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Applying Public Health Strategies to Primary Immunodeficiency Diseases

A Potential Approach to Genetic Disorders

INSIDE: Continuing Education Examination

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Applying Public Health Strategies to Primary Immunodeficiency Diseases

A Potential Approach to Genetic Disorders

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Summary

Primary immunodeficiency (PI) diseases are a group of primarily single-gene disorders of the immune system. Approximately 100 separate PI diseases have been described, but <20 probably account for >90% of cases. Although diverse, PI diseases share the common feature of susceptibility to infection and result in substantial morbidity and shortened life spans. Most important, prompt diagnosis and treatment can now lead to life-saving treatment and result in marked improvements in the quality and length of life for persons with PI diseases.

In November 2001, a workshop was convened by CDC in Atlanta, Georgia, to discuss ways to improve health outcomes among persons with PI disease. A multidisciplinary panel of persons knowledgeable in PI diseases and public health met to identify and discuss public health strategies that can be applied to PI diseases and possibly for other genetic disorders. A systematic assessment based on the established public health framework was applied to the growing group of PI diseases, whose diverse genetic mutations span multiple components of the immune system but all lead to increased incidence and severity of infections.

During the meeting, specialists in clinical immunology, public health, genetics, pediatrics, health communication, and ethics from state and federal agencies, academic centers, professional organizations, and advocacy foundations discussed the four components of the public health framework as they relate to PI diseases. These four components include 1) public health assessment (application of traditional public health methods to assess the occurrence and impact of PI diseases on communities); 2) population-based interventions (development, implementation, and evaluation of screening tests administered to newborns and clinical algorithms for early recognition of symptomatic persons to facilitate the earliest possible diagnosis and treatment for PI diseases); 3) evaluation of screening and diagnostic tools (to ensure their quality and appropriateness for identification of patients with PI diseases); and 4) communication (communication with and information dissemination to health-care providers and the public to facilitate prompt and appropriate diagnosis and intervention). The working group's deliberations focused on challenges and opportunities, priority research questions, and recommendations for future action for these four components. These recommendations, developed by workshop participants, will be useful to medical and public health professionals who are evaluating methods to increase recognition of PI diseases and other genetic disorders.

The material in this report originated in the National Center for Environmental Health, Richard J. Jackson, M.D., Director; the Office of Genomics and Disease Prevention, Muin J. Khoury, M.D., Ph.D, Director; and the Division of Laboratory Sciences, Eric J. Sampson, Ph.D., Director; the National Center on Birth Defects and Developmental Disabilities, José F. Cordero, M.D., Director, and the Division of Birth Defects and Developmental Disabilities, Gilberto Chavez, M.D., Director; the National Center for HIV, STD, and TB Prevention, Harold W. Jaffe, M.D., Director, and the Division of AIDS, STD, and TB Laboratory Research, Jonathan E. Kaplan, M.D., Director; and the Public Health Practice Program Office, Suzanne Smith, M.D., Acting Director, and the Division of Laboratory Systems, Robert Martin, Dr.P.H., Director.

Introduction

Advances in human genetics and the evolution of the Human Genome Project will play a central role in the practice of medicine and public health in the 21st century. However, gene discovery is only the beginning. For the majority of diseases, a gap exists between discovering or sequencing genes and using human genomic information to improve health outcomes (*1*). Public health research and policy have a crucial role in closing that gap. Moving from gene discovery to clinical and public health application requires full engagement of public health to 1) quantify the effect of genetic discoveries

on population health, 2) develop policies regarding and guidelines for the appropriate use of genetic tests and services, 3) develop interventions to improve health outcomes, 4) initiate and maintain behavior change among patients and healthcare providers, and 5) address the quality of and access to services. Genomic breakthroughs have been identified as major challenges for public health in the 21st century (*2*). However, the usefulness of these breakthroughs in clinical practice depends on the availability of population-based data to determine the prevalence of gene variants among different populations, the population-based risk for disease associated with gene variants, gene-environment interactions, and the effectiveness of genetic tests and services (*3–5*).

As part of efforts to highlight the emerging role of human genomics in the practice of public health in the United States, CDC, in collaboration with research, academic, clinical, and foundation partners, evaluated public health strategies that can be used to close the gap between gene discoveries and clinical practice for primary immunodeficiency (PI) diseases — approximately 100 primarily single-gene disorders of the immune system. Identification of the genes responsible for these conditions is progressing rapidly; therefore, a population-based framework is needed that can be applied also to other genetic disorders and gene discoveries. This report describes the concerns, challenges, and opportunities and provides recommendations for public health action regarding such a framework.

Background

With completion of the Human Genome Project, 30,000–35,000 genes have been mapped (*6–9*), each of which contains the code for a specific product, typically a protein. Through the proteins they encode, genes determine and regulate all human body processes. Human genomics includes a continuum from the study of single-gene disorders with high penetrance to common genetic variants or polymorphisms at multiple loci, with low penetrance, and that have complex gene-environment interactions (*10*). Genetic disorders are caused by mutations, or alterations, in a gene or set of genes. Mutations can be inherited or occur de novo. The effect of a mutation on a gene depends on how it alters the expression or function of the gene product and the role of that protein in the body. Mutations in certain genes have severe effects, whereas mutations in others do not.

The majority of genetic disorders result from a complex interplay of multiple genetic changes and environmental factors. However, certain disorders result when a mutation alters or causes an absence of the product of only one gene. Examples of such single-gene disorders are cystic fibrosis (CF) and phenylketonuria (PKU). Single-gene disorders can be either X-linked (i.e., caused by a defect in a gene on the X chromosome) or autosomal (i.e., caused by a defect in a gene on an autosome or nonsex chromosome). Single-gene disorders can result from either dominant or recessive patterns of inheritance or expression. Selected chromosomal disorders, which might be inherited, involve microdeletions of multiple genes at closely linked loci. Although single-gene disorders are individually rare, they collectively contribute to a substantial proportion of pediatric morbidity and mortality (*1*).

PI diseases are a group of primarily single-gene disorders of the immune system (*11–13*). *Primary* denotes the genetic nature of the defects, differentiating them from *secondary*, or acquired, immunodeficiencies caused by malnutrition, infection (e.g., human immunodeficiency virus [HIV] infection), chemotherapy, or other external agents. Approximately 100 separate PI diseases have been described, but <20 probably account for >90% of cases. The disorders vary in the severity and spectrum of symptoms, but without effective and early treatment, they can be fatal. A high index of suspicion and prompt diagnosis can lead to lifesaving treatment and substantial improvement in quality of life for persons with PI diseases. Causes of PI diseases vary, but single-gene defects can lead to a missing enzyme, a missing structural component, developmental arrest at a specific differential stage of immune development, or a nonfunctional protein. As with all single-gene disorders, selected PI diseases are known to be X-linked or autosomal, with both dominant and recessive patterns of inheritance or de novo mutations; others might have more complex modes of inheritance not yet understood. Approximately 80% of affected persons are aged <20 years, and because certain PI diseases are inherited in X-linked recessive fashion, 70% of cases occur among males (*13*).

Advances in human genomics have led to identification of the gene defects responsible for >60 PI diseases and have prompted development of new diagnostic and therapeutic tools and potential gene therapies (*14–20*). New molecular techniques have facilitated identification of different types of mutations underlying PI diseases. Single-nucleotide substitutions, or point mutations, involve an alteration in the sequence of nucleotides in a gene. These include missense mutations, which alter the amino acids in the protein product of a gene; nonsense mutations, which generate premature stop codons in the genetic code; RNA (ribonucleic acid) splice-site mutations, which can lead to frameshift mutations; and regulatory mutations, which affect aspects of gene expression. Mutations also can involve insertions or deletions of DNA (deoxyribonucleic acid) sequences. Progress in the delineation of the

mechanisms by which these genetic mutations cause PI diseases has added to the understanding of the normal immune system and the processes that underlie conditions that occur with far greater frequency than PI disease (*21*).

Clinical Characteristics and Effect of PI Diseases

The clinical hallmark of PI diseases is an increased susceptibility to infection, the severity of which varies by defect (*13,22*). In certain cases, the body fails to produce any or sufficient antibodies to fight infection. In other cases, the cellular (e.g., T-cell) defenses against infection fail to work properly. Shared features of the disorders are an unusual rate or severity of infection, infection with unusual or opportunistic organisms, and infection associated with specific syndromes (*13*). PI diseases also are associated with other immunologic disorders (e.g., autoimmune diseases) and carry an increased risk for cancer, particularly lymphoid malignancies (*22*). PI diseases often are classified according to the affected components of the immune system (Table 1).

Antibody Deficiencies

Approximately half of the diseases are associated with inadequate or defective antibody production, caused by too few antibody-producing B cells or B cells that do not function properly, resulting in inadequate production of antigen-specific antibodies (*23*). These disorders are characterized by recurrent sinus and pulmonary infections and septicemias with bacteria (*13,24*). The most severe defect in this category is X-linked agammaglobulinemia (XLA), typified by a limited number or no mature B cells or antibody-secreting plasma cells. Affected persons develop severe, recurrent bacterial infections, usually during the first year of life.

Other antibody defects are common variable immunodeficiency (CVID) and immunoglobulin A (IgA) deficiency. CVID is characterized by variably low levels of immunoglobulin G (IgG), immunoglobulin M (IgM), and IgA, and suboptimal antibody responses after vaccination. CVID patients usually experience recurrent bouts of pneumonia and infections of the joints, bones, and skin. These persistent infections lead to organ damage, often resulting in disability or death from chronic lung disease (*25*). Moreover, affected females with CVID had a >400-fold increased risk for lymphomas in their fourth and fifth decades of life compared with age-matched general population risks in one U.S. study (*25*). IgA deficiency, similar to other PI diseases, has a wide clinical spectrum. Although all affected persons lack IgA in the mucous membranes lining the airways and digestive tract, certain persons are asymptomatic whereas other have recurrent infections. For reasons not completely understood, the incidence of allergy or autoimmune disease is increased among patients with selective IgA deficiency. Certain IgA-deficient persons might have severe or fatal anaphylactic reactions to blood or blood-products containing IgA.

Combined B- and T-Cell Deficiencies

Combined B-cell and T-cell immunodeficiencies constitute approximately 20% of PI diseases (*23*). In the most serious forms (e.g., severe combined immunodeficiency [SCID] disorders), survival beyond the first year of life is rare without prompt immune reconstitution through hematopoietic stem cell transplantation (*15,16,19,26,27*). Immune reconstitution with gene therapy has been achieved for forms of SCID (*14,20*). Early diagnosis of SCID is critical because the chances for successful treatment are highest for infants who have not yet experienced severe opportunistic infections (*19*). Mutations in eight different genes cause SCID (*19,28*). Approximately half of all cases are linked to the X chromosome. X-linked SCID results from a mutation in the interleukin 2 receptor gamma (*IL2RG*) gene that produces the common gamma chain subunit, a component of multiple IL receptors. The product of the *IL2RG* gene activates a key signaling molecule, Janus-associated kinase 3 (*JAK3* gene product). A mutation in *JAK3* also can result in SCID. Other forms of SCID are associated with deficient activity in the enzyme adenosine deaminase (*ADA* gene product) or a defect in the recombination-activating gene (*RAG*). The genetic defect has not been identified for certain forms of SCID. Other combined immunodeficiencies are part of well-defined immunodeficiency syndromes (e.g., Wiskott-Aldrich syndrome [WAS], ataxia telangiectasia, and hyper-IgE syndrome), all of which are associated with recurrent infections and decreased life expectancy (Table 1).

Cellular immune deficiencies, resulting from defects in T-cell maturation or function, contribute an estimated 10% of PI cases (*23*). One example is DiGeorge syndrome, which is typified by aberrant development of the heart, parathyroid glands, or thymus. The absence of a thymus gland in patients with DiGeorge syndrome leads to low T-cell numbers and decreased function, but the degree of immunologic impairment varies considerably (*29,30*). Approximately 90% of these patients have a microdeletion in chromosome 22q11.2, such that multiple genes from this region are absent (additional information is available at http://www.genetests.org).

