Special Article

The Middle East and North Africa Diagnosis and Management Guidelines for Inborn Errors of Immunity

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Human inborn errors of immunity (IEI) are a group of 485 distinct genetic disorders affecting children and adults. Signs and symptoms of IEI are heterogeneous, and accurate diagnosis can be challenging and depends on the available human expertise and laboratory resources. The Middle East and North Africa (MENA) region has an increased prevalence of IEI because of the high rate of consanguinity with a predominance of autosomal recessive disorders. This area also exhibits more severe disease phenotypes compared with other regions, probably due to the delay in diagnosis. The MENA-IEI registry network has designed

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Abbreviations used
AR- Autosomal recessive
BCG- Bacillus Calmette-Guerin
CGD- Chronic granulomatous disease
CID- Combined immunodeficiencies
CMV- Cytomegalovirus
EBV- Epstein-Barr virus
ESID- European Society for Immunodeficiencies
G-CSF- Granulocyte colony-stimulating factor
HLA- Human leukocyte antigen
HSCT- Hematopoietic stem cell transplantation
IEI- Inborn errors of immunity
IFN-γ- Interferon-gamma
IgRT- Immunoglobulin replacement therapy
MENA- Middle East and North Africa
MIRN- MENA-IEI registry network
RAG- Recombination activating gene
SCID- Severe combined immunodeficiency
TRECs- T-cell receptor excision circles

protocols and guidelines for the diagnosis and treatment of IEI, taking into consideration the variable regional expertise and resources. These guidelines are primarily meant to improve the care of patients within the region, but can also be followed in other regions with similar patient populations. **© 2022 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2022;■:■-■)**

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Human inborn errors of immunity (IEI) are a heterogeneous group of inherited disorders characterized by recurrent infections, immune dysregulations, and malignancies. IEI are relatively rare diseases; however, the heterogeneity of clinical and immunologic phenotypes can result in underdiagnosis, which leads to inconsistent prevalence frequencies.[1-5] The recent Middle East and North Africa (MENA) registry study estimated the prevalence of IEI as 2.96 of 100,000, which is overall higher than in other regions of the world, creating a health concern about IEI in this area.[6]

The clinical and genetic diversities of IEI frequently pose challenges regarding establishing an accurate diagnosis and delivering appropriate therapy. However, the diagnosis should not be delayed, and treatment approaches should be promptly instituted by medical authorities, including primary care physicians (first-line referrals), specialists (second-line referrals mainly pediatricians, infectious diseases specialists, pulmonologists, hematologists, oncologists, gastroenterologists, and rheumatologists), and immunologists (third-line referrals). In this regard, several recommendations are available to guide and facilitate the diagnosis of IEI.[7-9] From 2011 onward, the European Society for Immunodeficiencies (ESID) has regularly updated the clinical diagnostic criteria regarding IEI.[5,10] Moreover, for molecular diagnosis and accurate classification, the International Union of Immunological Societies categorizes IEI into 10 subtypes to better define the clinical and mechanistic features of these diseases. This classification includes combined immunodeficiencies (CIDs), CIDs with syndromic features, predominantly antibody deficiencies, diseases of immune dysregulation, congenital defects of phagocytes, defects in intrinsic and innate immunity, autoinflammatory diseases, complement deficiencies, bone marrow failure syndromes, and phenocopies of IEI.[11-13] Recently, a Human Phenotype Ontology system has been integrated into IEI to gain better diagnostic capability for these disorders.[14] It is conceivable that pursuing the reported algorithms will improve the diagnosis and treatment of IEI; nevertheless, new regional-specific guidelines are also necessitated to cover all the local resources that can be helpful for early awareness of these diseases.

Regional differences in the genetic background indicated that some disease phenotypes and genetic defects are more relevant to the MENA region. The MENA and local area registries show bias toward autosomal recessive (AR) forms of diseases with higher frequencies of CID compared with European, Latin-American, and North American registries.[15-23] Heretofore, 161 of 485 described genes associated with IEI have been initially discovered in patients coming from the MENA region (33.1%; Figure 1, *A*, and Table E1, available in this article's Online Repository at www.jaci-inpractice.org), underlining the impact of this geographical region on IEI.[11,13,24] Furthermore, with the advances made in the genomic research era, novel defined genes increased exponentially in the region over time (Figure 1, *B*). However, albeit to the increased awareness among physicians, insufficient knowledge about IEI leads to diagnostic delays. In addition, untimely implementation of appropriate therapies with suboptimal health care delivery, the universal use of live-

