance.

All PCPs should be able to obtain, record, and interpret a three-generation pedigree, which is a construct that includes the health status of first-, second-, and third-degree relatives (three generations) of the individual's or child's family. Although the aim for clinical practice is a three-generation pedigree, asking about only two generations, or in some cases asking about four generations, may be more appropriate, depending on the trait or disorder and family size (see Table 3.4 for proportion of genetic material shared by family relationships).

There is a set of standardized pedigree symbols that have been adopted internationally (Bennett et al., 2008). An overview of the symbols, as well as how to connect them to illustrate various family relationships, is provided in Figs 3.10 and 3.11. There are also multiple Internet resources to assist children, families, and providers in obtaining and documenting family health histories, including Genetic Alliance's "Does It Run in the Family?" Toolkit (see Table 3.1: Genetic Alliance, NCHPEG Family History Collection and Risk Assessment, and Genes In Life).

The process of constructing a family pedigree should begin with the nuclear family, followed by added aunts and uncles, cousins, and grandparents. For all persons included in the pedigree, it is important to record their date of birth or age, relevant symptoms, traits, or disorders, as well as the ages of diagnosis, and the ages and causes of death. It is also important to record miscarriages, stillbirths, infertility, and any children relinquished for adoption. An additional query should be made about the presence or possibility of consanguinity or incest. When pieces of family history are missing, it is important to note the information as missing, because the absence of information does not mean the child has not acquired genetic risk.

Genetic Red Flags From the History. Genetic red flags indicate the potential for genetic risk. For some providers, it is easiest to remember the Rule of Too/Two. For some providers, it is easiest to remember simple rules (e.g., rule of too/two) or mnemonics (e.g., SCREEN, F-GENES) to remember the important components to look for or ask about when obtaining a family health history. (Table 3.5).

TABLE 3.3 General Screening for Genetic Conditions: The History

Question	Rationale/Comments
Does/has anyone in the family have/had a birth defect?	To identify conditions that affect others in the family. If answer is yes, try to get more information about the nature of the defect.
Has anyone in the family had a stillborn baby? A baby who died early? A baby who died unexpectedly?	To identify unrecognized syndrome. Babies who died very early may have inheritable metabolic disorders. Distinguish sudden unexplained infant death (SUID) and sudden infant death syndrome (SIDS).
Is there any chance that you and your partner are blood-related? Is this pregnancy a product of incest? Is there any history of consanguinity/incest in your extended family?	Consanguinity of partners closer than first cousins is a risk factor for autosomal recessive (AR) disorders. If yes, recommend genetics consultation.
Is there anyone in your family who routinely sees a health care provider for specific condition?	Significant if early onset, two or more close relatives affected. Remember to ask about hearing/vision, growth disorders. Genetic heart disease and genetic cancer risks are important. If yes, recommend genetic consultation and monitoring.
Have you or your partner, or any of your/your partners' parents/siblings had three or more miscarriages? How about infertility issues?	May indicate a chromosome translocation. If yes, order a karyotype of the mother or father (or both). Difficulties becoming/maintaining a pregnancy may indicate a genetic syndrome.
Does anyone in the family have learning problems, mental retardation/behavioral disorders, developmental delays?	Look for multiple members affected and associated with dysmorphic features. If yes, recommend genetic consultation.
What is your ethnic/geographic heritage background? Your partner's?	Discovering where an individual's ancestors come from can help identify certain ethnic and/or population risk factors.

TABLE 3.4 Degree of Relationship Between Individual Family Members and Shared Genetic Material

Relationship	Amount of Shared Genetic Material (%)	Example
First-degree relatives	50	Children, full siblings, biologic parents
Second-degree relatives	25	Grandparents, half siblings, aunts/uncles, nieces/nephews
Third-degree relatives	12.5	Cousins

In general, providers should pay attention if one or more of these genetic red flags emerge when taking a family health history: (1) multiple affected members with the same related disorder; (2) earlier age at onset than expected for the disorder; (3) a condition or disorder seen in the less-often affected sex; (4) the appearance of a disease in the absence of any known risk factors; (5) at-risk ethnicity or ancestral background; (6) unusual close relationships, such as consanguinity, by blood or through a common ancestor; (7) multifocal or bilateral occurrence in paired organs; (8) intellectual impairment with or without major or minor malformations; (9) women experiencing three or more miscarriages; and (10) individuals with two or more major malformations.

Physical Findings Indicating Inherited or Congenital Disorders

It is important not only to identify red flags in the history but also to identify physical findings that can point to the presence of a particular inherited or congenital condition(s). Findings that are particularly notable include physical abnormalities (e.g., multiple café au lait spots, growth problems, and congenital anomalies) and neurologic abnormalities (including hearing loss, vision loss, developmental delay, mental retardation, hypotonia, progressive muscle weakness, and hard-to-control seizure disorders). PCPs can hone their abilities by familiarizing themselves with advanced anthropomorphic measurement skills and by reviewing detailed descriptions and photographs of children and adults with various disorders (see Table 3.1: Positive Exposure).

Minor and Major Anomalies

Classification of features can appear somewhat arbitrary. A congenital anomaly or birth defect is an abnormality of structure or function that is present at birth. A physical finding is referred to as a *major* anomaly if it impairs normal body function (e.g., congenital heart disease, cleft palate), whereas a *minor* anomaly is more of a cosmetic variation, without impairing function (e.g., clinodactyly, small ear). This distinction is made because a genetic etiology is often considered when an individual has one major or more than two minor anomalies. Minor anomalies in the head, neck, and hand account for the majority of all minor anomalies (Table 3.6).