Defective Phagocytes

An estimated 18% of PI cases result from defective phagocytes (*23*). Phagocytic defects result in the inability of cells that normally engulf and kill invaders to remove pathogens or

TABLE 1. Examples of primary immunodeficiency diseases, by affected component of the immune system

Designation	Gene	Genetic locus	Mode of inheritance	Description/Pathogenesis
Antibody deficiencies				
X-linked agammaglobulinemia (XLA)	*BTK*	Xq21.3–q22	X-linked recessive	Mutations in the gene encoding Bruton's tyrosine kinase (BTK), a regulator of B-cell development; absence of mature circulating B cells and undetectable or substantially low serum immunoglobulin (Ig) levels lead to recurrent bacterial infections during the first year of life
Common variable immunodeficiency (CVID)	Unknown		Complex	Unknown variable defects in B- and T-cell function and regulation result in recurrent bacterial infections, usually during the second or third decade of life
ICOS deficiency	*ICOS*	2q33		One subset of CVID is ICOS deficiency, inducible host stimulator defect
Immunoglobulin A (IgA) deficiency	*IGAD1*	6p21.3	Autosominal dominant with variable penetrance	Absent or marked reduction of serum IgA; majority of patients are asymptomatic; others have recurring respiratory infections, chronic diarrhea, allergies, or autoimmune disease
Hyper-IgM syndrome type 2 (AID deficiency)	*AID* (*AICDA*)	12p13	Autosomal recessive	Defect in the activation-induced cytidine deaminase (AICDA) required for Ig isotope switching and somatic hypermutation in B cells; low IgG and IgA, normal or increased IgM
Hyper-IgM syndrome type 3	*CD40*	20q12–q13.2	Autosomal recessive	Low IgG, IgA; normal or increased IgM; bacterial and opportunistic infections
Cellular deficiencies				
DiGeorge syndrome	*DGCR*	22q11.2	Autosomal dominant	Hemizygous chromosomal deletion results in developmental defect of the thymus; also can cause congenital heart disease, hypoparathyroidism, and other congenital defects
Interferon gamma receptor deficiency	*IFNGR1* *IFNGR2*	6q23–q24 21q22.1–q22.2	Autosomal recessive	Autoimmune endocrinopathies; increased susceptibility to mycobacterial disease
IL-12 receptor deficiency	*IL12B* *IL12RB1*	5q31.1–q33.1 19p13.1	Autosomal recessive	Defect in the receptor for interleukin-12; increased susceptibility to mycobacterial disease
Combined B- and T-cell deficiencies				
T-negative, B-positive — severe combined immunodeficiency (SCID): T cells are missing, but B cells can be present				
X-linked SCID	*IL2RG*	Xq13.1	X-linked recessive	Most common form of SCID; caused by a mutation in the IL-2 receptor gene on the X chromosome needed for the normal growth and function of T cells and B cells; lymphopenia occurs primarily from the absence or near absence of T cells and natural killer cells; B cells are immature and defective
Jak3 deficiency	*JAK3*	19p13.1	Autosomal recessive	Mutation in the gene that encodes Janus-associated kinase 3 (*JAK3*) needed for differentiation of hematopoietic cells; lymphopenia occurs primarily from the absence or near absence of T cells and natural killer cells; B cells are present but defective
IL7R deficiency	*IL7R*	5p13	Autosomal recessive	Defect in the IL7 receptor needed for T-cell development; T-cell numbers are low; B cells are present but nonfunctional
CD45 deficiency	*PTPRC*	1q31-q32	Autosomal recessive/ Autosomal dominant	Mutation in the protein tyrosine phosphatase receptor type C CD45 gene results in a lack of expression of CD45; T-cell numbers are low; B cells are present but defective

TABLE 1. (*Continued*) Examples of primary immunodeficiency diseases, by affected component of the immune system

Designation	Gene	Genetic locus	Mode of inheritance	Description/Pathogenesis
T-negative, B-negative — SCID: both T cells and B cells are missing				
RAG1 deficiency	*RAG1*	11p13	Autosomal recessive	Mutations in recombinase-activating gene (*RAG1*) leads to absence of mature B and T cells
RAG2 deficiency	*RAG2*	11p13	Autosomal recessive	Mutations in recombinase-activating gene (*RAG2*) leads to absence of mature B and T cells
Artemis deficiency	*Artemis*	10p13	Autosomal recessive	Mutation in the Artemis gene affects DNA recombination; results in arrest of B- and T-cell development Found in Athabascan-speaking people
ADA deficiency	*ADA*	20q13.11	Autosomal recessive	Mutation in a gene encoding the enzyme adenosine deaminase (ADA); lymphopenia occurs from the death of T and B cells because of accumulation of toxic metabolites; functional antibodies are decreased or absent
Other combined deficiencies				
ZAP 70 deficiency	*ZAP70*	2q12	Autosomal recessive	Mutation in ξ-associated protein of *ZAP-70* kinase leads to lack of expression of CD8 T cells and abundant CD4 cells unresponsive to T-cell receptor-mediated stimuli
CD3 deficiency	*CD3E/G*	11q23	Autosomal recessive	Absent $CD3^+$ T cells result in recurrent infections in severe cases
PNP deficiency	*PNP*	14q13	Autosomal recessive	Defect in purine nucleoside phosphorylase (PNP) in the purine salvage pathway; T-cell numbers are decreased because of accumulation of toxic metabolites
Other combined immunodeficiency syndromes				
X-linked hyper-IgM syndrome	*CD40L*	Xq26.3-q27.1	X-linked recessive	Mutations in the CD40 ligand gene lead to impairment of T-cell/B-cell interaction, lack of Ig isotope switching; recurrent and opportunistic infections
Wiskott-Aldrich syndrome (WAS)	*WASP*	Xp11.22-Xp11.23	X-linked recessive	Defect in cytoskeletal WAS protein (WASP), affecting platelets and T cells, leads to thrombocytopenia, small defective platelets, eczema, lymphomas, autoimmune disease, and infections
Ataxia-telangiectasia	*ATM*	11q22.3	Autosomal recessive	Progressive multisystem disorder characterized by neurologic impairment with ataxia, telangiectasia of the conjunctiva and skin, malignancy, and radiation sensitivity
Chronic mucocutaneous candidiasis	Unknown		Autosomal recessive	Chronic mucocutaneal candidal infections and autoimmune endocrinopathies
	CMCT	2p	Autosomal dominant	Chronic mucocutaneal candidal infections with thyroid disease
Autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia (APECED)	*AIRE-1*	21q22.3	Autosomal recessive	AIRE encodes a protein belonging to a family of transcription factors
X-linked lympho-proliferative syndrome	*SH2D1A (SAP)*	Xq25	X-linked recessive	Uncontrolled lymphoproliferation induced by severe Epstein-Barr virus (EBV) infections, B-cell lymphoma
Hyper-IgE syndrome	Unknown	4q21	Autosomal dominant with variable penetrance	Elevated IgE, with recurrent staphylococcal infections of lung and skin
Ectodermal dysplasia associated with immune deficiency (EDA-ID)	*IKBKG* (*NEMO*)	Xq28	X-linked recessive	Molecular defect in NEMO causes impaired nuclear factor kappa-beta (NF-kb) signaling; clinical syndrome includes anhidrotic ectodermal dysplasia, conical teeth, atrichosis, recurrent infections, and dysgammaglobulinemia

TABLE 1. (*Continued*) Examples of primary immunodeficiency diseases, by affected component of the immune system

Designation	Gene	Genetic locus	Mode of inheritance	Description/Pathogenesis
Phagocytic defects				
Congenital neutropenia	Unknown		Autosomal recessive, sporadic	Persistent neutropenia from birth
Cyclic neutropenia	*ELASTASE2*	19p13.3	Autosomal recessive, sporadic	Neutropenia in 3–4-week cycles
Leukocyte adhesion defect (LAD)				
LAD1	*ITGB2*	21q22.3	Autosomal recessive	Disorder of neutrophil adhesion caused by lack of CD18; characterized by recurrent or progressive necrotic soft-tissue infection, periodontitis, poor wound healing, leukocytosis, and delayed umbilical cord detachment
LAD2	*FUCT1*	11	Autosomal recessive	Defect in GDP fucose transporter 1; associated with mental retardation, soft-tissue infection, and delayed healing
Chronic granulomatous disease (CGD)				
X-linked CGD	*CYBB*	Xp21.1	X-linked recessive	Disorder of white blood cell bactericidal function characterized by granulomatous lesions of the skin, lungs, and lymph nodes; hypergammaglobulinemia; anemia; defective killing of certain bacteria and fungi
Autosomal recessive CGD	*CYBA*	16q24	Autosomal recessive	All defects result in defective nicotinamide-adenine dinucleotide phosphate (NADPH) oxidase
	NCF1	7q11.23	Autosomal recessive	
	NCF2	1q25	Autosomal recessive	
Complement deficiencies				
Chédiak-Higashi syndrome	*CHS1* (*LYST*)	1q42.1-q42.2	Autosomal recessive	Defect in the lysosomal-trafficking regulator gene; results in partial albinism, bleeding tendency, and fatal lymphoproliferation from EBV; treatment is by bone-marrow transplantation
Deficiency of individual complement components C1q, C1r, C1s, C2, C3, C4, C5, C6, C7, C8, C9	CIQA, C1QB, C1QG, C1R, C15, C2, C3, C4A, C4B, C5, C6, C7, C8A, C8B, C8G, C9,	Various	Autosomal recessive	Absence of complement components; results in increased infections and lupus-like diseases; C1, C2, C3, C4 associated with autoimmunity and pyogenic infections
Factor B, Factor H1	BF, HF1			C5-C9 and properdin deficiencies associated with neisserial infections

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National Center for Biotechnology Information. OMIM™ Online Mendelian Inheritance in Man. Bethesda, MD: National Library of Medicine, 2000. Available at http://www.ncbi.nlm.nih.gov/omim.

infected cells from the body. Chronic granulomatous disease (CGD), caused by a defect in intracellular killing of bacteria by phagocytes, usually appears in childhood, but milder forms can appear in the second or third decade of life. It can be inherited as an X-linked or autosomal-recessive defect; affected persons experience frequent and severe infections of the skin, lungs, and bones and tumor-like masses called granulomas. In leukocyte adhesion defect (LAD), phagocytes lack an essential adhesion molecule, preventing them from migrating to sites of infection. The result is recurrent, life-threatening infections, especially of the soft tissues. Chédiak-Higashi syndrome is a rare and usually fatal disorder caused by granule defects in phagocytes, platelets, and melanocytes. Patients have partial oculocutaneous albinism and often experience overwhelming and fatal infections with Epstein-Barr virus. Both LAD and Chédiak-Higashi syndrome are inherited as autosomal-recessive defects.

Complement System Defects

Defects in the complement system occur less frequently than other PI diseases. They are associated with a nonfunctional protein or the absence of a complete complement molecule capable of attaching to antibody-coated foreign invaders and opsonizing bacteria. The most common defect, C2 deficiency, is an autosomal-recessive inherited defect in the gene for the complement protein C2. Affected persons have recurrent and severe infections with encapsulated bacteria, frequently meningitis, and a susceptibility to autoimmune diseases. Terminal complement protein (C6-8) deficiencies are associated with severe infections with *Neisseria meningitidis* and *N. gonorrhoeae*.

Prognoses for Patients with PI Diseases

Although PI diseases share selected clinical manifestations, both the timing of the onset of symptoms and the prognosis vary considerably. Patients with antibody or complement deficiencies can have near-normal life spans, if their deficiencies are diagnosed early, managed appropriately, and are not affected by concurrent chronic diseases. Persons with phagocytic disorders, combined immunodeficiency disorders, and antibody disorders with chronic infections have guarded prognoses; the majority are chronically ill and require intensive treatment. Certain severe PI diseases (e.g., SCID) become apparent early in life, with only a short asymptomatic period after birth. Without an effective early intervention, the majority result in death during the first years of life.

Incidence and Birth Prevalence Estimates

The true frequency of PI diseases in the general population, either individually or in the aggregate, has not been ascertained, but estimates have been reported. Certain countries have developed registries to collect information regarding cases of PI diseases (*31–36*). The minimum prevalence of PI has been estimated by using data collected from these registries. At least five factors cause these registries to underestimate the true prevalence of PI diseases: 1) lack of clinical recognition, 2) lack of reporting to the registries, 3) overrepresentation of certain referral centers, 4) lack of a standardized case definition, and 5) death before recognition. Population-based data related to incidence and prevalence are critically needed.

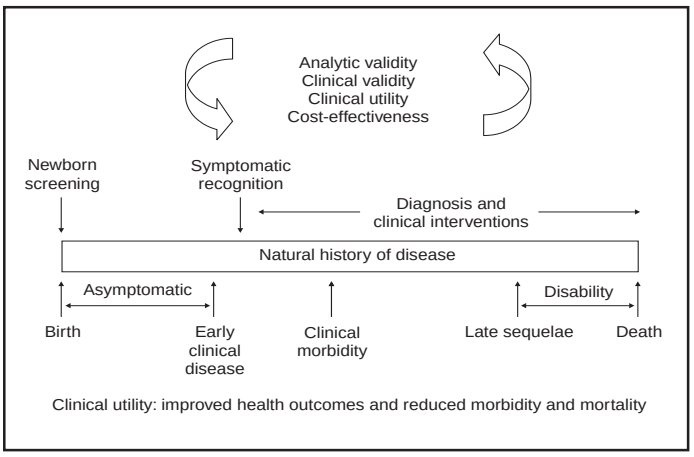
The reported minimal estimate of birth prevalence of SCID based on recognized cases is 1/100,000, but this underestimates the prevalence because of infant deaths occurring before diagnosis (*15*). In contrast, selective IgA deficiency, the most common immunodeficiency, was found in as many as 1/328 healthy blood donors (*37*). In aggregate, the estimated incidence of diagnosed PI diseases has been reported as 1/10,000 persons (*22,38,39*). As a comparison, incidence estimates for CF are 1/2,500 among whites and for PKU are 1/16,000 persons (*40,41*).