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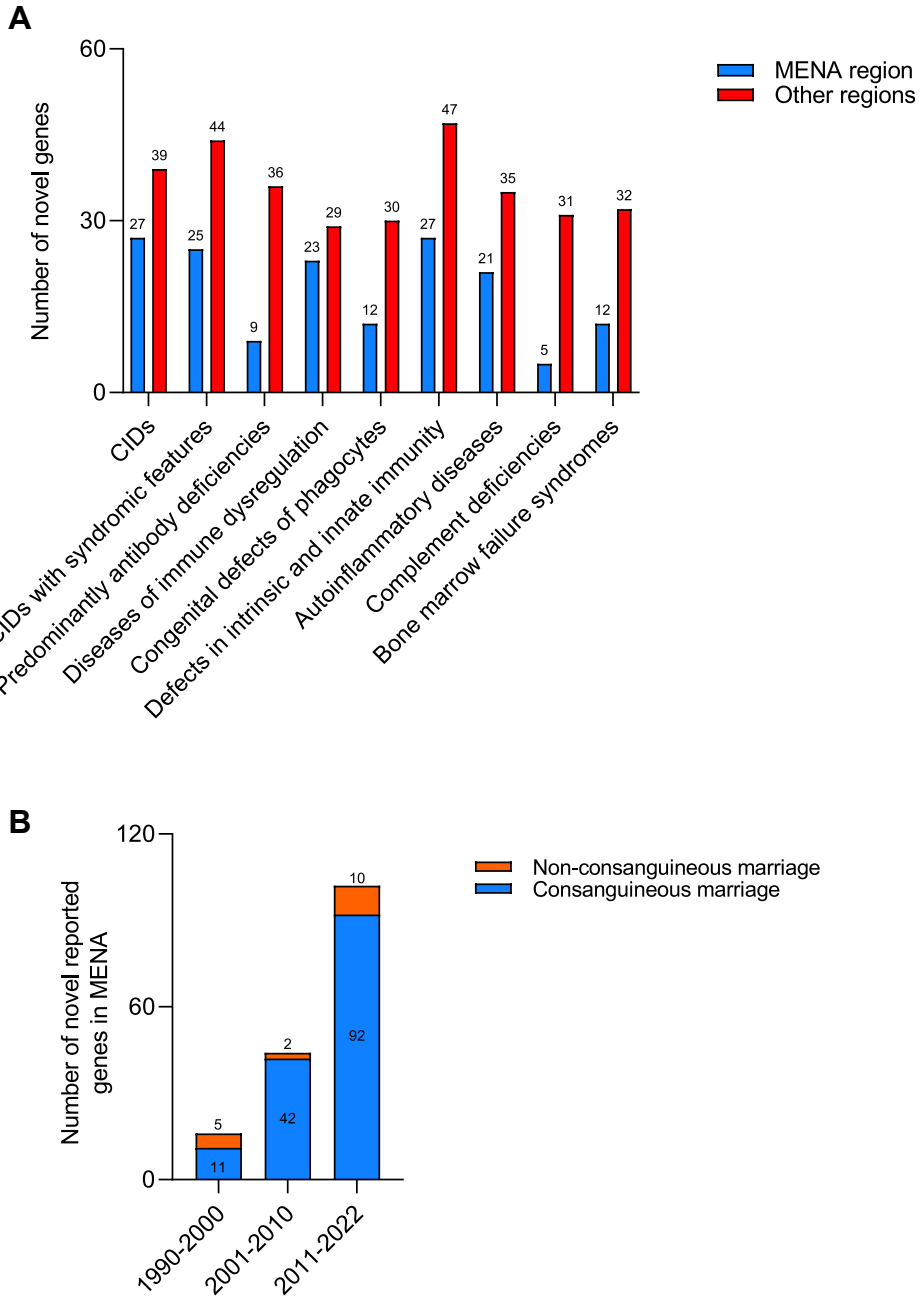

FIGURE 1. The role of the MENA region in the discovery of new IEI. (**A**) Novel diseases described between 1990 and 2022 in the MENA region compared with the other regions of the world. (**B**) The number of novel genes discovered in the last decades originating from patients in the MENA region. Different colors indicate the numbers of consanguineous and nonconsanguineous marriages. *CIDs*, Combined immunodeficiencies; *IEI*, inborn errors of immunity; *MENA*, Middle East and North Africa.

attenuated vaccinations like Bacillus Calmette-Guerin (BCG) and oral polio vaccine in early infancy, and lack of newborn screening are the main factors for the high mortality rate from IEI diseases in the MENA region.[25-37] For these reasons, a panel of expert clinical immunologists in the MENA-IEI registry network (MIRN) have reviewed the recent advances in the field of diagnosis and management of IEI and developed this new guideline pertaining to the MENA region to help primary, secondary, and tertiary care physicians in diagnosing and treating IEI. After a draft of the document was instituted, it was electronically distributed for the review and revision by the coauthors. These practical recommendations can also serve as a model for other regions in the world.