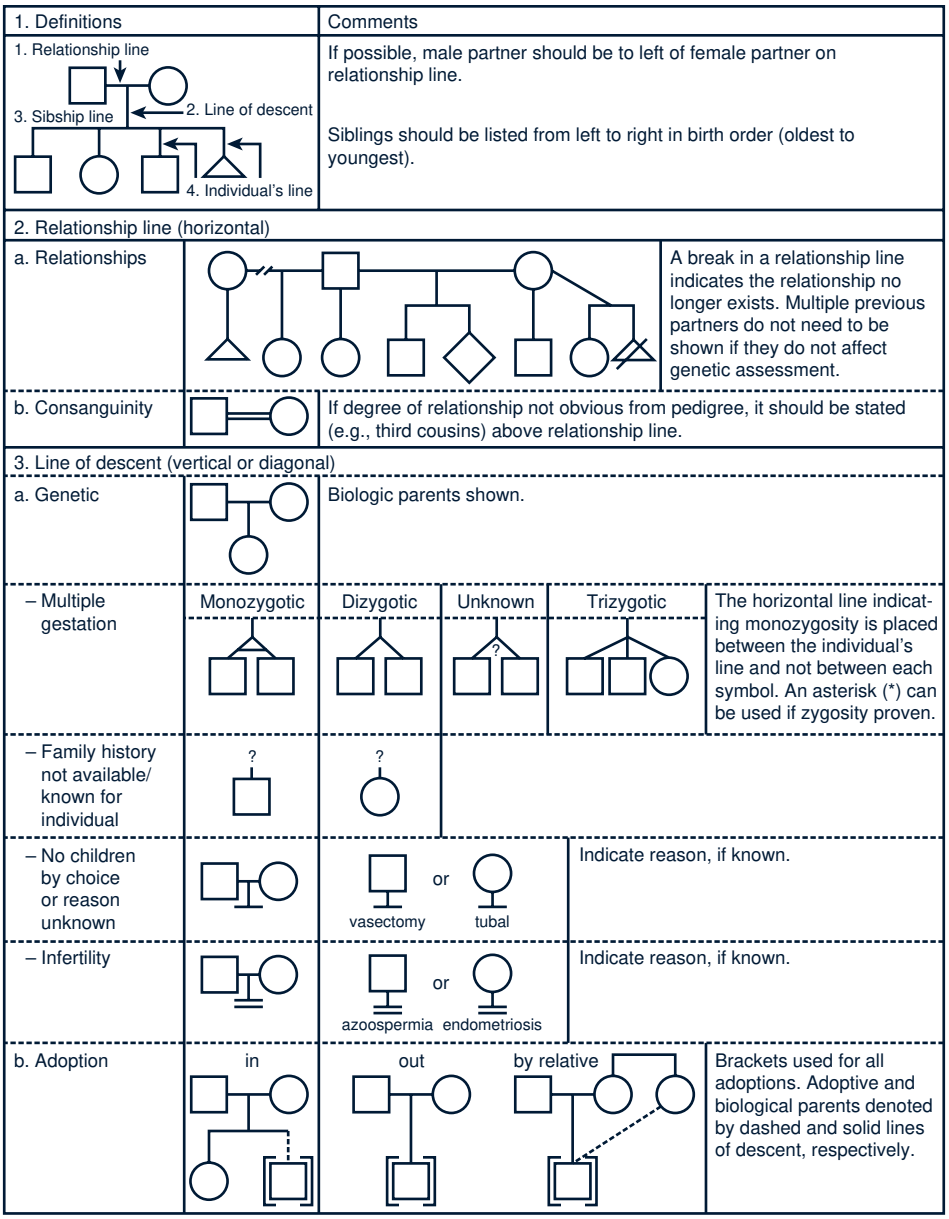
Instructions:
— Key should contain all information relevant to interpretation of pedigree (e.g., define fill/shading)
— For clinical (non-published) pedigrees include:
  a) Name of proband/consultand
  b) Family name/initials of relatives for identification, as appropriate
  c) Name and title of person recording pedigree
  d) Historian (person relaying family history information)
  e) Date of intake/update
  f) Reason for taking pedigree (e.g., abnormal ultrasound, familial cancer, developmental delay, etc.)
  g) Ancestry of both sides of family
— Recommended order of information placed below symbol (or to lower right)
  a) Age; can note year of birth (e.g., b. 1978) and/or death (e.g., d. 2007)
  b) Evaluation
  c) Pedigree number (e.g., 1-1, 1-2, 1-3)
— Limit identifying information to maintain confidentiality and privacy

	Male	Female	Gender not specified	Comments
1. Individual	b. 1925	30 y	4 mo	Assign gender by phenotype (see text for disorders of sex development, etc.) Do not write age in symbol.
2. Affected individual				Key/legend used to define shading or other fill (e.g., hatches, dots, etc.). Use only when individual is clinically affected.
				With ≥2 conditions, the individual's symbol can be partitioned accordingly, each segment shaded with a different fill and defined in legend.
3. Multiple individuals, number known	5	5	5	Number of siblings written inside symbol. (Affected individuals should not be grouped).
4. Multiple individuals, number unknown or unstated	n	n	n	"n" used in place of "?".
5. Deceased individual	d. 35	d. 4 mo	d. 60s	Indicate cause of death if known. Do not use a cross (†) to indicate death to avoid confusion with evaluation positive (+).
6. Consultand				Individual(s) seeking genetic counseling/ testing.
7. Proband	P	P		An affected family member coming to medical attention independent of other family members.
8. Stillbirth (SB)	SB 28 wk	SB 30 wk	SB 34 wk	Include gestational age and karyotype, if known.
9. Pregnancy (P)	P LMP: 7/1/2007 47, XY, +21	P 20 wk 46, XX	P	Gestational age and karyotype below symbol. Light shading can be used for affected; define in key/legend.

Pregnancies not carried to term	Affected	Unaffected	
10. Spontaneous abortion (SAB)	17 wks female cystic hygroma	< 10 wks	If gestational age/gender known, write below symbol. Key/legend used to define shading.
11. Termination of pregnancy (TOP)	18 wks 47< XY, +18		Other abbreviations (e.g., TAB, VTOP) not used for sake of consistency.
12. Ectopic pregnancy (ECT)	ECT		Write ECT below symbol.

• **Fig 3.10** Pedigree Model Common pedigree symbols, definitions, and abbreviations. (Adapted from Bennett RL, French KS, Resta RG, et al. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. *J Genet Couns*. 2008;17[5]:424–433.)

Malformations are birth defects that result from an intrinsic process, such as altered genetic or developmental processes. They typically result in a basic alteration in structure and occur early in gestation (e.g., cleft palate, anencephaly, limb agenesis). *Deformities* and *disruptions* are defects that result from an external process, resulting in an abnormal shape or positioning of a body part or organ. A deformity results from a distortion by a physical force, such as oligohydramnios or twins, on an otherwise normal structure (e.g., club foot), whereas a disruption refers to destruction of a tissue or structure that was previously normal (e.g., amniotic bands). In contrast, *dysplasia* is used to reflect abnormal cellular organization within tissues that results in a structural change (e.g., achondroplasia). When there is a set, recurrent pattern of features or malformations that often have a known genetic component,



• **Fig 3.11** Pedigree Line Definitions (Adapted from Bennett RL, French KS, Resta RG, et al. Standardized human pedigree nomenclature: update and assessment of the recommendations of the National Society of Genetic Counselors. *J Genet Couns.* 2008;17[5]:424–433.)

it is called a *syndrome.* An *association*, on the other hand, is a group of anomalies that occur more frequently than would be expected by chance alone. Associations do not have a predictable pattern or a unified etiology (e.g., VACTERL association—V = vertebral, A = anal anomalies, C = cardiac, TE = trachea-esophageal fistula, R = radial and/or renal anomalies, L = limb anomalies). The numbers of malformation syndromes described are increasing daily. Health care providers need to think in terms of phenotypic analysis, which begins with a complete physical and developmental assessment.

Diagnostic Studies

No single genetic test can identify all disorders. Equally important, findings from genetic testing completed for one individual can impact other family members. The increased availability and use of genetic screening and testing in children led the AAP and the American College of Medical Genetics and Genomics (ACMG) to update their policy statements on newborn screening, diagnostic genetic testing, carrier testing, predictive genetic testing in children, and the disclosure of genetic test results (Hamid, 2013). In addition, they added a statement about direct-to-consumer genetic testing, strongly discouraging the use of this type of genetic testing in children. As highlighted in their policy statement, decisions about whether to offer genetic screening and/or testing should be informed by the best interest of the child (AAP Committee on Bioethics, Committee on Genetics and ACMG Social, Ethical, and Legal Issues Committee, 2013). The Genetic Testing Registry (GTR) is a robust resource for health care providers, and it provides current information about available genetic tests and where they can be done (see Table 3.1: Genetic Testing Registry [GTR]). Chapter 32 discusses managing primary care for children with congenital and inherited disorders.