Diagnosis

Early detection is possible for the majority of PI diseases, is critical for the success of certain therapies, and can be lifesaving. Genetic diseases (e.g., single-gene disorders with high penetrance) can be detected along a continuum of symptomatic expression by using 1) screening tests to evaluate asymptomatic newborns for conditions that require early intervention and 2) clinical algorithms for early recognition of symptomatic persons before the onset of clinical morbidity, with confirmatory laboratory diagnosis (including genetic testing) (Figure 1). Effective treatment regimens then can be initiated early in the course of disease to reduce morbidity, disability, and mortality.

The first clinical clue in diagnosis of a PI disease is usually a history of infections that are persistent, recurrent, difficult to treat, or caused by unusual microbes. Because PIs are frequently inherited, a positive family history is also a key diagnostic tool (*42*); in a series of 70 PI patients identified in an immunology clinic, 18.6% (N = 13) had family histories of immunodeficiency (*43*). The type of infection identified in either the

FIGURE 1. Potential public health interventions regarding genetic diseases



patient or the family history also might indicate the nature of an immunodeficiency. Infections with bacterial organisms are frequently observed among patients with antibody deficiencies; severe infections from viruses, fungi, and other opportunistic organisms characterize T-cell immunodeficiencies. Recurrent infections with staphylococcal and other catalase-positive organisms indicate phagocytic defects, and recurrent *Streptococcus pneumoniae* or *Neisseria* infections characterize patients with complement deficiencies.

Physical examination can identify characteristic physical findings and anatomic changes secondary to infections. Patients with PI diseases often appear chronically ill, with pallor, malaise, and a distended abdomen caused by hepatosplenomegaly. Patients with XLA typically lack peripheral lymph nodes, adenoids, and tonsils. Lymphadenopathy is observed frequently among patients with CGD. In WAS, the genetic mutation causes thrombocytopenia as well as immune defects; children have bruising, petechiae, and eczematous rash (*44*). However, clinical symptoms can vary from patient to patient, even for identical mutations of the same gene (*45*). Typical radiographic findings include an absent thymus, which is the hallmark of DiGeorge syndrome and multiple types of SCID. Children with infant-onset ADA deficiency often have characteristic skeletal abnormalities of the ribs and hips readily apparent on radiograph.

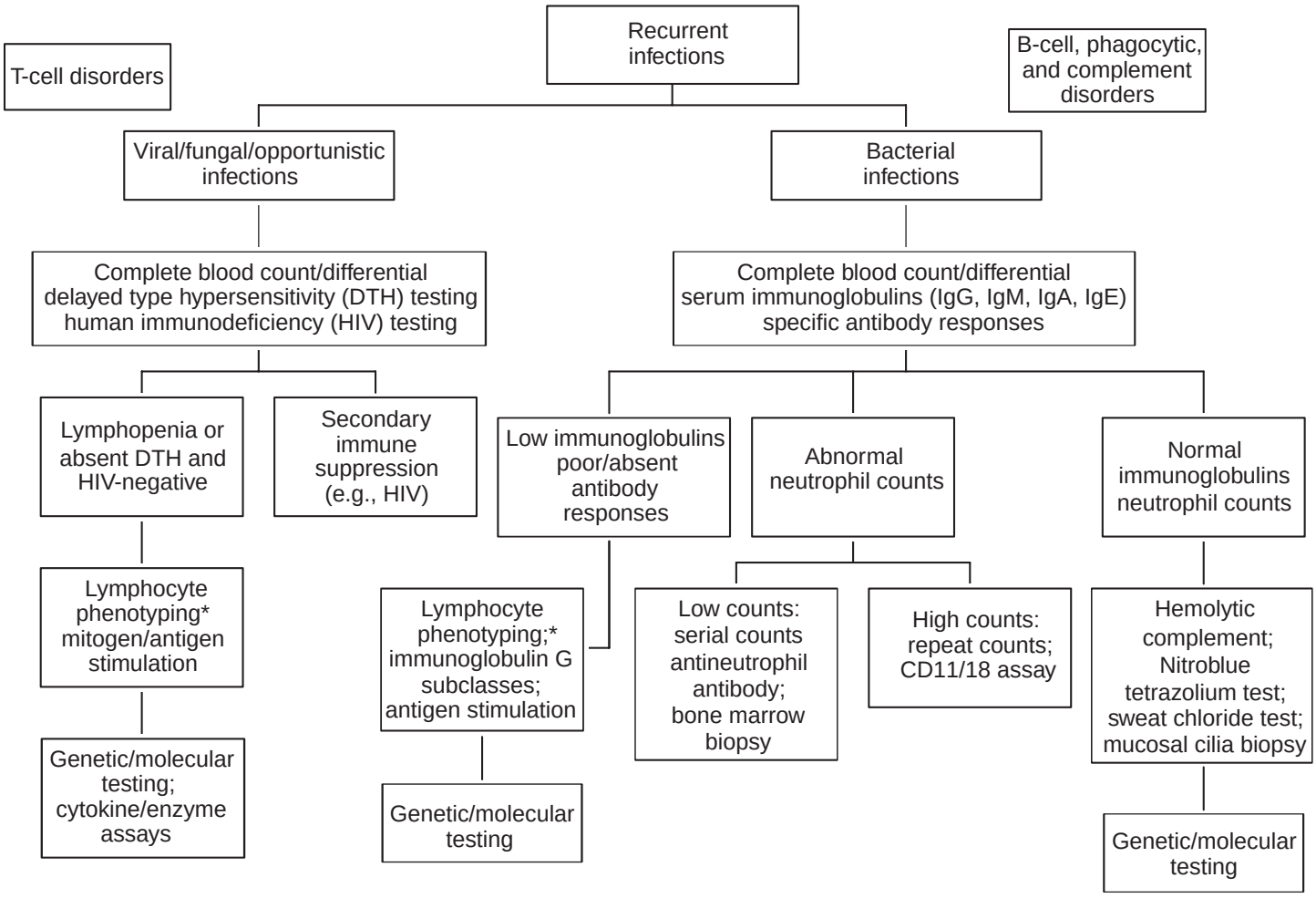
Laboratory tests are required to diagnose a PI disease (*46*). No single testing modality is appropriate for all situations. Given that certain PI diseases have overlapping features and that selected ones can be caused by combined immune defects, clinicians advocate a stepwise approach to screening the immune system (Figure 2). The majority of initial tests are available through commercial or hospital laboratories and include tests to assess humoral immunity (i.e., Ig proteins and specific antibodies), cellular immunity (e.g., lymphocyte/mononuclear cell quantitation or functional assays), phagocytic cell function, and complement components and function.

Genetic testing involves "analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites to detect heritable disease-related genotypes, mutations, phenotypes or karyotypes for clinical purposes" (*47*). In cases for which the location of the genetic defect is known, testing involves direct testing of the patient's DNA to identify specific mutations. In certain cases, an assay to measure mRNA (messenger RNA) (e.g., polymerase chain reaction [PCR]) or the protein product (e.g., immunoblotting or flow cytometry) can confirm a diagnosis when the gene product is absent; however, this method cannot detect disease associated with a nonfunctional protein. A simple, reliable way to evaluate function for T cells is delayed type hypersensitivity skin tests and for B cells, antibody responses after vaccination.

Treatment

Interventions for PI diseases are aimed at preventing infection, prolonging life, and improving quality of life (*48*). Use of antibiotics to treat and prevent infections is a key element in patient management. In certain cases, prophylactic antibiotics help to prevent infections (e.g., trimethoprim-sulfamethoxazole to prevent *Pneumocystis carinii* pneumonia among patients with T-cell defects and prevent recurrent infections among patients with CGD). Research has demonstrated the safety and efficacy of replacement therapy with intravenous Ig (IVIG) among patients with defects in antibody production (*49*). Enzyme replacement therapy for ADA deficiency also is effective (*50*). Curative interventions, primarily bone-marrow and stem-cell transplantation, have been used with varying degrees of success for an expanding array of PI diseases (*15,16,19,26,27,51,52*). Clinical trials also have demonstrated that gene therapy can restore near-normal immune function among patients with SCID caused by mutations in *IL2RG*, and similar types of therapy are promising for other immunodeficiencies (*14,17,20*). However, recently, the occurrence of T-cell leukemia in two of 10 children administered gene therapy for *IL2RG* SCID (mutant gamma-chain IL-2 receptor) has prompted a halt to all gene therapy using retroviral vectors for immunodeficiency. In these cases, the retroviral gene construct of the *IL2RG* gene inserted itself on the oncogene *LMO2* that is aberrantly expressed in acute lymphocytic leukemia of childhood. Thus, insertional oncogenesis was the probable cause of the T-cell leukemia in these two cases (*53–55*).

FIGURE 2. A diagnostic testing algorithm for primary immunodeficiency diseases



* Lymphocyte phenotyping includes enumeration of B, T, and NK cells.

Public Health Framework

The defining characteristics of PI diseases make them candidates for a public health intervention approach. Although the clinical manifestations and underlying genetic defects are diverse, PI diseases share the common feature of increased susceptibility to infection and collectively result in substantial morbidity and shortened life spans. Most important, prompt diagnosis and treatment can be life-saving and result in marked improvements in the quality and length of life.

The foundation for a public health intervention to improve the health status of persons with PI diseases is population-based information regarding the incidence, prevalence, and natural history of the diseases; the accuracy of diagnostic methods; and the efficacy of early interventions. However, the majority of these data are lacking. The heterogeneity of PI diseases and the limited understanding of the relation between genotype and phenotype also hinder intervention efforts. Additional obstacles include the difficulty of diagnosis in the absence of a high index of suspicion and the lack of awareness among health-care providers and the public, which impedes the timely recognition of affected persons by using a combination of clinical suspicion and diagnostic testing.

To address these impediments and improve health outcomes among persons with PI diseases, CDC and partners have adapted a population-based public health framework developed as part of CDC's strategic plan for genomics and public health, to the problem of PI diseases (*56*). The framework has four components as follows:

- public health assessment — application of traditional public health methods to assess the impact of PI diseases on community health;
- population-based interventions — development, implementation, and evaluation of screening tests administered to newborns and clinical algorithms for early recognition of symptomatic persons to facilitate the earliest possible diagnosis and treatment for PI diseases;
- evaluation of screening and diagnostic tools — evaluation of screening and diagnostic tools to ensure their quality and appropriateness for identification of patients with PI diseases; and
- communication — communication with health-care providers and the public to facilitate prompt and appropriate diagnosis and intervention.

CDC has begun to apply this framework in the context of ethical, legal, and social considerations to different conditions, most recently to hereditary hemachromatosis, a treatable, adult-onset, single-gene disorder of iron metabolism (*57–61*). For example, gaps in data related to the natural history of the disease, penetrance, optimal treatment for asymptomatic persons, and the psychosocial effect of genetic testing precluded recommendations for population screening for mutations in *HFE*, the associated gene (*62–64*). However, educational efforts are under way to facilitate early diagnosis (e.g., iron overload and *HFE* mutation testing). Lessons learned from applying the framework to hemochromatosis is being applied to other conditions, including PI diseases.

In November 2001, CDC convened a multidisciplinary panel of specialists to identify and discuss public health strategies that can be applied to PI diseases and also used as an approach for other genetic disorders (*65*). A systematic assessment based on the established public health framework was applied to the growing group of recognized PI diseases, for which diverse genetic mutations span multiple components of the immune system but all lead to the increased incidence and severity of infections. During the meeting, specialists in clinical immunology, public health, genetics, pediatrics, health communication, and ethics from state and federal agencies, academic centers, professional organizations, and advocacy foundations discussed the public health framework as it relates to PI diseases. The working group's deliberations were organized around the four components of the framework and centered on challenges and opportunities, priority research questions, and recommendations for public health action. The remainder of this report reflects their analysis of the problem, their conclusions and recommendations, and subsequent deliberations and findings.

Public Health Assessment

Assessment Tools

The majority of what is understood regarding PI diseases derives from accumulation of data from clinical case reports, case series, and case registries. This approach has advantages but has not provided a complete understanding of the incidence, prevalence, and natural history of PI diseases. A public health assessment of the magnitude and characteristics of the problem in the United States, using population-based data, is needed. Quantitative public health methods can be used to assess the effect of gene variants on the risk for disease, disability, and death and to determine the impact of population-based interventions on improved health outcomes. The traditional tools of public health assessment are 1) surveillance, 2) epidemiology, and 3) laboratory science.