CONSENSUS ON DIAGNOSTIC AND THERAPEUTIC APPROACHES TO IEI

In 2020, the MENA-IEI registry was established with more than 17,000 patients to better understand and characterize the

TABLE I. MENA algorithms for diagnostic evaluation of IEI

First-line approach/general practitioners	Second-line approach/specialists and nonimmunology subspecialists	Third-line approach/immunologists	Differential diagnosis of IEI
Recurrent, multiple, severe infections with usual pathogens			
In pediatric age group • Four or more ear infections in 1 y • Two or more severe sinus infections in 1 y • Two or more pneumonias per year • Insufficient weight gain or growth delay • Persistent thrush or fungal infection on skin or other sites • Persistent skin viral or bacterial infections and eczema • Chronic diarrhea • Two or more months of treatment with antibiotics with little effect • Need for intravenous antibiotics to clear infections • Specific pathogen detection (see Table II) • Abnormal findings other than infections like autoimmunities (see Table E2 in this article's Online Repository at www.jaci-inpractice.org) • Family history of an IEI Abnormal physical signs: • Absence of tonsils • Hearing loss and perforation or scarring of tympanic membrane • Facial dysmorphisms • Abnormal lung auscultation • Lymphoproliferation • Failure to thrive • Digital clubbing • Partial cutaneous albinism and grey silvery hair • Delayed umbilical cord separation Blood tests: • Complete blood count with differential • Quantitative serum immunoglobulins (IgG, IgA, IgM, and IgE) compared with age-matched references	In pediatric age group: In addition to the first-line approach: • Recurrent deep skin or organ abscesses (eg, liver, lungs) • Two or more deep-seated infections (eg, septicemia, meningitis) • Exclusion of atopic disorders and functional abnormalities • Unusual organisms like PJ, disseminated CMV, and chronic EBV • Complete blood count with differential • Quantitative serum immunoglobulins (IgG, IgA, IgM, and IgE) • Lymphocyte subset analysis by flow cytometry for T, B, and NK cells (CD3, CD4, CD8, CD19, and CD16 and 56) • Specific antibody production to vaccine (hepatitis B, tetanus/diphtheria, pneumococcal, and meningococcal, *Haemophilus influenzae* B) • Isohemagglutinins (IgM antibodies to A and B blood group antigens) • Respiratory and gastrointestinal tract viral panels • HIV testing • Microbiological cultures (bacterial, fungal) • Acid-fast stain and culture for mycobacterial infection • Imaging appropriate for the site of infection • Puncture appropriate for the site of infection • Evaluation of hair pigment and shaft abnormalities by microscopy • Sweat chloride test to exclude cystic fibrosis • Nasal mucosa biopsy to rule out immotile cilia syndrome	Humoral immunity: • IgG subclasses (IgG1, IgG2, IgG3, and IgG4) • Detailed immunophenotyping for B-cell subpopulations (naïve, class-switched memory, transitional ($CD24^{high}CD38^{High}$), and $CD21^{low}$ B cells ($CD21^{low}CD38^{low}$)) • Flow expression of Bruton tyrosine kinase (BTK) • Kappa-deleting recombination excision circles (KRECs) analysis • *In vitro* IgG synthesis by stimulation of cultured PBMCs or purified B cells (in the presence of anti-CD40 and IL-4, lymphokines) • Mutation analysis (Sanger, targeted, whole exome, or genome sequencing) Cellular immunity: • Detailed immunophenotyping for T-cell subpopulations (naïve, memory, DNT cells, RTE, $CD3^{+}TCR\alpha/\beta$, and γ/δ proportions) • *In vitro* proliferation of T lymphocytes to mitogens (anti-CD3/CD28, PHA, PMA/IO) and specific antigens (candida, tetanus toxoid) • Delayed-type hypersensitivity skin tests (Candida) • T-cell receptor excision circles (TREC) analysis • TCR Vβ repertoire analysis • Enzyme activities (ADA, PNP) • Expression of activation markers (eg, CD40L, CD69, CD25, ICOS) after mitogenic stimulation • Specific cell surface markers (IL-2Rγc) • Intracellular staining (DOCK8, WASP, ZAP70) • Enumeration of MHCI and MHCII expressing cells • Phosphorylation studies (STAT1/STAT3/STAT5) • Production of cytokines by activated T lymphocytes • Karyotype analysis (ICF, AT, NBS) • FISH analysis (22q11.2 deletion) • Microarray (syndromic combined immunodeficiencies) • Biopsies from the skin, bone marrow, GI mucosa, lymph node, and thymus	B-cell defects T-cell defects Diseases of immune dysregulation Defects of phagocyte number or function Defects in intrinsic and innate immunity Complement deficiencies
In adult age group • Two or more ear infections in 1 y • Two or more sinus infections in 1 y in the absence of allergies • One pneumonia per year for more than 1 y • Chronic diarrhea with weight loss • Repeated viral infections (colds, herpes, warts, and condyloma)	In adult age group: In addition to the first-line approach: • Recurrent deep skin or organ abscesses (eg, liver, lungs) • Two or more deep-seated infections (eg, septicemia, meningitis) • Unusual organisms like PJ, disseminated CMV, and chronic EBV • Complete blood count with differential		