TABLE 3.5 Mnemonics for Gathering and Interpreting the Genetic Health Data

Mnemonic	Meaning
Rule of Too/Two	***Too*** many of something: individual is *too* tall, *too* short, *too* early, *too* young, *too* different, and so on *or* ***Two*** birth defects, *two* cancers, *two* in a family, or *two* generations involved
SCREEN	**S**ome **C**oncerns about traits or diseases that run in the family **R**eproductive problems History of **E**arly disease, death, or disability **E**thnicity of the patient **N**ongenetic risk factors or conditions that run in the family
F-GENES	**F**amily history: Multiple affected siblings in the same or individuals in multiple generations **G**roups (two or more) of congenital anomalies or anatomic variations **E**xtreme or exceptional presentation of a common condition(s), including early onset, recurrent miscarriage, bilateral disease **N**eurodevelopmental delay or degeneration (regression) **E**xtreme or exceptional pathology **S**urprising laboratory values

Adapted from Genetics in Primary Care Institute (GPCI): genetic red flags. https://www.aap.org/en-us/advocacy-and-policy/aap-health-initiatives/pages/Genetics-in-Primary-Care-Institute.aspx. Accessed May 21, 2018.

TABLE 3.6 Minor Malformations and/or Variations of Normal

General	Short/tall stature Body/limb disproportion Failure to thrive or obesity
Craniofacial features	Unusual head shape/circumference/fontanels Synophrys (fused eyebrows) Long eyelashes Hyper/hypotelorism Epicanthal folds Up/down slanting and/or short palpebral fissures Heterochromia, ptosis, cataract, glaucoma Low nasal bridge Abnormal ear position/shape/tags/pits Short, long, or flattened philtrum Malar flattening Prominent metopic ridge Bifid uvula, high arched/cleft palate Natal teeth/central incisor Micrognathia
Hands/feet	Abnormal creases Short/long digit(s) Prominent digital pads Clinodactyly (incurved fingers) Syndactyly (fused digits) Polydactyly Camptodactyly (bent/flexed) Dysplastic nails
Hair/skin	Abnormal hair line or color Increased numbers or anterior location of hair whorl Hirsutism Hypopigmented/hyperpigmented patches Pigmented nevi
Neck	Short, webbing
Chest	Widely spaced or supernumerary nipples Abnormal chest shape
Abdomen/genitalia	Redundant umbilicus Shawl scrotum

Screening

Screening is used in asymptomatic populations to identify individuals who need further evaluation and/or testing. Pediatric providers need to be familiar with newborn and prenatal screening. The family health history and specific tests that screen for disorders increasingly thought to have a genetic basis, such as autism, are also important screening tools.

Newborn Screening. Newborn screening is used to identify inherited and congenital disorders that can benefit from early diagnosis and treatment. Today, effective newborn screening involves a sophisticated network of coordinated efforts among public health agencies, PCPs, and specialists. It involves individual and family education, mass screening for a select subset of congenital or inherited conditions, and short- and long-term follow-up plans for newborns who screen positive. Each state determines the conditions included on their newborn screening panel; however, there is a national Recommended Universal Screening Panel (RUSP), which currently lists 34 core conditions and 26 secondary conditions, for which every baby should be screened. The RUSP is not a law, serving only as a guide for states. Clinicians should check the Advisory Committee on Heritable Disorders in Newborns and Children and Baby's First Test (see Table 3.1: RUSP; Baby's First Test), where the latest information on the conditions included in each state's newborn screening is continually updated.

Following up a positive newborn screen is stressful for both the clinician and the family. Being well prepared will make the initial contact with the family more effective. The ACMG developed action (ACT) sheets that provide clinicians with the steps to be taken after an initial positive screening result with an accompanying algorithm. Their website contains the latest versions of the ACT sheets, which are regularly revised based on new tests and information (see Table 3.1: ACMG ACT Sheets and Confirmatory Algorithms).

Prenatal Screening. Screening and diagnostic tests to detect inherited and congenital disorders have become standard prenatal care. Prenatal screening tests are typically offered to all women to screen for common syndromes (such as Down syndrome) and congenital anomalies (such as NTDs), or to select women who might be at higher risk based on age, ancestral or ethnic background, or a specific family history of the disorder. All forms of genetic testing for the specific purpose of diagnosing a fetus can be performed directly on the fetus by collecting fetal cells through a chorionic villus sample (CVS) or amniocentesis. In contrast, preimplantation testing is used to detect genetic changes in embryos created through assisted reproductive techniques before they are implanted to initiate pregnancy in the woman.

Diagnostic Genetic Testing

Diagnostic testing is used to confirm a diagnosis and is used in a symptomatic individual or in response to a positive screening test. Such tests are selected depending on the type or specific disease one is trying to confirm. Specific practice guidelines can help

providers choose which test to order. For example, a chromosomal test would be used to confirm Down syndrome (trisomy 21) in a newborn, while a genetic test designed to identify missing or duplicated sections in the dystrophin (DMD) gene [Xp21.2] would be used to confirm Duchenne muscular dystrophy in a preschool male with delayed gross motor development and elevated CK/CPK levels. The test is designed to identify missing or duplicated sections in the dystrophin (DMD) gene [Xp21.2].

The main types of diagnostic genetic testing include karyotype, fluorescence in situ hybridization (FISH), biochemical testing, chromosomal microarray, molecular testing, and next-generation sequencing (Table 3.7). *Karyotype* is used to identify and evaluate the size, shape, and number of chromosomes. *FISH* is used to locate and detect a specific area of a particular chromosome, including subtle missing, additional, or rearranged chromosomal material by labeling a known chromosome sequence with fluorescent tags to see the location of genetic material. Unlike most other techniques used to study chromosomes, FISH does not have to be performed on cells that are actively dividing, making it more versatile. *Biochemical testing* is used to study the amount, activity level, or structure of proteins and enzymes that result from gene mutations. Many metabolic syndromes are screened for and diagnosed using biochemical testing. *Chromosomal microarray* is used to detect microdeletions or duplications (such as CNVs) in any of the chromosomes but not specific gene mutations. Microarray testing is noted to have a superior diagnostic yield over karyotyping for similar clinical features, including developmental disabilities (Ellison et al, 2012). *Molecular testing* is used to detect specific single gene mutations (e.g., deletions, insertions, and single base pair changes) known to cause single gene disorders. Molecular techniques are used to directly detect aberrant sequences changes in a targeted gene or short length of DNA or to indirectly detect aberrant changes in DNA structure by identifying size variations in fragments of DNA from the targeted locus or gene. *Next-generation sequencing* is used to detect a single mutation among many genes and can detect several sequence changes with one test.

Carrier Testing

Carrier testing is used to identify individuals who have one copy of a gene mutation that causes a known disorder when two copies are present (AR disorders). Individuals with one copy are often referred to as having the trait or being a carrier, rather than having the disease. Carrier testing is typically offered to individuals who are planning a family, focusing on information about the couple's risk of having a child with an AR or X-linked disorder. For example, parents can be tested to see if they are carriers of one of the mutations leading to cystic fibrosis or if they have sickle cell or thalassemia trait. Carrier testing is also done to identify nonmanifesting females of X-linked diseases. These women are referred to as "carriers" of X-linked diseases, such as Duchenne muscular dystrophy and hemophilia. Carrier testing in children is controversial. The AAP and ACMG do not recommend routine carrier testing in children, except when the carrier status has medical implications in childhood or for adolescents who are pregnant.

Other Testing

Predictive/presymptomatic tests are used when asymptomatic individuals are interested in learning if they have a gene mutation associated with a disorder and are typically offered when there is a family history of a single-gene disorder. This type of testing identifies mutations that increase an individual's *risk* of developing an inherited disorder (such as breast or colon cancer, Huntington disease, and hypertrophic cardiomyopathy), before they actually manifest signs or symptoms of the disease. The results help individuals and their providers make decisions about the need for increased screening, preventative measures, life planning, and reproductive planning. In general, these tests are not done in children because they are often associated with an adult onset. It is considered more ethical for children to make the decision about receiving this information when they are older and able to make such decisions as adults. However, there are single gene disorders that can and do manifest later in children, such as hypertrophic cardiomyopathy and certain forms of colon cancer. The use of predictive/presymptomatic testing should be guided by the child's best interests and should involve parental input (Hamid, 2013; Driessnack et al., 2013).