Surveillance Systems. Surveillance is the systematic collection, analysis, and interpretation of data related to health outcomes and other health-care events for use in planning, implementation, and evaluation of population-based health activities (*66,67*). Surveillance data can be derived from traditional data sets (e.g., vital records and health surveys) or obtained proactively from health-care providers, health-care institutions with electronic patient records, or laboratories. Effective surveillance requires standardized case definitions for each disorder of interest.

A surveillance system for PI diseases should be used to determine the incidence and prevalence of these conditions. Assuming routine performance of genotyping, a laboratory-based surveillance component should facilitate the calculation of the prevalence of gene variants among cases. The ability to link cases with other data sets will help determine the morbidity, mortality, disability, and health-care costs associated with PI diseases and help set priorities based on public health impact. The availability of outcomes data will allow evaluation of the effect of changes in health-care policy and practice.

Epidemiologic Research. Epidemiology is the study of the distribution and determinants of disease in specified populations, including assessment of the causal effect of preventive interventions on health outcomes. Although clinical research can identify gene variants and other risk factors for PI diseases, population-based analytic epidemiologic studies are needed to quantify the effect of gene variants on the risk for disease, death, and disability and to determine the relations between genotype and phenotype in the population (*1*). Epidemiologic studies that contribute to the understanding of the natural history and clinical course of PI diseases and the benefits of early detection and intervention can improve individual outcomes and reduce the public health burden of this group of diseases. Epidemiologic research methods also are

needed to assess the determinants and uses of genetic testing and other promising interventions and health-care practices.

Laboratory Science. Both surveillance and epidemiologic research are conducted in conjunction with laboratory efforts. These center on diagnostics, phenotypic characterization, genetic analysis, studies of genotype-phenotype relations, and development and evaluation of screening and diagnostic tests.

Existing Data-Collection Systems

Existing population-based data from which to derive a public health assessment of PI diseases are limited. Available data are derived from case-based disease registries that collect patient-specific information from multiple sources.

Disease and Mutation Registries. Case-based registries usually are designed to improve patient care but can be helpful for studying rare diseases. In 1992, the Immune Deficiency Foundation (IDF) initiated a registry of U.S. patients with CGD and 5 years later expanded the project to include seven other disorders — hyper-IgM syndrome, XLA, CVID, WAS, SCID, LAD, and DiGeorge syndrome (*36*). The most reliable data from these registries are for CGD, for which IDF has calculated a minimum estimated U.S. incidence of 1/200,000 live-born infants (*36*). The registry also is used to collect data related to natural history and clinical course, including the response to treatment. In 1995, IDF conducted a national, cross-sectional survey of approximately 17,000 immunologists and medical school faculty to estimate the burden of PI diseases in the United States, to describe characteristics of persons with these disorders, and to identify problems related to access to treatment. Approximately 1,500 physicians reported caring for an estimated 21,000 patients with PI disease (*68*).

Other countries have developed their own registry-based estimates of the frequency of PI diseases, ranging from an estimated prevalence of 2.1/100,000 in Australia (*31*) to 6.8/100,000 in Norway (*32–34*). A registry maintained by the European Society for Immunodeficiencies (ESID) collects data regarding patients from approximately 25 countries in Europe (*69*). As of July 2000, the ESID registry contained clinical data for approximately 8,900 patients from 26 countries (*70*). An example of a registry for another genetic disorder that might be a model for PI diseases is the CF registry, which is based on case ascertainment at comprehensive treatment centers. The Cystic Fibrosis Foundation (CFF) sponsors the National Cystic Fibrosis Patient Registry to collect data regarding all patients examined at CFF-supported and accredited care centers (*71*). Data are used to support epidemiologic studies, direct research, and design clinical trials, all with the goal of improving the survival of persons with CF (*72*).

Other sources of case-based information are the Internet-based, locus-specific immunodeficiency mutation databases established by ESID and expanded by other investigators (*73,74*). These databases contain information regarding specific mutations and certain clinical features of affected persons. The first Internet-based immunodeficiency mutation database, BTKbase, was initiated in 1995 to collect information related to mutations in the *BTK* gene (Bruton's tyrosine kinase), which causes XLA (*75*). Similar locus-specific mutation databases have been developed since then (*69,73*). Mutation databases can be used to analyze the types of mutations and their distribution in exons and introns, including their location in protein domains. Mutation databases that contain clinical information can be helpful in assessing genotype-phenotype relations and determining the presence of gene variants in asymptomatic family members (*76*).

Data from disease and mutation registries can be used to estimate the minimal incidence of a disorder, characterize epidemiologic features, and define a range of clinical characteristics in a cohort of patients (*36*). However, although each has its applications, current registries provide incomplete population-based data regarding the burden of PI diseases. Continued growth of disease and mutation registries relies on the submission of case reports by physicians, resulting in overrepresentation of certain clinical centers in the sample collection (*59*). Incomplete ascertainment limits the representativeness of the data. Moreover, the lack of standardized case definitions precludes the calculation of sound population-based rates from these sources. The value of mutation databases for public health assessment also is limited by the rarity of genetic laboratory confirmation of PI diagnoses. In other cases, the mutated sequence might be known but not submitted to the database.

Population-Based Morbidity and Mortality Data. To contribute to the study of the impact of single-gene disorders, existing population-based data sources were reviewed. Surveillance databases already have been used to evaluate the impact of hereditary hemochromatosis (*59*). Hospital discharge data provide information concerning short-stay hospitalizations for specific conditions and have been used, for example, to document the substantial morbidity rate and hospitalization charges associated with birth defects and genetic diseases among children (*57,77,78*). However, the national hospital discharge survey enumerates hospital discharges rather than individual patients, and for rare or underdiagnosed diseases might provide more limited information because of potential inaccuracy of coding and duplication caused by multiple hospitalizations for the same patient. Managed care organizations maintain substantial, linked, computerized inpatient and

outpatient databases that can be helpful in determining incidence rates (*79*). One example is the Vaccine Safety Datalink (VSD), a partnership between CDC and four health-maintenance organizations designed to evaluate vaccine safety among children. Computerized data concerning vaccinations, medical outcomes, and health services usage are provided for a well-defined population of approximately 1 million children (1993–1996). In addition to determining vaccine-related adverse events, this database could be examined for other relatively infrequent events, including PI diseases (*78–80*).

Mortality data can provide population-based information concerning survival and cause-specific mortality regarding genetic disorders (*60,81–83*). Since 1968, CDC's National Center for Health Statistics has compiled data from all death certificates filed in the United States and made these data available in Multiple-Cause Mortality Files (*82,84*). The files include demographic and geographic information regarding the decedent and *International Classification of Disease* (ICD) codes for the underlying cause of death and ≤20 conditions listed on the death certificate (*85,86*). Methodologic limitations include reliance on coding systems that are not unique or specific enough for birth defects and genetic diseases; delay between death and availability of data; and limited information regarding risk factors. Despite these limitations, mortality files and other population-based data sources will be critical for planning interventions for PI diseases, especially as the causes and treatments of these disorders are further elucidated by epidemiologic studies and human genome research (*75,87,88*).

Population-Based Disease Surveillance. Efforts to collect population-based epidemiologic and surveillance data related to patients with other genetic diseases also might be helpful models for assessment of PI diseases. Population-based birth-defects surveillance systems also hold promise for collection of data regarding PI diseases (*87*). Each state has a different approach to birth-defects surveillance. Data sources include vital records, hospital and clinic records, and administrative databases. The diversity of approaches — particularly methodologies used to generate timely data, applications to monitor prevention activities, and projects to improve access to health services and early intervention — provides useful resources for developing surveillance systems for other childhood diseases.

CDC's program to prevent complications from hemophilia and other bleeding and clotting disorders includes a national surveillance system, prevention interventions conducted through a nationwide network of hemophilia treatment centers (HTCs), and epidemiologic and prevention research. CDC's first state-based surveillance effort was designed to identify all patients with hemophilia in six states, characterize the patient population, and identify risk factors and outcomes of care (*89,90*). Through this effort, CDC derived the first population-based estimate of hemophilia prevalence in the United States and demonstrated the effectiveness of the HTC model. In 1996, to address gaps in this system (e.g., lack of patient follow-up and specimen collection), CDC and the HTCs initiated a prospective universal data collection (UDC) system. The UDC system is designed to guide clinical practice, monitor blood safety, develop a specimen repository, and monitor the clinical extent and progression of joint disease (*91*). Although the UDC system is more comprehensive than the initial surveillance effort, the requirement for informed consent might affect its population-based representativeness.

Workshop Recommendations for Action. The goal of public health assessment for PI diseases is to collect population-based data to define the incidence and prevalence of the disorders. Recommendations from the workshop for public health assessment for PI diseases include the following:

- Collect population-based data regarding the incidence, prevalence, and natural history of PI diseases.
- Collect population-based data regarding the relations between genotype and phenotype for these diseases.
- Collect population-based data regarding the effect of early recognition and effective therapies on morbidity and mortality.
- Target three subsets of PI diseases as priorities for a systematic public health assessment; possibilities include
  - — profound T-cell defects, because of their resulting high mortality in the absence of interventions;
  - — antibody deficiencies, because of the substantial number of persons affected and the high burden of morbidity; and
  - — CGD, because of the existence of an established IDF data set.
- Conduct pilot activities to improve the collection, use, and quality of surveillance and epidemiologic data. These might include
  - — convening a working group of clinical immunologists and scientists to provide guidance regarding case definitions for registry and surveillance activities;
  - — developing collaborations between public and private advocacy groups to expand data collection and completeness of disease registries and to conduct further analyses;
  - — exploring use of existing population-based databases for their potential in yielding useful information regarding the incidence, prevalence, and natural history of PI diseases; and

— developing collaborative state-based surveillance activities for genetic diseases, including PI diseases. For the short term, these might include implementing pilot surveillance systems, similar to birth-defects surveillance, in states with large population sizes because of the estimated rare incidence of these diseases. In addition, linking surveillance to existing databases should be explored (e.g., Vaccine Safety Datalink, hospital-discharge data, IDF registry, or laboratory-based reporting). In the future, surveillance can be expanded beyond the pilot states.

- Participate in ICD revisions to promote development of unique and specific codes for PI diseases.
- Promote development of a network of centers of excellence, and encourage the use of these centers for epidemiologic data collection, specimen repository, and special studies. Possibilities for special studies are longitudinal spectrum-of-disease studies, clinical trials, and evaluations of genotype/phenotype relations.

Population-Based Interventions

Two major areas were discussed at the workshop, 1) early clinical recognition of PI diseases and 2) newborn screening.

Early Clinical Recognition

Background and Rationale. Timely and effective population-based interventions can reduce morbidity and mortality from genetic diseases (Figure 1). For PI diseases, these interventions center on early diagnosis and implementation of effective therapy (e.g., hematopoietic stem cell transplantation, Ig replacement, and administration of antibiotics). The intervention component of the public health framework for PI diseases therefore involves development of strategies for early diagnosis, implementation of pilot demonstration projects, and evaluation of the effect of these interventions on morbidity, disability, health-care costs, and mortality.

When evidence indicates that early diagnosis and treatment will avert the late stages of disease and prevent morbidity, disability, and premature mortality, increased early clinical recognition is one component of a public health response. The goal is to identify persons who have early symptoms indicative of a PI disease so they can receive diagnostic testing to confirm the presence or absence of disease and receive appropriate interventions to prevent adverse outcomes. Although data regarding the benefits of early symptomatic screening are limited, information from clinical centers supports improved outcomes for certain PI diseases through early intervention (*25,92–94*). The effect might vary, depending on the genetic defect, the age at diagnosis, presence of prior infections, and history of vaccination and blood transfusion (*93*).

Symptom-Based Screening — Clinical Algorithm. Increasing early symptomatic screening for PI diseases requires concerted efforts to increase awareness of these conditions among physicians and health-care systems. Primary-care clinicians, particularly pediatricians and family practice physicians, provide the first point of contact for persons with PI diseases by recognizing the possibility of an immunologic problem and the need for appropriate evaluation. Clinicians need to be aware of the estimated prevalence of PI diseases, the natural history of the disorders, the availability and efficacy of treatment, and most importantly, the common early symptoms. Early recognition of PI diseases in the clinical setting can be facilitated by development and evaluation of a symptom-based screening algorithm. Such an algorithm can be designed to 1) identify persons with a frequency of infections who fall outside the normal range of infections; 2) increase physicians' awareness of the types, frequency, and appearances of PI diseases; 3) facilitate physicians' understanding of useful screening approaches (e.g., family history); and 4) trigger appropriate action without overburdening the medical care system.