- Persistent thrush or fungal infection on the skin or other sites
- Recurrent need for intravenous antibiotics to clear infections
- Infection with harmless nontuberculous mycobacterial agents
- Specific pathogen detection (see Table II)
- Abnormal findings other than infections like autoimmunities (see Table E2 in this article's Online Repository at www.jaci-inpractice.org)
- Family history of an IEI

Abnormal physical signs:

- Absence of tonsils
- Hearing loss and perforation or scarring of tympanic membrane
- Facial dysmorphisms
- Abnormal lung auscultation
- Lymphoproliferation
- Digital clubbing

Blood tests:

- Complete blood count with differential
- Quantitative serum immunoglobulins (IgG, IgA, IgM, and IgE)
- Quantitative serum immunoglobulins—IgG, IgA, IgM, and IgE
- Lymphocyte subset analysis by flow cytometry for T, B, and NK cells (CD3, CD4, CD8, CD19, and CD16 and 56)
- Specific antibody production to vaccines (hepatitis B, tetanus/diphtheria, pneumococcal and meningococcal, and Haemophilus influenzae B)
- Isohemagglutinins (IgM antibodies to A and B blood group antigens)
- Respiratory and gastrointestinal tract viral panels
- HIV testing
- Microbiological cultures (bacterial, fungal)
- Acid-fast stain and culture for mycobacterial infection
- Imaging appropriate for the site of infection
- Puncture appropriate for the site of infection
- Sweat chloride test to exclude cystic fibrosis
- Mutation analysis (Sanger, targeted, whole exome or genome sequencing)

Phagocyte number and function-related immunity:

- Neutrophil counts, peripheral smear, and white blood cell turnover
- Antineutrophil antibodies
- Enzyme activities (MPO, G6PD, NADPH oxidase activity by DHR or NBT)
- Adhesion molecules by flow on granulocytes (CD18, CD11a/b/c)
- Bone marrow biopsy
- Chemotactic and phagocytic activities
- Mutation analysis (targeted, whole exome or genome sequencing)

Immune regulation−related immunity:

- Intracellular specific molecular staining (FOXP3, LRBA, CTLA4, etc)
- Treg cell number and suppression assay
- Broad autoantibody screening panel
- Lymphocyte-mediated cytotoxicity and degranulation—NK and CLT cells
- Determination of apoptosis by *in vitro* tests

Complement system:

- Total complement (CH50) and alternative complement (AH50) activities for screening
- Analysis of quantity and function of components
- Chemotactic activity of complement split products (C3a, C5a)
- Mutation analysis (Sanger, targeted, whole exome or genome sequencing)

ADA, Adenosine deaminase; *AT*, ataxia-telangiectasia; *CLT*, cytotoxic T lymphocyte; *CMV*, cytomegalovirus; *CTLA4*, cytotoxic T lymphocyte−associated protein 4; *DNT*, double negative T cell; *DHR*, dihydrorhodamine; *DOCK8*, dedicator of cytokinesis 8; *EBV*, Epstein-Barr virus; *FISH*, fluorescence *in situ* hybridization; *FOXP3*, forkhead box P3; *G6PD*, glucose-6-phosphate dehydrogenase; *ICF*, immunodeficiency, centromeric instability, facial dysmorphism; *ICOS*, inducible T-cell costimulatory; *IEI*, inborn errors of immunity; *LRBA*, LPS-responsive beige-like protein; *MENA*, Middle East and North Africa; *MPO*, myeloperoxidase; *NADPH*, nicotinamide-adenine dinucleotide phosphate; *NBS*, Nijmegen breakage syndrome; *NBT*, nitro blue tetrazolium; *PBMC*, peripheral blood mononuclear cell; *PHA*, phytohemagglutinin; *PJ*, *Pneumocystis jirovecii*; *PMA/IO*, phorbol myristate acetate/ionomycin; *PNP*, purine nucleoside phosphorylase; *RTE*, recent thymic emigrants; *STAT*, signal transducer and activator of transcription; *WASP*, Wiskott-Aldrich syndrome protein; *ZAP70*, zeta-chain−associated protein kinase 70.