Pharmacologic testing (PGx testing) examines a person's genes to look at how drugs would move through the body, be broken down, or affect the body (Cheek, Bashore, and Brazeau, 2015). The primary purpose of PGx testing is to learn ahead of time what the best drug or best dose of a drug will be for a person, given their genotype. One of the biggest barriers to implementation of pharmacogenomic testing in primary care is the difficulty in translating genetic laboratory test results into actionable prescribing decisions. The Clinical Pharmacogenomics Implementation Consortium (CPIC) is an international consortium of professional volunteers and staff who facilitate the use of pharmacogenomic tests for patient care. CPIC's goal is to offset the translation barrier.

To facilitate clinical implementation of pharmacogenomic tests, CPIC created, curated, and made available peer-reviewed, evidence-based, updatable, and detailed gene/drug clinical practice guidelines. CPIC guidelines follow standardized formats and are published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics), with simultaneous posting to their website. Entries are regularly updated (see Table 3.1: Clinical Pharmacogenomics Implementation Consortium [CPIC]).

Forensic testing is most often used in pediatric practice to establish biologic relationships between individuals, such as establishing paternity. Forensic testing can also be used to identify catastrophic victims and/or crime victims/suspects.

Ethical Issues

From the inception of the Human Genome Project, the National Human Genome Research Institute (NHGRI) had the foresight to anticipate the string of ethical, legal, and social issues that were to arise as part of advancing the science of genomic research. Housed within NHGRI is the Ethical, Legal, and Social Implications (ELSI) program. A few of the ethical issues include the rights to privacy and confidentiality, the rights to know, not know, the duty to warn, disclosure of incidental findings, and genetic discrimination.

The Genetic Information Nondiscrimination Act (GINA) was passed in 2008, with all aspects of the law in effect in November 2009. The intent of the legislation was to protect individuals from the misuse of genetic information in health insurance and employment and remove barriers to the use of genetic services. GINA does not affect healthcare. However, under GINA, *health insurers* cannot use an individual's genetic information to set eligibility requirements, establish insurance premiums, or request certain genetic tests. Further, *employers* cannot request, require, or purchase genetic information about an employee or family member, and they cannot use an individual's genetic information

TABLE 3.7 Diagnostic Genetic Testing

	Karyotype	Fluorescence In Situ Hybridization (FISH)	Chromosomal Microarray	Molecular Testing[a]
Detects ***large*** deletions or duplications	X	X	X	
Detects deletions or duplication in ***part*** of a chromosome		X	X	
Detects ***small*** deletions or duplications			X	
Detects translocations	X			
Detects ***very small*** structure and sequence changes and single gene mutations				X

[a]Including DNA sequencing.

in decisions about job hiring, firing, assignments, or promotions. Unfortunately, GINA does not provide protection when a condition is already diagnosed or manifest, even if that condition is genetic. Further, GINA does not apply to life, disability, or long-term insurers. The types of genetic information protected under GINA include family health history, carrier testing, prenatal genetic testing, predictive testing, and other assessments of genes, mutations, or chromosomal changes. There are a few groups exempt from GINA, which include members of the military, veterans receiving care through the Veteran's Administration, those using the Indian Health Service, and federal employees enrolled in the Federal Employees Health Benefits program. However, military, veterans, and federal employees have other protections that mirror GINA.

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4

Environment and Child Health

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Introduction

The environment is a basic determinant of human health and illness. Although a direct cause-effect relationship between health and the environment is often difficult to determine, indoor and outdoor air pollution, second-hand smoke, unsafe water, lack of sanitation, and inadequate hygiene are responsible for one-third of the global burden of disease (World Health Organization [WHO], 2014). Children are particularly vulnerable to environmental factors due to their rapid growth and development in early childhood. Worldwide, one in four deaths of children younger than 5 years old can be attributed to unhealthy environments (WHO, 2017). Climate change, rising global temperatures, and increased levels of carbon dioxide have resulted in increased rates of asthma in children. Globally, it is estimated that 44% of asthma symptoms are related to environmental exposures, and the prevalence of children 5 years of age and older who report symptoms of asthma is 11% to 14% (WHO, 2017).

Principles for Understanding Children's Environmental Health

Children go through critical developmental periods or *windows of vulnerability* prenatally and during early childhood due to rapid brain development in the first 2 years of life. There are sensitive periods throughout childhood when rapid growth occurs and during which exposure to toxic or other harmful substances affects growth or damages organs or body systems. See Table 4.1 for environmental risk factors for children at different stages of development. Toxic substances are those chemicals in the environment capable of causing harm. *Toxicants* are environmental hazards from chemical pollutants, and *toxins* are environmental hazards from biologic sources. Toxicants that cross the placenta (e.g., drugs, carbon monoxide [CO], mercury, lead, and cotinine [from environmental tobacco smoke]) can contribute to low birth weight, spontaneous abortion, intrauterine growth retardation, and birth defects. The burden of disease and cost of environmental hazards stems primarily from exposure to toxic chemicals and air pollutants, and the related health conditions affecting children include lead poisoning, exposure to mercury pollution, childhood cancers, asthma, autism, intellectual and learning disabilities, and attention-deficit/hyperactivity disorder (Transande et al., 2015).

Children's rapidly developing and growing tissues more readily absorb environmental toxins; the lungs, skin, and gastrointestinal (GI) tract of newborns are highly permeable. At the same time, newborns' immature organ systems metabolize drugs more slowly and make it difficult for infants to detoxify and excrete harmful substances. Children consume more fresh fruit, water, milk, and juice per pound of body weight, and breathe more pollutants than adults, which increases exposure to pesticides or other chemicals (Axelrad et al., 2013). Children also engage in more outdoor activities and are physically closer to potentially harmful substances than adults. Running and rolling in grass are behaviors that increase exposure to pesticide poisoning and can trigger respiratory problems, including asthma exacerbations. For infants, crawling on floors and chewing on objects can result in lead poisoning. Children living in low-income communities are at higher risk than others due to poor nutrition, deteriorating housing with high levels of environmental lead contamination, and limited access to quality health screening and treatment. In addition to the immediate risk during childhood, children have a longer time span for exposure to environmental toxins (Landrigan, 2016). Adolescents are at increased risk if occupational hazards are present.

Epidemiologic Model of Environmental Health Hazards: Assessment of Risk

Using principles of epidemiologic relationships and toxicology, providers can better understand and explain to their patients and families the intersection between the environment and health.

A first step using an epidemiologic approach identifies the interactive factors in the environment, including *receptors* (hosts or living things that are susceptible or exposed to environmental agents); *toxins* or the agents (harmful substances that might cause damage); and the environmental *medium* or route (air, soil, water, or food) by which exposure could occur.

A second step of risk assessment using an epidemiologic model determines the possibility that harm could occur (National Research Council, 2003). A number of questions are asked when making this determination:

- *Hazard:* source of risk, a substance or action that can cause harm
  - How susceptible is the receptor to the agent (e.g., age, gender, genetics, diet, and general health)?