The enhanced early clinical recognition approach has multiple advantages. Symptom-based screening occurs in the usual health-care setting and requires no additional screening infrastructure. Although certain children and adults seen in primary-care settings might have clinical symptoms suggesting PI disease, the number tested still will be considerably lower than that required for universal screening. Finally, including a PI disease as a suspected diagnosis will occur in a clinical setting that offers options for follow-up and referral.

However, the benefits of the symptom-based approach will be limited if diagnostic testing and treatment are unavailable or delayed. For example, researchers at Mt. Sinai School of Medicine are studying whether PI diseases are underrecognized among minority and economically disadvantaged persons. The percentage of white non-Hispanic patients among whom PI diseases are diagnosed and treated at Mt. Sinai is disproportionately high (92%), compared with the population of the hospital's catchment area of East Harlem, which is predominately Hispanic (52%) and black non-Hispanic (37%). Possible reasons for the disparity include receipt of care in emergency departments and clinics with multiple providers, lack of regular contact with a primary-care physician, and lack of continuity of care. Investigators are evaluating use of profiles of diagnostic codes that might indicate probable PI diseases and help providers identify patients earlier. Improvements in the specificity and accuracy of coding have been identified

as needs. Mt. Sinai also is undertaking outreach and educational efforts directed toward providers serving minority populations to increase their awareness and improve the timely diagnosis of PI diseases (*65*). Such efforts at other centers and in a population-based approach might substantially affect the care of patients with PI diseases.

Assessment and Evaluation of Impact. Initiation of treatment after identification of a PI disease and early in the course of disease might be sufficient to prevent premature mortality, but a patient's quality of life will not improve if the sequelae are not reversible or the disease progression cannot be halted. Thus, systematic studies of the natural history of disease and the effectiveness of interventions in modifying health outcomes are critical. In addition, if the clinical validity of an early recognition algorithm is not sufficiently sensitive, cases will be missed; if the algorithm is not specific enough, too many persons will be referred for testing. Proposed algorithms therefore need to be assessed for analytic validity (e.g., comparing the number and type of infections reported by patients to the documentation in the medical record), clinical validity (e.g., determining the proportion of persons with specific symptoms who have or do not have a PI disease), and clinical utility (e.g., determining whether early detection of a specific disorder affects long-term outcomes and is cost-effective).

The limited experience with symptom-based screening methods for a group of diverse disorders demonstrates the challenges in establishing clinical algorithms that can be applied readily in busy clinical practices with accuracy and efficiency (*43,95*). Findings indicate that clinical algorithms vary in their analytic and clinical validity, especially depending on the age of the population. Therefore, algorithms must be refined to improve sensitivity and avoid missed cases and to increase specificity to reduce costs associated with the immunologic workup of unaffected children and adults. New practice parameters, including information related to diagnosis and treatment, are in development, and physicians need to be made aware of these to assist in the early identification and management of these patients (L. Kobrynski, M.D., Emory University, Atlanta, Georgia, personal communication, 2003).

Workshop Recommendations for Action. Different approaches for early clinical recognition have been used in clinical settings, but none have been systematically evaluated. Workshop recommendations for early clinical recognition are as follows:

- Collect data related to the effect of early interventions on morbidity and mortality associated with PI diseases.
- Identify a group of diseases that can benefit from using an early clinical recognition algorithm. Possibilities include SCID, XLA, CVID, CGD, and WAS.
- Establish a working group to create a system of clinical algorithms for early clinical recognition of PI diseases. The working group should include primary-care physicians. Possible early-recognition tools are scoring systems, lists of warning signs, questionnaires, or alert bulletins.
- Select target audiences and adjust the early-recognition tools for each audience.
- Before widespread application of the algorithms, evaluate the usefulness and accuracy of early clinical signs and symptoms and initial laboratory tests for early recognition of PI diseases. Explore existing databases to test proposed algorithms.
- Report on the effectiveness of the tools among the original target audiences and amend the tools as indicated.
- Evaluate the usefulness of family history in recognizing single-gene disorders early.
- Conduct collaborative studies among clinical centers to examine the natural history of selected PI diseases.
- Conduct research regarding impediments to access to treatment and case management.
- Conduct needs assessments related to timely diagnosis, access to treatment, and ongoing care.

Newborn Screening

Certain severe PI diseases become apparent early in life, with only a short asymptomatic period after birth. Without an effective intervention, the majority result in irreversible complications and death before the end of the first year of life. The most useful method for improving the outcomes of diseases with such a narrow window for detection and intervention might be population-based newborn screening (NBS).

Existing Newborn Screening Programs. NBS programs began in the 1960s with the development of an accurate and sensitive test for PKU, an inherited disorder of metabolism (*96*). Children affected with PKU are unable to metabolize the amino acid phenylalanine. If untreated, affected children will be severely mentally retarded and experience other neurologic symptoms. However, dietary therapy started soon after birth will reduce symptoms and allow affected children to develop normally. The average incidence of PKU is approximately 1/16,000 births.

The PKU assay uses a dried blood spot (DBS) specimen. Blood is collected from the heel of an infant 1–2 days after birth. The heel is pricked, and a few drops of blood are spotted onto a filter paper card, dried, and sent to a state or regional public health laboratory. Small filter-paper disks containing dried blood are punched from the specimens and used to test the newborn for PKU and other disorders. This simple, easily transported, and inexpensive specimen-collection method has led to development of population-based

screening of newborns throughout the world (*41,97–99*). Babies in the United States are screened for 4–30 different metabolic, hematologic, and endocrinologic disorders within a few days of birth. All of these tests are performed by using DBS specimens. As a population-based public health activity, NBS programs are the responsibility of state public health agencies and operate under policies determined at the state level, although laboratory screening might be contracted to other states or to academic or private laboratories (*97,100*).

Newborn Screening Quality Assurance Program. CDC's Newborn Screening Quality Assurance Program (NSQAP) produces, certifies, and distributes DBS materials for external quality control and performance surveillance to help NBS laboratories evaluate and improve the quality of their testing and to foster standardization of NBS services (*101*). Approximately 250 national and international screening laboratories from 45 countries participate in the quality assurance program. NSQAP recently added quality assurance materials for disorders detected by tandem mass spectrometry (*102,103*) and CF (*101*).

Principles for Evaluating Evidence for Newborn Screening. Guidelines for NBS programs are linked to ethical, legal, and social considerations and are based on the premise that screening should be conducted only when science and technology can serve both the individual person and the public good. Certain landmark reports (*47,98,104*) identify criteria for population-based NBS programs. The criteria typically follow standard principles of population screening developed in 1968 (*105*). These principles emphasize the

- importance of a specific condition to public health;
- availability of an effective screening test;
- availability of diagnosis and treatment;
- existence of a recognizable latent or early symptomatic phase for the condition and an adequately understood natural history;
- an agreed upon policy regarding whom to treat;
- a balance between screening costs and health expenditures; and
- availability of case-finding capabilities.

These criteria have been discussed and modified multiple times (*64,100*). With the advent of new testing technologies, the criteria and corresponding evidence and ethical problems are being revisited at the state and national levels (*64*).

Newborn Screening and SCID. Among PI diseases, SCID is a candidate for development of an NBS protocol. SCID is characterized by profound deficiencies of T- and B-cell function and is usually lethal during infancy without successful immune reconstitution, ideally during the first months of life (*15,16,19*).

Efficacy of Early Identification and Treatment. Research indicates that infants with SCID who receive hematopoietic stem-cell transplants from related donors in the first 3.5 months of life have approximately 95% chance of survival, compared with a survival rate of 76% for infants receiving this treatment after 3.5 months (*27*). Infants who received stem cell transplants during the first 28 days of life demonstrated higher levels of T-cell reconstitution and thymic output than did those who received a transplant later; updated survival estimates were 95% (N = 21/22) for infants receiving transplants during the first 28 days, compared with 74% (N = 71/96) for infants receiving transplants after the neonatal period (*19*). An analysis of registry data for 475 SCID patients from 37 centers in 18 European countries reported that long-term survival among patients who received stem-cell transplants has improved, probably because of more effective prevention of complications (*106*). Differences were identified by SCID phenotype, with poorer outcomes occurring among SCID patients without B cells than among those with B cells. Immune reconstitution using gene therapy in clinical trials has also been achieved for forms of SCID (*14,17,18,20,52*); however, as discussed previously, the unexpected complication of T-cell leukemia occurred among 2 of 10 children receiving therapy for *IL2RG* SCID (*53–55*). Similar types of therapy are promising for other immunodeficiencies (*26*).

The need to identify at birth children with SCID, as evidenced from clinical studies, permits time to institute therapies for immune reconstitution before the onset of opportunistic and other infections associated with negative outcomes. SCID meets certain traditional criteria for NBS, as follows (*105*):

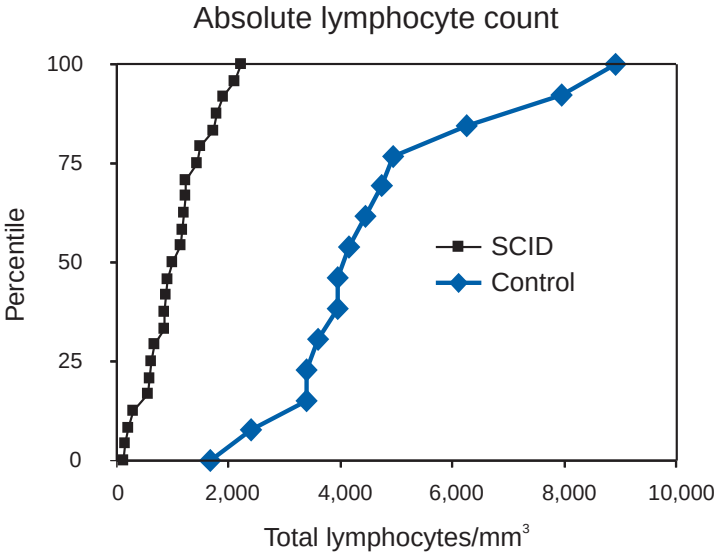
- SCID is fatal during infancy without immune reconstitution.
- A short asymptomatic period exists after birth.
- Effective treatments are available.
- Early intervention improves outcome.
- Profound deficiencies of cellular and humoral immunity might be detectable with screening tests.

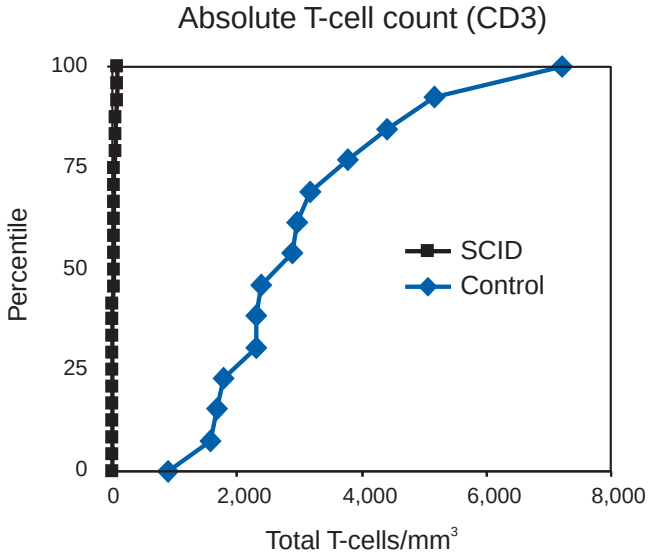
Development and Evaluation of Screening Tests. Data regarding the analytic and clinical validity of the screening tests are critical in considering an NBS program. One study, which was conducted in New York state in the 1970s, assessed the effectiveness of a DBS screening test for ADA deficiency based on ADA enzyme activity (*107,108*). This led to the detection of 12 partially ADA-deficient patients (i.e., persons whose erythrocytes lacked ADA but who had substantial ADA in other cell types and who were clinically and immunologically normal) (*109*), but no cases of ADA SCID were detected.

However, because of variability in the tests used, two patients with ADA SCID were missed at one hospital. Data regarding genotype-phenotype correlation are now accumulating for ADA deficiency and is important to consider in NBS (*110*). The majority of ADA-deficient patients have SCID, but in 15%–20% of these, the condition is diagnosed late in childhood or in adulthood with more variable immunodeficiency; normal persons with partial ADA deficiency also have been identified (*111*).