TABLE II. The spectrum of infectious pathogens in IEI

Specific unusual pathogen detection	Differential diagnosis of IEI
Staphylococcus aureus	Antibody deficiencies Chronic granulomatous disease Hyper-IgE syndrome T-cell deficiencies (SCID/CID)
Streptococcus species	Antibody deficiencies IRAK4 deficiency NEMO deficiency MyD88 deficiency Complement deficiencies (C1q, C1r, C1s, C2, C3, C4, factor I) Congenital asplenia
Mycobacteria and Bacillus Calmette−Guerin	MSMD Chronic granulomatous disease T-cell deficiencies (SCID/CID) GATA2 and PD-1 deficiencies NEMO deficiency and NFKBIA GOF
Burkholderia cepacia	Chronic granulomatous disease
Mycoplasma/Ureaplasma	Antibody deficiencies
Neisseria meningitides	Deficiencies of complement system: C5, C6, C7, C8α/β/γ, C9, factor D, properdin, factor I and H Innate immune system defects: IRAK4 and MyD88 deficiencies
Nocardia spp.	Chronic granulomatous disease
Pseudomonas aeruginosa	Antibody deficiencies, congenital neutropenia, chronic granulomatous disease
Salmonella spp.	Chronic granulomatous disease MSMD
Serratia marcescens	Chronic granulomatous disease
Cytomegalovirus (CMV)	T-cell deficiencies (SCID/CID) APDS, VODI, NOS2, ZNFX1, and MCM10 deficiencies
Epstein-Barr virus (EBV)	EBV-related immune deficiencies (SAP, XIAP, CD27, CD70, CD137, CTPS1, RASGRP1, RLTPR, MAGT1, PRKCD, FAAP24, CD122, STK4, ITK, MCM4, CD16, IRF8, NFKB1, TET2, HELIOS, AIOLOS)
Herpes simplex virus (HSV)	T-cell deficiencies (SCID/CID) Herpes simplex encephalitis−related innate defects (TLR3, UNC-93B, TRAF3, TRIF, TBK1, IRF3, DBR1, and SNORA31 deficiencies) MCM4 deficiency APDS, STAT1 LOF/GOF Susceptibility to HSV type 2: ATG4A and MAPILC3B2 deficiencies
Influenza (severe)	TLR3 and IRF9 deficiencies
Human herpesvirus 8 (HHV-8)	Severe T-cell deficiencies, Wiskott-Aldrich syndrome, OX40 deficiency
Varicella (severe)	T-cell deficiencies (SCID/CID), CD16, MCM4, RNA polymerase III, TLR3, and CTPS1 deficiencies
Molluscum contagiosum	DOCK8, RLTPR, and POLD2 deficiencies
Human papilloma virus	Combined immunodeficiencies (DOCK8, ARTEMIS, STK4, RhoH, ADA, and GATA2 deficiencies) Warts, hypogammaglobulinemia, infections, myelokathexis syndrome (WHIM) EVER1 and EVER2 deficiencies (epidermodysplasia verruciformis) CD28 deficiency
JC (John Cunningham) virus	Combined immunodeficiencies (DOCK8 and SASH3 deficiencies)
SARS-CoV-2 (severe)	TLR3 (AD), UNC93B1 (AD), TICAM1 (AD), TBK1 (AD), IRF3 (AD), IRF7 (AD, AR), IFNAR1 (AR), IFNAR2 (AD), and X-chromosome−linked TLR7 deficiencies Pre-existing autoantibodies neutralizing IFN-α, IFN-β, and/or IFN-ω
Aspergillus	Chronic granulomatous disease Congenital neutropenia T-cell deficiencies (SCID/CID)
Candida	Chronic granulomatous disease Congenital neutropenia T-cell deficiencies (SCID/CID) Autoimmune polyendocrinopathy with candidiasis and ectodermal dystrophy CMC (STAT1 GOF, IL-17F, IL-17RA, IL17RC, ACT1, and JNK1 deficiencies) MSMD (IL12Rβ1 and IL12p40 deficiencies)

(continued)