TABLE 4.1 Environmental Risk Factors for Children at Different Stages of Development

Developmental Stage	Developmental Characteristics	Exposure Pathways (Physical Environment)	Biologic Vulnerabilities	Appropriate Responses in the Social Environment
Preconception	Maternal and paternal health status	Maternal/paternal reproductive organs may be compromised Maternal stores of toxicants in bones and fatty tissue can be mobilized during pregnancy	Problems with fertilization, implantation of ovum Damage to ovum or sperm	Research and education regarding long-term effects of environmental contaminants on reproductive system and subsequent offspring
Prenatal	Fetal development dependent on maternal health status and environmental exposure	Maternal blood supply via placenta Radiation Noise Heat	Tissue differentiation Rapid cell division and growth Organ development Metabolic pathways incomplete	Prenatal education, programs, and regulations regarding: • Alcohol • Cigarettes • Drugs • Metals
Newborn (0-2 months old)	Nonambulatory Restricted environment High calorie, water intake High air intake Highly permeable skin Alkaline gastric secretions (low gastric acidity to about 3 years old)	Food: Breast milk, infant formula Dyes in clothing Soaps and shampoos Indoor air Tap/well water in home	Brain: Cell migration, neuron myelination, creation of neural synapses Lungs: Developing alveoli, rapid air exchange, narrow airways Bones: Rapid growth and hardening Other organs: Rapid growth Poor enzyme detoxification	Newborn-sensitive programs and regulations regarding polychlorinated biphenyls Lead in drinking water and dust particles ETS Educate parents and policy makers concerning environmental hazards
Infant/toddler (2 months to 2 years old)	Beginning to walk Oral exploration (mouthing) Restricted environment and near floors Increased time away from parents Minimal variation in diet: High intake of fruits, vegetables, and milk products per body weight	Food: Baby food, food additives, milk and milk products Air indoor layer effects: Air near floor contains more toxicants Tap/well water in home and day care Surfaces: Rugs, floors, lawns, playgrounds	Brain: Creation of synapses Lungs: Developing alveoli, rapid air exchange, narrow airways	Child-sensitive programs and regulations regarding: • Radon in the home • Residential pesticide use • Lead abatement • ETS Educate parents and policy makers concerning environmental hazards
School-age child (6-12 years old)	Beginning school Playground activities Increased involvement in group activities	Food at home and school Air: School, outdoor Water: School water fountains, tap/well water, swimming areas Playgrounds: Wood preservatives, pesticides, and fertilizers Other: Arts and crafts supplies, personal electronic equipment	Brain: Specific synapse formation, dendritic trimming Lung: Volume expansion Metabolic enzymes more active than in younger child	Child-sensitive programs and regulations regarding: • Asbestos abatement • Lead in school drinking water • Hazards in arts and crafts materials • ETS Educate parents and policy makers concerning environmental hazards
Adolescent (12-18 years old)	Development of abstract thinking Puberty Growth spurt Increased adherence to peer norms	Food Air Water Personal electronic equipment Other occupation Self-determination: Smoking, inhalations	Brain: Continued synapse formation Lung: Volume expansion Gonad maturation: Ova and sperm maturation Breast development Bone growth and calcification Muscle growth	Adolescent-sensitive programs and regulations regarding child labor and other issues, especially ETS Educate parents and policy makers concerning environmental hazards

ETS, Environmental tobacco smoke.

Adapted from Gitterman BA, Bearer CF. A developmental approach to pediatric environmental health. *Pediatr Clin North Am.* 2001;48(5):1071–1083.

- *Exposure:* contact with a hazard where effective transmission of the agent may occur.
- *Dose-response relationship:* a change in amount or intensity to time of exposure is associated with increased risk.
  - At what quantity (i.e., dose) will the agent present a problem or cause a response in this receptor?
- *Risk:* likelihood (probability) and magnitude (severity) of an adverse event:
  - What is the concentration of the toxic agent? How much is there? How potent is it? What is the extent of contact of the toxic agent with the receptor?

A final step in this process compares the actual environmental condition with the applied action level, asking the following question:

- *Risk management:*
  - How long will it stay around? With the amount of exposure present, is the individual at risk for health problems?

Principles of Toxicology

Toxicology is the science dealing with detection, interpretation, and treatment of toxins or poisons. Toxicologic principles assess the exposure, absorption, distribution, metabolism, tissue sensitivity, and therapeutic or toxic effects related to the exposure to environmental toxins.

Exposure

Contact of a biologic, chemical, or physical agent with the skin, lungs, and GI tract constitutes exposure. The extent to which exposure creates a health problem depends on factors such as frequency and duration of exposure, concentration of the agent at the point of contact, and the susceptibility of the organism (e.g., an infant's skin burns much more easily than an adult's).

Absorption

Absorption is the process by which an agent is taken into the organism. It occurs in the skin, mucous membranes, lungs, or GI tract, and involves active or passive transport. Examples such as polychlorinated biphenyls (PCBs), which are lipid-soluble chemicals, are passively absorbed through the gut and stored in fat; lead is taken up through active transport in the GI tract and respiratory system and stored in bone *or other tissues* (Agency for Toxic Substances and Disease Registry [ATSDR], 2015).

Distribution

Toxic agents are distributed throughout the organism via the blood and lymph systems. The ability of an agent to cross the blood-brain barrier, the amount of blood flow to an organ, and the tissue uptake of a particular agent influence the degree to which a toxicant will be distributed throughout the body.

Metabolism

Metabolic enzymes in the body interact with toxic agents through oxidation, reduction, and hydrolysis of the agent or through conjugation and breakdown to promote elimination or excretion. Metabolism is influenced by the individual's age, gender, nutritional status, genetic makeup, presence of other drugs, and disease or illness.

Tissue Sensitivity

Susceptibility and reaction of tissue to a particular agent varies with increased tissue susceptibility during critical periods of gestation and early child development.

Toxic Effects

Toxic effects include a wide range of pathologic conditions. Prenatal exposures can result in sterility, infertility, miscarriage, stillbirth, congenital malformations, fetal growth retardation, prematurity, and chronic illnesses. Environmental toxins such as endocrine disruptors in small doses can have deleterious effects during pregnancy.

Children's Increased Risk for Environment-Related Illness

Clinical Findings

History

Assessment of environmental health hazards should be integrated into health visits of both well child visits and illness visits. Boxes 4.1 and 4.2 present questions to ask when screening children and families for environmental health history. Fig 4.1 presents environmental health history questions for pediatric asthma patients.

Physical Examination and Clinical Findings

The physical examination should cover all body systems. Evaluate agent-specific findings (e.g., burns caused by chemicals and neurotoxicity caused by mercury), but also look for subtle, nonspecific signs and symptoms (e.g., skin rashes, fatigue, headaches of unclear etiology). The effects of toxicants on the body are more commonly subclinical but may be readily noted. Moreover, effects can occur immediately or a period of time after the exposure. These factors may contribute to a provider missing physical manifestations of toxicant exposure if one does not have an index of suspicion.

• BOX 4.1 Screening Environmental History

The questions below are most often asked about the child's primary residence(s). One should always consider all places where the child spends time, such as day care centers, schools, and relatives' homes.

- Where does your child live and spend most of his/her time?
- What are the age, condition, and location of your home?
- Have you recently renovated or repaired your home, or do you have plans to do so?
- Does anyone in the family smoke?
- Do you have indoor pets?
- Do you have smoke detectors?
- Do you have a carbon monoxide detector?
- Have you had your home tested for radon?
- What type of heating/air system does your home have?
- Is your heating/air system inspected and maintained?
- What is the source of your drinking water?
  - Well water
  - City water
  - Bottled water
- What are the occupations of all adults in the household?
- Is your child protected from excessive exposure to the sun?
- Is your child exposed to any toxic chemicals of which you are aware?
- Does your child eat any odd items, such as paint chips, or chew on windowsills or other painted surfaces?
- Do you have any other questions or concerns about your child's home environment or symptoms that may be a result of his or her environment?