Identification of SCID at birth will require developing a high-throughput screening test. Data indicate that a T-cell count might be an effective screening tool. The phenotypic hallmark of SCID is profound T-cell lymphopenia, with counts substantially below the first percentile of normal; transplacental maternal T-cell engraftment might cause this number to be higher only in a limited number of cases. Compared with healthy infants, whose total lymphocyte counts at birth are 2,000–11,000 cells/µL (*112*), counts in SCID patients are usually <1,500–2,000 cells/µL (Figure 3). $CD3^+$ T-cell counts in infants with SCID are typically <500 cells/µL (normal: 3,000–6,500 cells/µL) (*15,16,28,113*). In a study of a large urban, primarily minority cohort of 800 healthy children, median total lymphocyte counts at ages 0–3 months were 5,400 cells/µL (10^{th} –90^{th} percentile, 3,400–7,600 cells/

FIGURE 3. Absolute lymphocyte count distributions in severe combined immunodeficiency (SCID) — 25 newborns with SCID and 14 healthy newborns at birth evaluated at Duke University*





Range of absolute lymphocyte counts (cells/mm^3) at birth*
25 SCID newborns (age 0–16 days) 114–2,210
14 normal infants (age 0–8 days) 1,670–8,910

Range of T-cell counts (cells/mm^3) at birth for*
25 SCID infants (age 0–16 days) 0–84
14 normal infants (age 0–8 days) 903–7,226

Normal number of lymphocytes (percentage of total leukocytes) at different ages†
Birth 5,500 (2,000–11,000) cells/mm^3 (31%)
6 months 7,300 (4,000–13,500) cells/mm^3 (61%)
21 years 2,500 (1,000–4,800) cells/mm^3 (34%)

Distribution of total lymphocytes and T-cell subsets in normal healthy children at ages 0–3 months§
(N = 800) Median total lymphocyte counts 5,400 cells/µL (10^{th}–90^{th} percentile 3,400–7,600 cells/µL)
(N = 699) Median CD3 T-cell counts 3,680 cells/µL (10^{th}–90^{th} percentile 2,500–5,500 cells/µL)
(N = 699) Median CD4 T-cells counts 2,610 cells/µL (10^{th}–90^{th} percentile 1,600–4,000 cells/µL)

***Source:** Kalman L, Lindegren ML, Kobrynski L, et al. Mutations in genes required for T-cell development: *IL7R*, *CD45*, *IL2RG*, *JAK3*, *RAG1*, *RAG2*, *ARTEMIS*, and *ADA* and severe combined immunodeficiency. Genetics in Medicine. (In press).
†**Source:** Altman, PL. Blood and other body fluids. Washington, DC: Federation of American Societies for Experimental Biology, 1961:125.
§**Source:** Shearer WT, Rosenblatt HM, Gelman RS, et al. Lymphocyte subsets in healthy children from birth through 18 years of age: the pediatric AIDS clinical trials group P1009 study. J Allergy Clin Immunol 2003;112:973–80.

μL); median $CD3^+$ T-cell counts were 3,680 cells/μL (10^{th}–90^{th} percentile, 2,500–5,500 cells/μL); and $CD4^+$ T-cells were 2,610 cells/μL (10^{th}–90^{th} percentile, 1,600–4,000 cells/μL) (*114*).

Development of a DBS-based high-throughput test for T-cell lymphopenia will make possible integration of screening for SCID into the existing NBS system. Screening tests might detect markers on mummified T-cells (and other leukocytes) present on DBS. Multiple types of soluble T-cell–specific biomarkers that theoretically can be recovered from DBS have been indicated as potential surrogates for a T-cell count. One such biomarker is the family of cell-membrane antigens unique to T-cells, most notably CD3, CD4, and CD8. Measurements of these T-cell markers from DBS might be possible by using antibody-based detection assays (*115*). Another potential biomarker is the circular DNA removed when T-cell–receptor variable genes rearrange during T-cell development. These molecules are called T-cell antigen receptor excision circles (TRECs) (*19,116*). Detection and quantitation of TRECs from DBS should be possible by using PCR amplification (*117*). TRECs, located in recently formed T cells, should be abundant in normal newborns but absent in newborns with SCID. Quantitation of TRECs from NBS with high-throughput application has not been developed.

Total lymphocyte counts, as obtained in a complete blood count, also have been proposed as a screen for lymphopenia. However, because affected newborns often have increased B-cell counts that cause an approximate 20% overlap with the normal lymphocyte distributions, this approach can potentially miss cases of SCID and require supplemental testing for certain normal newborns (*19*). Detection of all cases will require enumeration of total lymphocyte counts with a manual differential and subsequent subset analysis by using flow cytometry, neither of which can be performed on DBS specimens. Detection of specific DNA sequences from DBS is also possible. However, although genomic DNA-based tests to detect the disease-causing alleles can be developed on the basis of the detection of one or a limited number of specific mutations, the number and wide spectrum of molecular defects and lack of data regarding genotype-phenotype relations that can cause SCID currently precludes development of a specific DNA test.

Evaluation of Newborn Screening. In addition to developing a screening test, other steps need to be taken before routine screening of newborns for SCID can be considered. These include

- determining the analytical validity of the proposed assay;
- developing a standardized case definition of the disorder;
- developing effective follow-up protocols for screen-positive infants;
- identifying treatment centers;
- conducting pilot testing to assess the assay's clinical validity, clinical utility, outcomes, and costs;
- determining cost-benefit; and
- assessing ethical, legal, and social implications.

The possibility of detecting lymphopenia caused by other genetic causes or HIV infection also needs to be considered. Although children with these conditions do not have SCID, any child identified with severe lymphopenia requires further evaluation. By testing all infants, children with a fatal but treatable disease can be identified and treated, and valuable information can be obtained regarding the incidence of these disorders in the population and the frequency of different mutations among affected persons and in the population.

In considering SCID as a possible addition to state newborn screening, evidence-based criteria should be used but might require re-examination in terms of weighting of different criteria. For example, the question of whether a condition is a key public health problem often is decided on the basis of prevalence. Such disorders as SCID with a prevalence of perhaps 1/100,000 might not be considered a critical public health concern by everyone. Cost concerns (i.e., cost-effectiveness or cost-benefit of proposed screening tests) are also important and need to be considered systematically. Detection of a disorder with a low prevalence might be more cost-effective than detection of a much more common disorder, depending on the severity of the health outcomes, effectiveness of interventions, and cost of screening and treatment (*118*). Economic analysis is a way of systematically integrating and evaluating multiple screening criteria. State newborn screening advisory committees should consider this more objective process (*119*).

Workshop Recommendations for Action. Workshop recommendations for NBS are as follows:

- Determine the feasibility of NBS for SCID.
- Establish partnerships among investigators and CDC laboratory personnel to develop assays to measure T-cell lymphocytes from DBS.
- Establish partnerships among investigators and CDC laboratory personnel to validate methods to measure T-cell lymphocytes or TRECs from DBS. Validation methods can include blinded comparisons of T-cell counts by using the proposed assays from DBS, with a manual differential count from cord blood samples as the benchmark.
- Collaborate with partners to review data regarding population-based normal ranges of T-cells, $CD4^+$ cells, and TRECS at birth.

- Pilot test a validated assay. Integrate the proposed assays into an existing NBS panel on an investigational basis with Institutional Review Board (IRB) approval. Demonstrate adequate follow-up capacity and ability to ensure access to treatment without financial barriers. After pilot testing has demonstrated that NBS for T-cell lymphopenia can be performed with an extremely high degree of accuracy at acceptable cost and that follow-up services and treatment can be provided to all affected children identified through screening, a national-level body might recommend that states include this test in the standard NBS panel. Each state should have an advisory committee to consider such a recommendation.

Evaluation of Screening and Diagnostic Tests

Genetic Tests and PI Diseases. Advances in molecular biology and genetic technology have facilitated localization of disease genes and identification of disease-causing mutations, allowing for more rapid development of new genetic tests. PI diseases are among the approximately 800 health conditions for which genetic tests are available in clinical practice (*120,121*). As the genetic defects associated with PI diseases continue to be discovered, more genetic tests will become available for clinical diagnosis, carrier detection, prenatal diagnosis, and disease management (*13,45,122*).

The genetic aspects of PI diseases and their implications for diagnosis and patient management have been extensively reviewed (*22*). Mutation detection is the most reliable diagnostic method (*45*). However, because of the substantial number of mutations across the spectrum of genes that characterize immunodeficiency, targeting one or a limited number of mutations is inappropriate. Methodologically, DNA-based detection involves different molecular techniques, although DNA sequencing is the usual diagnostic method. Evaluation of mRNA or protein also can be used because absent or low levels of specific mRNA or protein are diagnostic for certain PI diseases. Finally, in conjunction with a family history, clinical and laboratory findings in certain X-linked disorders can also provide a diagnosis.

As tools for the diagnosis and screening of PI diseases evolve, defining and pursuing measures that will ensure their safe and effective use become increasingly critical. Genetic testing in the United States has developed successfully, providing options for avoiding, preventing, and treating inherited disorders. Nonetheless, application of genetic tests is increasing in clinical and public health practice. Concerns related to rapid commercialization of genetic tests are complex and controversial. Appropriate use of tests, quality of laboratory testing, direct-to-consumer marketing, and the potential for discrimination and stigmatization call for public health leadership. Such leadership is needed to protect the public from inappropriate testing and to ensure that tests are properly evaluated and integrated into medical and public health practice (*47,56*).

Evaluation of Genetic Tests. In 1999, the National Institutes of Health (NIH)-U.S. Department of Energy Task Force on Genetic Testing published recommendations to promote safe and effective genetic testing (*47*). The Task Force recognized the need to evaluate genetic tests in population-based settings before their use in clinical practice. To ensure the appropriate level of review, the panel recommended that genetic tests be evaluated according to three criteria, analytic validity, clinical validity, and clinical utility. Systematic assessment based on these measures provides data to determine whether a genetic test being considered for use in population-based screening or clinical diagnosis is safe and effective as the technology moves from research to clinical settings (*123,124*). The criteria also can be applied to screening tests and clinical algorithms.

Analytic validity is the ability of a test to measure the analyte of interest. In the case of a genetic test, analytic validity refers to the ability of the test to classify the genotype or analyte related to the genotype (*125*). The four main elements of analytic validity are analytic sensitivity, analytic specificity, laboratory quality control, and assay robustness. However, an analytically valid test is useful only if it helps to diagnose or predict disease (i.e., the test must also be clinically valid) (*125*). Clinical validity is the accuracy with which a test predicts a particular clinical outcome. It reflects both the sensitivity of the test — the proportion of affected persons with a positive test — and specificity of the test, penetrance of the mutations identified by the test, and the prevalence of disease (*123,124*). Penetrance is the proportion of persons with the mutation who develop the disease. Clinical utility is the usefulness of the test and the value of the information to the person being tested. Clinical utility is assessed according to the benefits and risks associated with the test and the ensuing result or interventions. Clinical utility focuses on health outcomes associated with testing and requires an understanding of the natural history of the disorder.

The Foundation for Blood Research, in collaboration with CDC, has developed a framework for assessing the availability, quality, and usefulness of data related to genetic tests and testing protocols (*126*). This approach, called ACCE (analytic validity; clinical validity; clinical utility; and ethical, legal, and social implications), derives from the three evaluation criteria described previously, in addition to a fourth that addresses the safeguards and impediments that should be considered in the context of the others (*126,127*). The evaluation process begins only after the clinical disorder and the test setting (e.g., diagnosis or population screening) have been established. Specific questions (Table 2) help to define the disorder,

TABLE 2. Targeted questions for evaluating genetic tests, considering analytic validity; clinical validity; clinical utility; and ethical, legal, and social considerations

Element	Component	Question
Disorder/Setting	Disorder	What is the specific clinical disorder to be studied?
		What are the clinical findings defining the disorder?
	Setting	What is the clinical setting in which the test is to be performed?
	Testing	What DNA tests are associated with this disorder?
		Are preliminary screening questions used?
		Is it a stand-alone test or one of a series of tests?
		If it is part of a series of screening tests, are all tests performed in all instances (parallel), or are only certain tests performed on the basis of other results (series)?
Analytic validity		Is the test qualitative or quantitative?
	Sensitivity	How often is the test positive when a mutation is present?
	Specificity	How often is the test negative when a mutation is not present?
	Quality control	Is an internal quality-control program defined and externally monitored?
		Have repeated measurements been made on specimens?
		What is the within- and between-laboratory precision?
		If appropriate, how is confirmatory testing performed to resolve false-positive results in a timely manner?
	Robustness	What range of patient specimens have been tested?
		How often does the test fail to give a usable result?
		How similar are results obtained in multiple laboratories by using the same or different technology?
Clinical validity	Sensitivity	How often is the test positive when the disorder is present?
	Specificity	How often is the test negative when the disorder is not present?
		Do methods exist to resolve false-positive results in a timely manner?
	Prevalence	What is the prevalence of the disorder in this setting?
		Has the test been adequately validated on all populations to which it might be offered?
	Predictive value	What are the positive and negative predictive values?
	Penetrance	What are the genotype/phenotype relations?
		What are the genetic, environmental, or other modifiers?
Clinical utility	Natural history	What is the natural history of the disorder?
	Intervention	What is the effect of a positive (or negative) test on patient care?
		If applicable, are diagnostic tests available?
		Is an effective remedy, acceptable action, or other measurable benefit available?
		Is that remedy or action easily accessible?
		Is the test being offered to a socially vulnerable population?
	Quality assurance	What quality assurance measures are in place?
	Pilot trials	What are the results of pilot trials?
	Health risks	What health risks can be identified for follow-up testing or intervention?
	Economics	What are the financial costs associated with testing?
		What are the economic benefits associated with actions resulting from testing?
	Facilities	What facilities and personnel are available or easily put in place?
	Education	What educational materials have been developed and validated, and which of these are available?
		Is informed consent required?
	Monitoring	What methods exist for long-term monitoring?
		What guidelines have been developed for evaluating program performance?
Ethical, legal, and social considerations	Impediments	What is known regarding stigmatization; discrimination; privacy/confidentiality; or personal, family, and social concerns?
		Do legal problems exist regarding consent, ownership of data or samples, patents, licensing, proprietary testing, obligation to disclose, or reporting requirements?
	Safeguards	What safeguards have been described and are these safeguards in place and effective?