TABLE II. *(Continued)*

Specific unusual pathogen detection	Differential diagnosis of IEI
Histoplasmosis	STAT1 GOF, DOCK8, CD40L, and GATA2 deficiencies
Deep dermatophytosis	CARD9 deficiency
Cryptosporidia	CD40/CD40L and Ig CSR deficiencies T-cell deficiencies (IL-21R, MHCII, NIK, DOCK8 deficiencies)
Giardia	Antibody deficiencies
Pneumocystis jirovecii	T-cell deficiencies (SCID/CID) NEMO deficiency
Toxoplasmosis	Severe T-cell deficiencies, Ig-CSR deficiencies
Immunodeficiency-related vaccine-derived poliovirus	SCID, XLA, CVID
Disseminated vaccine-strain measles after MMR vaccine	STAT2 deficiency

AD, Autosomal dominant; *ADA*, adenosine deaminase; *APDS*, activated phosphoinositide 3-kinase delta syndrome; *AR*, autosomal recessive; *CID*, combined immunodeficiency; *CMC*, chronic mucocutaneous candidiasis; *CSR*, class switch recombination; *CTPS1*, cytidine triphosphate synthetase 1; *CVID*, common variable immune deficiency; *EVER*, endoplasmic reticulum transmembrane proteins; *GOF*, gain-of-function; *IEI*, inborn errors of immunity; *IRAK1*, interleukin-1 receptor-associated kinase 4; *LOF*, loss-of-function; *MHC*, major histocompatibility complex; *MMR*, measles-mumps-rubella; *MSMD*, Mendelian susceptibility to mycobacterial disease; *NEMO*, nuclear factor-kappa B essential modulator; *RhoH*, Ras homolog gene family H; *SCID*, severe combined immunodeficiency; *STAT*, signal transducer and activator of transcription; *TLR*, toll-like receptor; *XLA*, X-linked agammaglobulinemia.

prevalence and clinical manifestations of IEI.[6] In general, the recommended diagnostic scope of IEI includes clinical evaluation, basic and functional immunological workup, genetic testing with regular follow-up and updates of the diagnosis, and clinical management as appropriate. To make a prompt diagnosis of IEI, it is essential to educate clinical experts capable of evaluating clinical findings and integrate these tips with basic and advanced functional testing. Thus, the panel of experts in the MENA network recognized the importance of providing clear guidelines that facilitate the diagnosis of patients with IEI and their referral to third-line physicians for definitive diagnosis and treatment.

GENERAL STATEMENTS FOR THE DIAGNOSTIC APPROACH TO IEI

Unifying the stepwise diagnostic approach by physicians will help diagnose patients and use the available resources most efficiently. Although the history of recurrent infections is accepted as a touchstone for diagnosis (Table I), family history of IEI, consanguinity, and sibling death due to IEI are also other significant signs for referring these patients to specialists or immunologists and would significantly lower the threshold for a diagnostic workup.[38] During the decision-making, it is also important to recognize that recurrent infections can be associated with many other disorders, including acquired immunodeficiencies, such as HIV infection, rheumatological disorders, malignancies, immunosuppressive drug usage, and neutralizing autoantibodies, which could be a phenocopy of IEI.[8,39] Apart from infections, it should be kept in mind that autoimmune and inflammatory diseases like autoimmune cytopenia, inflammatory bowel disease, autoimmune endocrinopathies, and severe dermatitis can be other presenting features of IEI. Especially patients with more than 1 autoimmune manifestation should be prioritized for evaluation (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). To establish a timely diagnosis and initiate effective therapeutic options, MIRN suggests using the specific aspects mentioned in Tables I and E2 (available in this article's Online Repository at www.jaci-inpractice.org) and focusing on the common pathogens (Table II) and disorders (Table III) with integrated diagnostic criteria (Table IV). In the first- and second-line referrals by general practitioners, pediatricians, and infectious disease specialists, the assessment of complete blood counts, quantitative serum immunoglobulin levels, and lymphocyte subpopulations, and the evaluation of the natural or postvaccine immune responses are crucial for early diagnosis (Figure 2). On the other hand, awareness of the common IEI (especially the AR forms) in the MENA region could enhance the likelihood of a genetic diagnosis using a targeted single-gene sequencing approach, particularly in areas with low resources, such as in the case of leukocyte adhesion defect type 1 and major histocompatibility complex class II deficiency, which are commonly observed in North African patients,[16,20,40] Janus kinase 3 deficiency with $T^{-}B^{+}$ phenotype in Egypt,[41] and recombination activating gene (RAG1) and RAG2 deficiencies as the most common cause of CID in many MENA countries.[3,29,42,43] For other cases, next-generation sequencing approaches including sequencing a targeted gene panel or whole exome/genomes can be used to establish the molecular diagnoses in many patients with IEI. These molecular techniques are increasingly being used in certain centers in the MENA region.[15,16,44-48] It is worth noting that because of the delay in diagnosis and high incidence of severe(S)CID, the implementation of newborn screening using T-cell receptor excision circles (TRECs) for early diagnosis is a mandatory task for the region. However, the restricted resources hinder this program from wide use. Currently, Lebanon is the only country in the region where newborn screening for SCID is performed at the national level using the TREC assay, whereas a few other countries undertook pilot research studies to implement newborn screening.[35,43,49,50] In the near future, governmental policies regarding newborn screening should initiate and negotiate to establish the diagnosis as much earlier.