Data adapted from Agency for Toxic Substances and Disease Registry (ATSDR). *ATSDR Case Studies in Environmental Medicine. Taking a Pediatric Exposure History.* Atlanta: Centers for Disease Control and Prevention; 2013 and Etzel RA, Balk SJ. *Pediatric Environmental Health.* 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

• BOX 4.2 Supplemental Environmental History

If a positive response is given to one or more of the questions in the Screening Environmental History, the primary care provider can ask the following questions:

General Housing Characteristics

- Do you own or rent your home?
- Was your home built before 1978? Before 1950?
- Has your child been tested for lead? If yes, what were the results?
- Is there a family member or playmate with an elevated blood lead level?
- Does your child spend significant time in a location other than your home?

Indoor Home Environment

- If a family member smokes, do they want to quit?
- Is your child exposed to smoke at school, day care, or a babysitter or relative's home?
- Do regular visitors to your home smoke?
- Does your home have carpet?
- Is the room where your child sleeps carpeted?
- Do you use a wood stove or fireplace?
- Have you had water damage, leaks, or a flood in your home?
- Do you see cockroaches or other pests in your home?
- Do you see rats and/or mice in your home?

Outdoor Environment/Air Pollution

- Is your home near an industrial site, hazardous waste site, or landfill?
- Is your home near major highways or other high traffic roads?
- Are you aware of Air Quality Alerts in your community?
- Do you change your child's activity when an Air Quality Alert is issued?
- Do you live on or near a farm where pesticides are used regularly?

Food and Water Contamination

- If you use well water, has it been tested? When? With what results?
- Have you tested your water for lead?
- Do you mix infant formula with tap water?
- What types of seafood do you and your child normally eat?
- How many times a week do you and your child eat: shark, swordfish, tilefish, king mackerel, albacore tuna, other?
- How often do you and your child eat organically grown fruits and vegetables?
- How often do you wash fruits and vegetables before giving them to your child?

Toxic Chemical Exposures

Consider this set of questions for patients with seizures, frequent headaches, or other unusual or chronic symptoms.

- How often are pesticides applied inside your home?
- How often are pesticides applied outside your home?
- Where do you store chemicals/pesticides?
- How often do you use solvents or other cleaning or disinfectant chemicals?
- Do you have a deck or play structure built of pressure-treated wood?
- Have you applied a sealant to that wood in the past year?
- What do you use to prevent mosquito bites to your children?
- How often do you apply that product?

Occupations and Hobbies

- What type of work does your child/teenager do?
- Do any adults who live with the child work around toxic chemicals?
- If so, do they shower and change clothes before returning to the home?
- Does the child or any family member have arts, crafts, ceramics, stained glass work, or similar hobbies?

Health-Related Questions

- Have you ever relocated due to concerns about an environmental exposure?
- Do symptoms seem to occur at the same time of day?
- Do symptoms seem to occur after being at the same place every day?
- Do symptoms seem to occur during a certain season?
- Are family members/neighbors/coworkers experiencing similar symptoms?
- Are there environmental concerns in your neighborhood, child's school, or day care?
- Has any family member had a diagnosis of any of the following: asthma, autism, cancer, and/or learning disability?
- Does your child suffer from any of the following recurrent symptoms: cough, headaches, fatigue, and/or unexplained pain (describe)?

Data adapted from Agency for Toxic Substances and Disease Registry (ATSDR). *ATSDR Case Studies in Environmental Medicine: Taking a Pediatric Exposure History.* Atlanta: Centers for Disease Control and Prevention; 2013 and Etzel RA, Balk SJ. *Pediatric Environmental Health.* 3rd ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012.

Diagnostic Studies

Laboratory studies can be considered based on suspicion of exposure, overt signs and/or symptoms (Box 4.3). Regional Pediatric Environmental Health Specialty Units (PEHSU; www.pehsu.net) are a valuable resource, particularly in the event a patient needs evaluation for a less common substance.

Prior to ordering tests, the primary care provider (PCP) should understand that very few childhood exposures can be accurately identified, much less quantified and definitively linked to symptoms. Many agents have no defined reference or toxic ranges and have poorly defined toxic kinetics. How the offending agent is metabolized and potentially stored in the body (e.g., heavy metals in bone, persistent organic pollutants in adipose tissue) will affect the validity of serum testing. Also, many factors affect the outcome of exposure: dose, child's age, nutritional status, psychosocial and socioeconomic status, and developmental delay or genetic predisposition. These factors underscore how children may respond differently to the same exposure, further complicating exposures and their effects in children.

If the PCP has suspicion for an uncommon exposure, the regional PEHSU will provide expert advice on whether and how

• BOX 4.3 Laboratory Tests Available to Test for Environmental Toxins

- Plasma lead levels
- Gas-liquid chromatography (for polychlorinated biphenyls)
- Atomic absorption spectrometry (for mercury)
- Carboxyhemoglobin (for carbon monoxide poisoning)
- 24 hr urine (for heavy metals)
- Plasma cholinesterase levels (for pesticide metabolites, organophosphates)
- Urinary cotinine assays (for tobacco metabolites)

Fig 4.1 Environmental History Form for Pediatric Asthma Patient.

Specify that questions related to the child's home also apply to other indoor environments where the child spends time, including school, daycare, car, school bus, work, and recreational facilities.

				Follow up/ Notes
Is your child's asthma worse at night?	❑ Yes	❑ No	❑ Not sure	
Is your child's asthma worse at specific locations? If so, where? _____	❑ Yes	❑ No	❑ Not sure	
Is your child's asthma worse during a particular season? If so, which one? _____	❑ Yes	❑ No	❑ Not sure	
Is your child's asthma worse with a particular change in climate? If so, which?_____	❑ Yes	❑ No	❑ Not sure	
Can you identify any specific trigger(s) that makes your child's asthma worse? If so, what? _____	❑ Yes	❑ No	❑ Not sure	
Have you noticed whether dust exposure makes your child's asthma worse?	❑ Yes	❑ No	❑ Not sure	
Does your child sleep with stuffed animals?	❑ Yes	❑ No	❑ Not sure	
Is there wall-to-wall carpet in your child's bedroom?	❑ Yes	❑ No	❑ Not sure	
Have you used any means for dust mite control? If so, which ones? _____	❑ Yes	❑ No	❑ Not sure	
Do you have any furry pets?	❑ Yes	❑ No	❑ Not sure	
Do you see evidence of rats or mice in your home weekly?	❑ Yes	❑ No	❑ Not sure	
Do you see cockroaches in your home daily?	❑ Yes	❑ No	❑ Not sure	
Do any family members, caregivers or friends smoke?	❑ Yes	❑ No	❑ Not sure	
Does this person(s) have an interest or desire to quit?	❑ Yes	❑ No	❑ Not sure	
Does your child/teenager smoke?	❑ Yes	❑ No	❑ Not sure	
Do you see or smell mold/mildew in your home?	❑ Yes	❑ No	❑ Not sure	
Is there evidence of water damage in your home?	❑ Yes	❑ No	❑ Not sure	
Do you use a humidifier or swamp cooler?	❑ Yes	❑ No	❑ Not sure	
Have you had new carpets, paint, floor refinishing, or other changes at your house in the past year?	❑ Yes	❑ No	❑ Not sure	
Does your child or another family member have a hobby that uses materials that are toxic or give off fumes?	❑ Yes	❑ No	❑ Not sure	
Has outdoor air pollution ever made your child's asthma worse?	❑ Yes	❑ No	❑ Not sure	
Does your child limit outdoor activities during a Code Orange or Code Red air quality alert for ozone or particle pollution?	❑ Yes	❑ No	❑ Not sure	
Do you use a wood burning fireplace or stove?	❑ Yes	❑ No	❑ Not sure	
Do you use unvented appliances such as a gas stove for heating your home?	❑ Yes	❑ No	❑ Not sure	
Does your child have contact with other irritants (e.g., perfumes, cleaning agents, or sprays)?	❑ Yes	❑ No	❑ Not sure	

What other concerns do you have regarding your child's asthma that have not yet been discussed?