Sources:
Haddow JE, Palowmaki GE. ACCE: a model process for evaluating data on emerging genetic tests. In: Khoury MJ, Little J, Burke W, eds. Human genomic epidemiology. New York, NY: Oxford University Press, 2003.
Foundation for Blood Research. FBR: Foundation for Blood Research [Website]. Scarborough, ME: Foundation for Blood Research, 2003. Available at http://www.fbr.org.

the setting, and the type of testing and to address ACCE. The first disorder to undergo an ACCE review was CF (*61*). Others in progress include hereditary hemochromatosis and breast cancer.

Development and Availability of Genetic Tests. The Task Force has addressed the need to encourage development and maintenance of tests for rare genetic diseases, establish a comprehensive system to collect data related to rare diseases, and assess the validity of genetic tests for these conditions (*47*). Evaluation of genetic tests involves collection and analysis of data regarding analytic validity, clinical validity, clinical utility, and other aspects from laboratories and users. However, for selected PI diseases, genetic testing is available from only a limited number of laboratories, or even only one laboratory, worldwide. Immunodeficiency diseases for which clinical genetic tests or research testing are available, based on information from the GeneTests Laboratory Directory (*121*), are provided in this report (Table 3). The directory lists 11 PI diseases for which clinical genetic tests are offered in only one laboratory; three diseases for which testing is available only

TABLE 3. Genetic testing and research in primary immunodeficiency diseases listed in GeneTests* — retrieved January 27, 2003

Disorder	Genes and loci	Clinical genetic testing	Research
Adenosine deaminase deficiency	Adenosine deaminase (*ADA*), 20q13.11	1 laboratory in United States (biochemical)	1 laboratory in United States
Ataxia-telangiectasia	Serine-protein kinase *ATM*, 11q22.3		1 laboratory in United States
Autoimmune polyendocrinopathy syndrome type 1 (APECED)	Autoimmune regulator (*AIRE-1*) 21q22.3	1 laboratory in Italy	1 laboratory in Italy†
Bloom syndrome	Bloom syndrome protein (*BLM*), 15q26	11 laboratories in United States; 2 laboratories in Israel (DNA-based)	1 laboratory in United States
Cartilage-hair hypoplasia	*RMRP*, 9p21-p12	1 laboratory in Switzerland (DNA-based)	1 laboratory in Switzerland;† 2 laboratories in United States
Chronic granulomatous disease	Cytochrome *B-245* light chain (*CYBA*), 16q24 Cytochrome *B-245* heavy chain (*CYBB*), Xp21.1 Neutrophil cytosol factor 1 (*NCF1*), 7q11.23 Neutrophil cytosol factor 2 (*NCF2*), 1q25	1 laboratory in United States (biochemical and DNA-based)	
Familial atypical mycobacteriosis	Interferon-gamma receptor alpha chain (*IFNGR1*), 6q23-q24 Interferon-gamma receptor beta chain (*IFNGR2*), 21q22 Interleukin-12 beta chain (*IL12B*) 5q31-q33 Interleukin-12 receptor beta-1 chain (*IL12RB1*), 19p13	1 laboratory in France (DNA-based and biochemical)	1 laboratory in France†
Hyper Immunoglobulin D syndrome	Mevalonate kinase (*MVK*), 12q24	1 laboratory in United States (DNA-based)	
Lymphoproliferative disease, X-linked	*SH2D1A* (*SAP*), Xq25	1 laboratory in United States (DNA-based)	
Nijmegen breakage syndrome	Nibrin (*NBS*), 8q21	1 laboratory in Russia	1 laboratory in Japan; 2 laboratories in United States
Properdin deficiency, X-linked	(*PFC*, *PFD*) Xp11.4-p11.23	1 laboratory in the Netherlands (DNA-based)	
Purine nucleoside phosphorylase deficiency	Purine nucleoside phosphorylase (*PNP*), 14q13	1 laboratory in United States (biochemical)	
Wiskott-Aldrich syndrome	Wiskott-Aldrich syndrome protein (*WASP*), Xp11	1 laboratory in United States; 1 laboratory in Israel; 1 laboratory in the Netherlands; 2 laboratories in Canada (DNA-based)	3 laboratories in United States; 1 laboratory in Israel;† 1 laboratory in Canada†
X-linked agammaglobulinemia	Bruton's tyrosine kinase (*BTK*), Xq21.3-q22	1 laboratory in United States (DNA-based)	2 laboratories in United States
X-linked severe combined immunodeficiency	Interleukin-2 receptor gamma chain (*IL2RG*), Xq13.1	2 laboratories in United States (DNA-based and biochemical)	2 laboratories in United States

* Additional information is available at http://www.genetests.org.
† Indicates the same laboratory performing both clinical testing and research for the disorder.

outside the United States; and one disease for which testing is available only on a research basis. The limited availability of testing poses challenges for test development and evaluation and presents needs and opportunities for public health research. Data collection will require a long-term, collaborative effort and a comprehensive, sustainable system to assess the validity and reliability of genetic tests for PI diseases and other rare diseases.

Guidance and criteria for transferring genetic tests from the research and development phase to clinical and public health practice also are needed. Certain genetic tests were developed in research laboratories and then made available for patient testing. For such rare diseases as PI, a laboratory that primarily conducts research might be the only clinical testing site available. A mechanism needs to be established to enable these laboratories to participate in and contribute to the continu-

ous test evaluation and validation process. Concurrently, criteria need to be developed to guide the transition of genetic testing from research into clinical and public health use.

For certain PI diseases, genetic tests are available only from non-U.S. laboratories (Table 3). The Clinical Laboratory Improvement Amendments (CLIA) require that U.S. laboratories refer a specimen for testing only to a CLIA-certified laboratory or a laboratory meeting equivalent requirements as determined by the Center for Medicare and Medicaid Services.* To ensure access to quality genetic testing, a process is needed to evaluate the tests and practices of non-U.S. laboratories that receive test referrals from the United States, determine performance equivalence to CLIA standards, and ensure access to and availability of testing for rare disorders.

Additional needs include 1) collection of population-based data regarding analytic validity, clinical validity, and clinical utility for immunologic tests used to diagnose PI diseases (Figure 2); 2) development of algorithms for use of laboratory tests and clinical information to increase the likelihood of early clinical diagnosis of PI diseases; and 3) population-based research to evaluate the utility of genetic tests as early diagnostic tools for PI diseases, both as part of NBS programs and for confirmatory or follow-up diagnosis.

Workshop Recommendations for Action. Recommendations from the workshop include the following:

- Evaluate potential genetic tests for their validity, utility, and feasibility as both screening tests and confirmatory or follow-up diagnostics in combination with other tests.
- Ensure that CLIA-compliant laboratory testing is accessible, available, and valid for diagnosing rare genetic diseases, including suspected PI diseases, in collaboration with agencies providing oversight for CLIA, NIH Office of Rare Diseases, CDC, and others.
- Support the formation of treatment networks and referral centers to ensure access to diagnosis and care for persons with PI diseases.
- Collect data regarding the analytic and clinical validity of molecular tests used for diagnosis and any proposed screening tests.
- Review gene databases in the United States and Europe to highlight the availability and possible sources of data regarding the validity and quality of tests.
- Identify centers for pilot testing of any proposed screening assays to determine clinical validity, in collaboration with states, CDC, other federal agencies, and other partners. Integrate any proposed validated assay into an existing NBS panel on an investigational basis with IRB approval. Demonstrate adequate follow-up capacity and ability to ensure access to treatment without financial barriers.

Education and Communication

To encourage early recognition of PI diseases, followed by appropriate referral and treatment, primary-care providers, parents, and other caregivers must be educated regarding the symptoms of PI diseases, resources for referral, and treatment options. The effectiveness of a health communication and education campaign depends on the consistency of the messages and the coordination of communication strategies to reach targeted audiences among the groups involved in PI research and education.

Existing Efforts. Multiple agencies and organizations sponsor outreach and educational efforts designed to increase awareness of PI diseases. NIH, Mt. Sinai Hospital, the Jeffrey Modell Foundation (*128*), and IDF (*129*) have all targeted proactive outreach efforts to a range of audiences (e.g., health-care providers, patients, families, and teachers), although health-care providers have been the primary focus. Outreach activities and resources include conferences and workshops, Internet-based training and resources, community-based training, distribution of awareness posters, media briefings and news releases, consulting networks, and a visiting professor program. The National Organization for Rare Disorders (NORD) also provides print and online resources for health-care providers on multiple rare diseases, including PI diseases (*130*).

Although these educational efforts have been ongoing for years, outcomes have not been formally evaluated. In addition, various educational activities or messages have not been coordinated, and consensus has not been developed among the organizations or scientists involved in educational research related to PI diseases. Because the diseases vary in severity, symptoms, etiology, and outcomes, coherent messages regarding groups of PI diseases are difficult to create, and no agreement exists concerning which disorders should be the focus of a health communication campaign. Although educational efforts should highlight PI diseases that can benefit from and be targeted for early recognition and that have established criteria for early clinical recognition, priorities for educational efforts have yet to be established.

Components of Effective Programs. Effective health communication and education programs should be preceded by consensus in the scientific community regarding which PI diseases to include in an educational program, the associated symptoms, and the recommended screening and management steps. To encourage early recognition, education regarding PI diseases also will need to reach multiple audiences, including the general public, parents, physicians, school nurses, child care providers, and policy makers. Reaching each audience

* 42 CFR§493.1242(c).

with consistent but targeted messages will require careful coordination among different agencies.

Attempts to reach primary-care providers, recognized as the front line in the fight against PI diseases, must overcome multiple barriers. Other diseases with higher prevalence command the attention of physicians. Primary-care providers with heavy caseloads and limited time for continuing education activities probably focus their continuing education efforts on problems encountered most frequently among primary-care providers. Health-care providers are most likely to attend to the most prevalent health problems among their patients. The prevalence of PI diseases (individually or collectively) has not been established, although estimates classify them as rare to extremely rare. With such high-prevalence diseases as asthma claiming high priority for providers' attention and concern, focusing on less prevalent health problems might be difficult.

Development of a broad health communication campaign for providers and the public is premature. Research to determine the prevalence and etiology of PI diseases and the efficacy of early treatment must be completed before effective messages and educational materials for the public and providers can be developed. However, pending delineation of defined symptoms, disease groups, and treatment recommendations, health communication efforts still can be useful. Although research has not yet yielded a defined set of educational goals related to PI diseases, health communication efforts can be used in the interim to increase awareness among scientists and clinicians. Certain health-care providers might be unaware of PI diseases and research, and researchers might be unaware of opportunities for funding and participation in PI investigations.

Workshop Recommendations for Action. Workshop recommendations include the following:

- Target health-care providers and scientists for early-stage communication activities. Increase their awareness of studies under way, questions motivating research programs, opportunities for participation and funding, and resources.
- Use research concerning the outcomes of previous and ongoing educational programs to determine how best to reach target audiences with information related to PI diseases. Systematically analyze the range of outreach efforts to determine 1) information reach, 2) frequency of message contact, and 3) interaction of messages from different organizations. Use evidence-based outcome assessments to determine awareness, knowledge, and uses of information from previous education and communication programs.
- Convene a working group of health communication specialists to establish campaign goals, audiences, and strategies, even as research continues and consensus is reached regarding disorders to include in a health communication campaign and case definitions and clinical recommendations are developed. The working group should
  - — determine additional formative research needed to assess target audiences' awareness, knowledge, and behaviors related to PI;
  - — develop or revise materials that are consistent with campaign goals;
  - — develop additional materials as needed to achieve campaign goals;
  - — pretest materials with target audiences;
  - — disseminate messages that are consistent with recommendations from pretesting, and
  - — include process and evidence-based outcome evaluations as part of campaign planning.