The MENA-IEI diagnostic criteria we are proposing are tailored toward centers with limited expertise and resources in recognizing and diagnosing IEI, respectively, and include clinical features combined with basic immunological assessment that can be easily implemented in daily practices with minimal requirements of sophisticated tests. We believe that this integrated approach will lead to a rapid and cost-effective diagnosis of IEI in the MENA region. Of note, after a definitive diagnosis, timely genetic counseling for the patient and family should be offered to minimize the occurrence of diseases.[51]

TABLE III. Common IEI in the MENA region

Disease	Symptoms	Special notes
Severe combined immunodeficiency	Severe/disseminated viral and bacterial infections (CMV, EBV, HSV, MC, HPV, *Staphylococcus aureus,* and *Pseudomonas*), opportunistic infections (PJ, BCG, *Candida*, *Aspergillus*, *Cryptosporidium*, and Giardiasis), erythroderma, failure to thrive, diarrhea, dysmorphic features (Cernunnos, DNA ligase IV, DNA-PKcs deficiencies), bone abnormalities (ADA)	Autosomal recessive forms are more prevalent than in other regions (the most common is *RAG*-related SCIDs). Special features of Omenn syndrome are erythroderma, alopecia, organomegaly, high IgE and eosinophilia. Low lymphocyte number in classical SCID is an important warning sign for diagnosis (<1 y: <3000/mm^3, >1 y: <1500/mm^3). Granulomatous lesions can be observed in atypical SCID patients
Combined immunodeficiency	Severe/disseminated viral and bacterial infections (CMV, EBV, HSV, MC, HPV, varicella, *Staphylococcus aureus,* and *Pseudomonas*), opportunistic infections (PJ, BCG, *Candida*, *Aspergillus*, *Cryptosporidium*, and Giardiasis), autoimmunities (mainly immune-mediated cytopenias), diarrhea, failure to thrive, hepatitis, vasculitis, lymphoproliferation, and malignancies (mainly leukemia and lymphoma)	Autosomal recessive forms are more common. Persistent thrombocytopenia, eczema, and bleeding are suggestive of Wiskott-Aldrich syndrome
Ataxia-telangiectasia	Ataxia with telangiectasia, recurrent infections, malignancies (leukemia, lymphoma)	Increased blood α-fetoprotein and radiosensitivity. Low IgA, IgE, and IgG subclasses. High IgM in some patients
MHC class II deficiency	Respiratory and gastrointestinal infections, chronic diarrhea with failure to thrive, hepatitis, and sclerosing cholangitis. Decreased CD4$^+$ T cells with reduced MHCII expression	Most patients are of North African origin (Tunisia, Morocco, and Algeria) with a common founder mutation: c.338-25_338del26 in the *RFXANK* gene
DiGeorge syndrome	Dysmorphic features (low-ear set, micrognathia, hypertelorism, short palpebral fissure, and velopalatal insufficiency), hypoparathyroidism; cardiac malformation, intellectual disability, umbilical hernia, and renal abnormalities	22q11.2 large deletion is the most common form (autosomal dominant or *de novo*). Consider TBX1 deficiency and CHARGE syndrome in 22q11.2 negative patients
Hyper-IgE syndrome	Recurrent infections, eczema, coarse face, hyperextensibility, eosinophilia, high IgE level, skin and organ abscesses	DOCK8 deficiency is higher than other forms (STAT3-DN, PGM3, IL6ST, IL6R, and ZNF341)
Other combined immunodeficiency syndromes	ICF syndromes (types 1, 2, 3, and 4)	Facial dysmorphism, hypo/agammaglobulinemia with centromeric instability of chromosomes 1, 9, and 16
Agammaglobulinemia	Recurrent otitis media, sinusitis, bronchitis, pneumonia by encapsulated pyogenic bacteria, namely *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus.* Gastrointestinal infections	X-linked agammaglobulinemia is more common than other autosomal types
Common variable immunodeficiency	Recurrent sinopulmonary infections with encapsulated bacteria, gastrointestinal infections, autoimmunity, granulomatous disease, and lymphoproliferation	Low IgG and IgA and/or IgM with impaired memory B-cell formation and antibody responses. Usually diagnosed beyond 2 y
Other antibody deficiencies	APDS types 1 and 2	APDS1 is more common than APDS2. Both are characterized by recurrent respiratory tract infections, bronchiectasis, herpesvirus infections, lymphoproliferation, autoimmunity, lymphoma, elevated IgM, and transitional B cells with low memory B and naïve T cells