(Used with permission of the National Environmental Education Foundation, Washington, DC. www.neefusa.org/resource/asthma-environmental-history-form. Accessed October 2, 2018.)

to test. Prior to ordering any tests, key questions for the PCP to consider include (American Academy of Pediatrics, 2012):

- Could the current health problem be related to an environmental exposure? What are the possible exposures in the child's environment?
- Did the potential exposure clearly occur prior to the onset of the health problem?
- Are laboratory tests available to document the exposure? Will the laboratory measurements accurately reflect toxicity if present? What is the cost of testing? What is the timeline from testing to receive results?
- Will the results change the treatment plan for the child and family? Will it inform care?

The diagnostic testing of hair is not recommended routinely, except for exposure to drugs in forensic examinations, but specimens must be sent to specialized, certified laboratories. Since toxins and toxicants are so ubiquitous in our environment (e.g., air pollution, personal care products, processed foods), hair is often contaminated with a multitude of chemicals, so hair levels may not accurately reflect serum levels of a toxicant or substance. Also, capillary finger sticks are not recommended due to the multitude of chemicals patients' hands come into contact with daily.

Approach to Management of Environmental Health Risks

In 2016, the Frank R. Lautenberg Chemical Safety for the 21st Century Act was passed in Congress, which modernized the Toxic Substances Control Act (TSCA) passed in 1976, the nation's primary chemicals management law. Provisions of the new law include (1) a mandatory requirement for the Environmental Protection Agency (EPA) to evaluate existing chemicals with clear and enforceable deadlines, (2) new risk-based safety standards, (3) increased public transparency for chemical information, and (4) a consistent source of funding for EPA to carry out the responsibilities under the new law. The EPA oversees management of approximately 85,000 chemicals in the United States, with a current pace of 2000 new substances annually. Only a small percentage of these chemicals have been tested for safety and risk to children and families due to the TSCA provision that "grandfathered in" many chemicals in existence prior to 1976. The new law has an improved process for monitoring safety of existing chemicals: prioritization, risk evaluation, and risk management (EPA, 2017). The law was enacted to minimize those populations most at risk for environmental hazards and to look more comprehensively at risk through enacting risk assessment of chemicals coming to market. The EPA has yet to execute a comprehensive framework in order to implement the law and has moved slowly to implement the rules.

The level of knowledge of the toxicology, human exposure, and interactions for numerous toxins and toxicants used in daily life is insufficient to permit definitive decision-making regarding protection of human health (American Academy of Pediatrics, 2012). Because of these uncertainties, the "precautionary principle" to controlling environmental health risks is favored by many leading U.S. health organizations, the European Union (EUR-Lex, 2016), and multiple international agreements also support this principle. The *precautionary principle* states that scientific uncertainty should not be used as a reason to postpone preventive measures. Invoking this principle allows action to be taken when there is valid concern that a chemical could be toxic. In effect, this principle moves the burden of proof of safety to the manufacturer when concern (meeting certain standards) has been raised, instead of recipients having to prove harm before action can be taken. Many scientists, organizations, and governments favor and have adopted the precautionary principle, yet the precautionary principle is not currently applied to chemical policy and has not been adopted by the United States.

Low-income populations are at higher risk for ill effects from environmental toxins and toxicants. The recent crisis in Flint, Michigan, highlights the dangers stemming from unacceptable levels of lead in the water system. The community water supply, previously drawn from Lake Erie, was changed by the State of Michigan and Flint administrators to the Flint River. This water supply changed the pH of the water, activating the lead in the pipe connectors in aging pipes connecting the city water supply to homes in Flint. Increased lead levels in the children in Flint doubled in the 2 years following the change in the water supply, and low rates of breastfeeding and also lead testing rates in the community compounded the risk to children and families. Significant activism by the pediatric community and environmental advocates over the course of 3 years, and a court decision was required to effect change in the community.

Entire communities can be threatened by aging infrastructure and resulting exposure to lead and other toxins. Providers should be aware of current inequities in their community and advocate for environmental justice issues. The environmental justice movement aims to rectify these inequities, and it includes the Office of Environmental Justice (OEJ), housed within the EPA (EPA, 2014), as well as numerous other non-governmental organizations.

Ambient Air Pollution

Outdoor Air

The Clean Air Act was revised and expanded in 1990, providing the EPA broader authority to implement and enforce public protections to reduce outdoor air pollutants. Since the implementation of the Clean Air Act, many gains have been made (e.g., six common air pollutants have decreased, automobiles have become cleaner over time, and ozone-depleting chemical production has decreased; EPA, 2017a).

However, despite these achievements, approximately 40% of the U.S. population lives in areas that still exceed safe levels for at least one of six air pollutants: CO, nitrogen dioxide, ground level ozone, lead, sulfur dioxide, and particulate matter (PM_{10}, complex mixtures of solid and liquid particles; EPA, 2017b). Coarse PM_{10}, such as dust and pollen, are 2.5 to 10 μm in diameter, whereas fine $PM_{2.5}$ such as combustion particles and organic compounds are less than 2.5 μm in diameter. Among the outdoor air pollutants, coarse, fine, and ultrafine particulate matter (from dust, dirt, soot, smoke, and liquid drops) have the greatest effects on human health (World Health Organization, 2017). Greenhouse gases (GHGs) (e.g., carbon dioxide, methane, nitrous oxide) are also now classified as pollutants, given their effects on the environment, thereby affecting human health.

The EPA has been charged with regulating emissions of 180 more pollutants (Table 4.2). Outdoor air pollution is responsible for 3.3 million premature deaths annually worldwide. This is in addition to the 3.5 million deaths per year caused by indoor air pollution (Lelieveld, 2015). Updated outdoor air quality information for anywhere in the United States is available at https://airnow.gov/.

Indoor Air

Indoor air quality can be affected by the same pollutants as outdoor air quality. In addition, indoor air exposures include tobacco smoke, cannabis (marijuana) smoke, carbon, asbestos, formaldehyde, volatile organic compounds (VOCs), radon, pesticides, and biological pollutants (National Institute on Drug Abuse, 2018). The EPA does not have regulatory power over indoor air quality. See Table 4.2 for more information on indoor air pollutants and their health effects.

Like most toxins/toxicants, effects can be acute, subacute, or chronic. The likelihood of acute effects to indoor air pollutants depends on age, preexisting medical conditions, individual susceptibility (based on genetics, nutrition, and other factors), and history of exposure (sensitization) to the pollutant compound(s). Certain pollutant exposures can mimic viral respiratory infections, asthma, pneumonitis, pulmonary hemorrhage, rhinitis, sinusitis, and recurrent hoarseness (AAP, 2012), causing difficulty in confirming the diagnosis. For this reason, it is important for the PCP to note the time and place where symptoms occur. If symptoms improve upon the patient leaving a certain area, then indoor air quality may be contributing to the problem. Long-term adverse effects from indoor air pollutants can erroneously be thought to be harmless, since they are not identifiable in the short-term. Radon is an example, as it causes no acute effects and is imperceptible in the air, yet long-term exposure to radon is the second leading cause of lung cancer in the United States. See Table 4.2 for strategies for limiting exposure to radon.