Conclusion

This report presents a framework for stakeholders and policy makers who will collaborate to define the future of an emerging and promising field of study that can markedly improve health in persons with PI diseases. The recommended interventions encompass multiple goals — helping children, educating clinicians, developing and maintaining awareness of PI diseases, and providing information for policy development and change. Additional efforts are needed to define priorities in future public health actions and associated costs and benefits. The proposed public health framework is critical for PI diseases and serves as a model for other genetic disorders that can benefit from early diagnosis and opportunities for interventions to improve health outcomes.

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Terms and Abbreviations Used in This Report*

ACCE	analytic validity; clinical validity; clinical utility; and ethical, legal, and social implications
ADA	adenosine deaminase gene
AICDA	activation-induced cytidine deaminase gene
allele	alternative form of a gene that exists at a specific gene location (locus) on a chromosome
analyte	substance measured by a laboratory test
APECED	autoimmune polyendocrinopathy with candidiasis and ectodermal dysplasia
autosome	nuclear chromosomes other than sex chromosomes; the diploid human genome consists of 46 chromosomes: 22 pairs of autosomes, and one pair of sex chromosomes (the X and Y chromosomes)
autosomal dominant	abnormal gene on one of the autosomal chromosomes from either parent, transmission of which can cause a particular trait or disorder
autosomal recessive	abnormal gene on one of the autosomal chromosomes from each parent, transmission of both abnormal genes is required to cause a particular trait or disorder
B cell	antibody-producing lymphocyte; a type of white blood cell
birth defect	defect present at birth, whether caused by mutant genes or by prenatal events that are not genetic
BTK	Bruton's tyrosine kinase gene
CF	cystic fibrosis
CFF	Cystic Fibrosis Foundation
CGD	chronic granulomatous disease
chromosome	one of the thread-like structures in the cell nucleus; consists of chromatin and carries genetic information (DNA); human cells normally contain 46 chromosomes (23 pairs)
CLIA	Clinical Laboratory Improvement Amendments

* Additional definitions are available at http://www.genome.gov/glossary.cfm.

codon	three-base sequence of DNA or RNA that specifies an amino acid
complement	a set of serum proteins that binds antigen-antibody complexes to kill microorganisms
CVID	common variable immunodeficiency
DBS	dried blood spot
deletion	particular kind of mutation; loss of a piece of DNA from a chromosome
DNA	deoxyribonucleic acid
EDA-ID	ectodermal dysplasia associated with immune deficiency
enzyme	protein that facilitates a specific biochemical reaction
ESID	European Society for Immunodeficiencies
exon	protein-coding DNA sequence of a gene
gene	functional and physical unit of heredity, consisting of a segment of DNA arranged linearly along a chromosome; the majority of genes contain the information for making a specific protein leading to a particular characteristic or function
gene product	biochemical material, either RNA or protein, resulting from expression of a gene
gene therapy	treatment of a genetic disorder by replacing, supplementing, or manipulating nonfunctional genes with normal genes
genetic marker	landmark for a target gene, either a detectable trait that is inherited with the gene or a distinctive segment of DNA
genetic testing	examining a sample of blood or other body fluid or tissue for biochemical, chromosomal, or genetic markers that indicate the presence or absence of genetic disease
genome	complete DNA sequence, containing all genetic information and supporting proteins, in the chromosomes of a person or species
genomics	study of the functions and interactions of all the genes in the genome, including their interactions with environmental factors
genotype	a person's genetic makeup, specifically the alleles present at specific gene loci
genotype/phenotype correlation	association between the presence of a certain mutation or mutations (genotype) and the resulting physical trait, abnormality, or pattern of abnormalities (phenotype)
HIV	human immunodeficiency virus
HTCs	hemophilia treatment centers
Human Genome Project	international research project to map each human gene and to completely sequence human DNA
IDF	Immune Deficiency Foundation
Ig	immunoglobulin
ILR2G	interleukin 2 receptor gamma gene
incidence	number or proportion of new cases of a specified condition among a population during a specified period
inherited	transmitted through genes from parents to offspring
insertion	type of mutation in which a DNA sequence is inserted into a gene, disrupting the normal structure and function of that gene
IRB	Institutional Review Board
IVIG	intravenous immunoglobulin
JAK3	Janus-associated kinase 3 gene
LAD	leukocyte adhesion defect
locus	position on a chromosome where a specific gene is located
microarray technology	methods for measuring expression of multiple genes simultaneously under specific conditions relative to baseline (i.e., up regulation or down regulation)
missense	a genetic mutation that alters the amino acids in the protein product of a gene
mRNA	messenger RNA
mutation	permanent heritable change in the molecular sequence of a gene
NADPH	nicotinamide-adenine dinucleotide phosphate

NBS	newborn screening
Negative predictive value	likelihood that a person with a negative test result is actually not affected by the disease
NHGRI	National Human Genome Research Institute
NIH	National Institutes of Health
nonsense	a genetic mutation in single base-pair substitution in DNA resulting in premature stop codons in the genetic code
NORD	National Organization for Rare Disorders
NSQAP	Newborn Screening Quality Assurance Program
PCR	polymerase chain reaction
penetrance	frequency with which a genotype manifests itself in a specific phenotype
phenotype	clinical presentation or expression of a specific gene or genes, environmental factors, or both
PI	primary immunodeficiency
PKU	phenylketonuria
positive predictive value	likelihood that a person with a positive test result is actually affected by the disease
prevalence	number or proportion of existing cases of a specified condition in a population
RAG	recombination-activating gene
regulatory (gene)	a genetic mutation that affects aspects of gene expression
RNA	ribonucleic acid
SCID	severe combined immunodeficiency
screening	testing on a population basis to identify persons at risk for developing specific disorders
sensitivity	frequency with which a test yields a positive result when the abnormality or disease in question is actually present in the person being tested
sequencing	process by which the nucleotide sequence is determined for a segment of DNA
sex chromosome	the X and Y chromosomes
single-gene disorder	a disorder caused by one or a pair of mutant alleles at a single locus
specificity	frequency with which a test yields a negative result when the abnormality or disease in question is not present in the person being tested
splice site	a genetic mutation that can lead to frameshift mutations
T cell	a white blood cell or lymphocyte that develops in the thymus and mediates cellular immune responses
TRECs	T-cell antigen receptor excision circles
UDC	universal data collection
WAS	Wiskott-Aldrich syndrome
X-linked recessive	genes transmitted on the X chromosome
XLA	X-linked agammaglobulinemia

Applying Genetic and Public Health Strategies to Primary Immunodeficiency

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Goal and Objectives

This *MMWR* provides recommendations regarding public health strategies for primary immunodeficiency (PI) diseases. These recommendations were prepared by CDC staff and other specialists in PI diseases after consultation with a multidisciplinary panel. The goal of this report is to familiarize readers with a public health framework for addressing health problems resulting from a group of primarily single-gene disorders. Upon completion of this continuing education activity, the reader should be able to describe 1) the four components of a public health framework; 2) how public health assessment can be applied to PI and other genetic diseases; 3) the framework for evaluating genetic tests, including analytic validity, clinical validity, clinical utility, and ethical, legal, and social considerations; 4) two public health interventions to increase early diagnosis and treatment for genetic diseases (i.e., newborn screening and early clinical recognition); and 5) the key components of an effective health education program for PI diseases.

To receive continuing education credit, please answer all of the following questions.

1. Primary immunodeficiency diseases are usually . . .
- A. single-gene disorders of the immune system.
- B. fatal without early treatment.
- C. disorders characterized by recurrent bacterial/viral infections.
- D. all of the above.

2. Common variable immunodeficiency (CVID) is characterized by all of the following features, except . . .
- A. low levels of immunoglobulin G, M, or A.
- B. recurrent infection of the respiratory or gastrointestinal tract.
- C. an increased incidence of lung cancer.
- D. death from chronic lung disease.

3. Population-based surveillance for PI diseases should involve . . .
- A. active assessment of inpatient hospitalization records, outpatient clinic records, and vital records in a defined geographic area.
- B. evaluation of population-based mortality data from death certificates.
- C. computerized inpatient databases from hospital discharge or managed care organizations.
- D. prevalence estimates based on case-based disease registries.
- E. all of the above.
- F. A, B, and C.

4. The goal of early clinical recognition is to . . .
- A. reduce disability and premature mortality from PI disease.
- B. identify newborns with PI disease.
- C. identify those persons with symptoms of PI diseases for referral to an immunologist.
- D. A and C.
- E. all of the above.

5. Which of the following is not true regarding newborn screening?
- A. Newborn screening programs were first begun to identify infants with phenylketonuria.
- B. Severe combined immunodeficiency (SCID) is a candidate for newborn screening because it is fatal during infancy without treatment and because intervention before appearance of clinical symptoms can improve outcomes.
- C. Newborn screening for SCID can be performed by screening for B-cell lymphopenia.
- D. Detecting specific DNA sequences for disease-causing alleles for SCID is possible by using dried blood spots.

6. The clinical validity of a genetic test is . . .
- A. the ability of a test to measure the gene of interest.
- B. dependent on the penetrance of the genetic mutation.
- C. focuses on the health outcomes associated with testing.
- D. reflective of the proportion of affected persons with a positive test.
- E. B and D.

7. Educational efforts for PI diseases need to . . .
- A. tailor messages to targeted groups of health-care providers.
- B. use outcome assessments to determine knowledge and uses of education messages.
- C. provide consistent messages regarding symptoms, screening, and management.
- D. include different strategies for disseminating information.
- E. be evidence-based.
- F. all of the above.

8. Diagnostic testing for T-cell disorders involves all of the following, except . . .
- A. complete blood count (CBC) with differential.
- B. lymphocyte phenotyping.
- C. mitogen stimulation.
- D. nitroblue tetrazolium (NBT).

9. Which of the following statements is true?
- A. Defects in Bruton's tyrosine kinase (*BTK*) gene results in defects of B-cell function.
- B. SCID caused by defects in the adenosine deaminase (*ADA*) gene is inherited as an X-linked disorder.
- C. Lack of CD18 results in a disorder known as Chédiak-Higashi.
- D. Patients with Wiskott-Aldrich syndrome have defective platelets caused by antiplatelet antibodies.

10. Indicate your work setting.
- A. State/local health department.
- B. Other public health setting.
- C. Hospital clinic/private practice.
- D. Managed care organization.
- E. Academic institution.
- F. Other.

11. Which best describes your professional activities?
- A. Physician.
- B. Nurse.
- C. Health educator.
- D. Office staff.
- E. Other.

12. I plan to use these recommendations as the basis for . . . (*Indicate all that apply.*)
- A. health education materials.
- B. insurance reimbursement policies.
- C. local practice guidelines.
- D. public policy.
- E. other.

13. Each month, approximately how many patients do you treat?

A. None.
B. 1–5.
C. 6–20.
D. 21–50.
E. 51–100.
F. >100.

14. How much time did you spend reading this report and completing the exam?

A. <2.0 hours.
B. >2.0 hours but <3.0 hours.
C. >3.0 hours but <4.0.
D. >4.0 hours.

15. After reading this report, I am confident I can describe the four components of a public health framework.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

16. After reading this report, I am confident I can describe how public health assessment can be applied to PI and other genetic diseases.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

17. After reading this report, I am confident I can describe the framework for evaluating genetic tests, including analytic validity, clinical validity, clinical utility, and ethical, legal, and social considerations.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

18. After reading this report, I am confident I can describe two public health interventions to increase early diagnosis and treatment for genetic diseases (i.e., newborn screening and early clinical recognition).

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

19. After reading this report, I am confident I can describe the key components of an effective health education program for PI diseases.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

(Continued on pg CE-4)

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January 16, 2004/Vol. 53/No. RR-1
Applying Public Health Strategies to Primary Immunodeficiency Diseases
A Potential Approach to Genetic Disorders

To receive continuing education credit, you must
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3.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	[ ]F		16.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E													
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13.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	[ ]F		26.	[ ]A	[ ]B	[ ]C	[ ]D	[ ]E	[ ]F												

Signature *Date I Completed Exam*

20. The objectives are relevant to the goal of this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

21. The teaching strategies used in this report (text, figures, and tables) were useful.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

22. Overall, the presentation of the report enhanced my ability to understand the material.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

23. These recommendations will affect my practice.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

24. The content of this activity was appropriate for my educational needs.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

25. The availability of continuing education credit influenced my decision to read this report.

A. Strongly agree.
B. Agree.
C. Neither agree nor disagree.
D. Disagree.
E. Strongly disagree.

26. How did you learn about this continuing education activity?

A. Internet.
B. Advertisement (e.g., fact sheet, *MMWR* cover, newsletter, or journal).
C. Coworker/supervisor.
D. Conference presentation.
E. *MMWR* subscription.
F. Other.

Correct answers for questions 1–9.

1. D; 2. C; 3. F; 4. D; 5. C; 6. E; 7. F; 8. D; 9. A.

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