Management of Outdoor and Indoor Air Pollution

Over the last 50 years, air pollution has improved in the United States due to governmental protections and regulations by the EPA. Other large countries (e.g., China, India) without similar programs have not made these gains. Since air ignores political borders, it is important that we proceed with collective (societal), global action to control air pollution. Governmental protections and oversight of industry are necessary to ensure clean air for both children and adults. Thus, to improve our air quality for the 40% of Americans currently living in areas not meeting benchmarks, PCPs need to advocate for increasingly robust and modernized government and international protections.

For outdoor air pollution, protective measures include staying indoors when outdoor air pollution levels are high, utilizing portable or central air cleaning systems, limiting exercise (to reduce respiratory volumes), avoiding high air pollutant areas (e.g., traffic) when outside, and use of an M95 respirator mask (Laumbach, 2015). The efficacy of a respirator mask depends on the type of contaminant, type of filter, conditions of use, and fit. These masks are less likely to fit a child correctly. For indoor air pollution, source control (e.g., seal or enclose sources of asbestos), ventilation improvements (e.g., open windows and use fans while painting), and mitigation (e.g., install air cleaners) are options to improve air quality. CO detectors should be in every home and building. Homes or buildings with poorly vented heating appliances are most at risk for elevated CO levels.

Tobacco smoke has long been recognized as harmful to children's health. In addition, emerging research on cannabis smoke reveals harm to children's health (Herrmann, 2015). Smokers in the household should be educated and reminded that first-hand (direct smoking), second-hand (indirect smoking by being near active smokers), and third-hand (residual nicotine and other chemicals left on indoor surfaces) smoke are all harmful. It is imperative that the PCP educate and discuss the risks of smoking with adolescents, since 90% of smokers begin their habit by 18 years of age (CDC, 2017). See Table 4.2 for smoking cessation interventions.

Endocrine Disruptors

Endocrine disruptors are chemicals that mimic or disrupt naturally occurring hormones in the body, such as estrogens, androgens, and thyroid hormones. Endogenous hormones, and thus disruptors of these hormones, can affect the reproductive, neurological, and immune system of the developing fetus, infant, or child. Endocrine disruptors alter the function of endocrine hormones through a variety of mechanisms, including binding to hormone receptors to mimic natural hormones (potentially producing overstimulation), blocking/antagonizing hormone receptors, or altering the production or metabolism of endogenous hormones. Developing tissue is more vulnerable to endocrine disruption than mature tissues (Kabir et al., 2015). Further, endocrine disruptors can interfere with gene expression, changing developing tissues in permanent ways. There is also concern for latent effects of endocrine disruptor that are not apparent during the critical exposure period, but rather manifest in adulthood or during aging. Extremely low doses and extremely high doses may have significant effects; the toxicologic concepts of "dose-response" may not always apply to exposure to endocrine disruptors. Concentrations as low as one-tenth of a trillion of a gram (g) can alter the womb environment.

Endocrine disruptors are found extensively in the environment, including in food, water, soil, air, plastics, cosmetics, and drugs. They have a high degree of stability and do not degrade rapidly once discarded; thus they persist and continue to pollute the environment even in waste form. They are primarily ingested, but exposure can also occur topically, transplacentally, or perhaps in other unknown ways. The incidence of endocrine disruption is difficult, if not impossible, to quantify. Endocrine disruption generally does not result in acute illness for which the patient or caregiver would seek care, but rather is typically insidious. Specific chemicals or groups of chemicals, common exposure sources, health effects, and alternatives to their use are reviewed in Table 4.3. Reproductive system derangements caused by diethylstilbestrol (DES) is a high-profile, classic example of a severe endocrine disruptor. Millions of pregnant women were prescribed DES to prevent miscarriage, which was later proven ineffective, and their offspring had an unusually high incidence of genitourinary malformations, malignancy (clear cell adenocarcinoma of the vagina and/or cervix), pregnancy complications, and infertility. Bisphenol A (BPA) used in the current production of polycarbonate plastics and epoxy resins, DEHP Di (2-ethylhexl) phthalates used in the manufacture of consumer food packing, and polyvinyl chloride (PVC) medical devices are being studied in humans, as there is evidence for long-term effects of these chemicals in animal studies (PEHSU, n.d.). DES and other potential toxins under study highlight the danger and often latent effects endocrine disrupting agents can have on a developing human.

TABLE 4.2 Air Pollutants and Relationship to Disease

Substance	Source	Health Effects/ Systems Affected	Signs and Symptoms	Prevention Strategies
Environmental tobacco smoke	First-, second-, or third-hand smoke from cigarettes, cigars, pipes Novel sources include e-cigarettes, snus, kreteks, bidis, hookahs, and dissolvable tobacco	Respiratory Cardiac Growth Neurologic	Bronchitis Bronchiolitis Pneumonia Asthma Otitis media Premature coronary artery disease Low birth weight Sudden infant death syndrome Cognitive delays	Adults and siblings in child's environment stop smoking or limit exposures as much as possible Enroll child in day care that is smoke-free Prevent child from starting smoking Recommend smoking cessation programs Health care provider recommendation of and support for decision to stop smoking
Radon	Air Water Generally concentrated in basements and underground	Respiratory	Lung cancer	Test air in basements and first floor of home for radon levels Avoid having children play in basements of homes with radon Consult mitigation company to reduce high levels Provide good ventilation in basement areas
Particulate matter	Outdoor: • Industrial pollution • Gasoline and diesel exhaust • Pollens • Natural phenomena (e.g., forest fires, volcanic activity) Indoor: • Wood stoves • Dust mites • Animal dander • Cockroach particles • Molds and more	Respiratory Cardiovascular	Bronchitis Pneumonia Wheezing Chronic cough Decreased lung function Asthma Lung cancer Cardiovascular conditions	When outdoor air pollution is high, keep children indoors Use high-efficiency particulate air filters for heating/air conditioning, vacuuming Check heating system to ensure it is clean Cover mattresses, wash bedding frequently, launder or discard stuffed animals
Molds	Damp areas (leaking roofs/walls/floors, wet basements, backed-up sewers) Humidifiers Steam from shower, bath, or cooking Wet clothes House plants Dry leaves	Respiratory Dermatologic Central nervous system	Cough Wheezing, dyspnea Sinus congestion Watery, itchy, light-sensitive eyes Sore throat Skin rash Headaches, memory loss, mood changes Myalgias, pain Fever	Maintain dry, clean environment Affected areas can be cleaned with hot water and detergent; may require deep scrubbing Bleach solutions are not routinely recommended; exceptional circumstances (i.e., the environment of immunocompromised patient) may require bleach solution to remove mold If unable to thoroughly clean, discard moldy materials to prevent spores from being released when materials dry Use dehumidifiers and air conditioners as necessary Fix leaks promptly Use exhaust fans in kitchens and bathrooms Ensure carpets do not stay damp
Asbestos	Construction materials: • Insulation • Ceiling and floor tiles • Shingles	Respiratory	Lung irritation Lung disease later in life with repeated exposure	Prevent exposure to asbestos products: If buildings that contain asbestos are in good repair, leave asbestos in place; if there is a question of possible exposure, contact a certified asbestos professional to check it Use asbestos abatement measures as appropriate when renovating If parents' workplace is a source of asbestos exposure, remove clothing and bathe before coming in contact with children