(continued)

TABLE III. *(Continued)*

Disease	Symptoms	Special notes
Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome	Autoimmune enteropathy, early-onset diabetes, eczema, multiple autoimmunities (thyroiditis, hemolytic anemia, thrombocytopenia, hepatitis), and failure to thrive	X-linked disorder. Patients usually have high serum IgE and IgA levels. Lack/reduced $CD4^+CD25^+FOXP3^+$ regulatory T cells with impaired suppressive function. Atypical IPEX patients can present late with localized symptoms like chronic diarrhea, failure to thrive, and organ-specific autoimmunities
Familial hemophagocytic lymphohistiocytosis	Fever, HSM, hemophagocytosis, and cytopenias	Perforin deficiency is the most common observed defect
Other immune dysregulation disorders	LRBA deficiency and CTLA4 insufficiency	LRBA deficiency is detected more than CTLA4 insufficiency. Both exhibit recurrent infections, hypogammaglobulinemia, autoimmunities (cytopenias, type 1 DM, arthritis), enteropathy, interstitial lung disease, and lymphoproliferation
Severe congenital neutropenia	Skin and organs abscesses, gingivitis, umbilical cord separation defect, severe bacterial and fungal infections, susceptibility to MDS and leukemia	Absolute neutrophil counts are below 500/mm^3. HAX1 and G6PC3 are more common than ELANE deficiency
Chronic granulomatous disease	Deep-seated infection, abscess with granuloma formation, severe bacterial and fungal infections, and osteomyelitis	Autosomal recessive forms (P22, P47, P67) are frequently observed followed by X-linked (gp91)
Mendelian susceptibility to mycobacterial diseases (MSMD)	Severe mycobacterial and *Salmonella* species infections, disseminated BCG disease (BCGosis)	*IL12RB1* is the most frequent known genetic cause of MSMD
Chronic mucocutaneous candidiasis	Chronic skin and mucous membrane fungal infections, folliculitis (IL-17RA and IL-17F deficiencies), autoimmunities (cytopenias, diabetes, thyroiditis)—STAT1 GOF	STAT1 gain-of-function is the most common observed disorder
Complement deficiency	Recurrent bacterial infections (encapsulated strains: *Streptococcus pneumoniae* and *Haemophilus influenzae, Neisseria* species), angioedema, autoimmunity, atypical hemolytic-uremic syndrome, and protein-losing enteropathy	Autosomal recessive forms are more common

ADA, Adenosine deaminase, *APDS*, activated phosphoinositide 3-kinase delta syndrome; *BCG*, Bacillus Calmette-Guerin; *CHARGE*, coloboma, heart defects, atresia choanae, growth retardation, genital and ear abnormalities; *CMV*, cytomegalovirus; *CTLA4*, cytotoxic T lymphocyte–associated protein 4; *DN*, double negative; *EBV*, Epstein-Barr virus; *ELANE*, neutrophil elastase; *G6PC3*, glucose-6-phosphatase catalytic subunit 3; *GOF*, gain-of-function; *HAX1*, HCLS1 associated protein X-1; *HPV*, human papillomavirus; *HSM*, hepatosplenomegaly; *HSV*, herpes simplex virus; *ICF*, immune deficiency centromeric instability and facial dysmorphism; *IEI*, inborn errors of immunity; *IPEX*, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; *LRBA*, LPS-responsive beige-like protein; *MC*, molluscum contagiosum; *MDS*, myelodysplastic syndrome; *MENA*, Middle East and North Africa; *MHC*, major histocompatibility complex; *PGM3*, phosphoglucomutase 3; *PJ*, *Pneumocystis jirovecii*; *RAG*, recombinant activating gene; *STAT*, signal transducer and activator of transcription.

GENERAL STATEMENTS FOR THE THERAPEUTIC APPROACH TO IEI

Establishing an early and correct diagnosis helps implement specific and proper treatments. The presented MENA therapeutic guideline provides major management aspects for IEI disorders and includes cyclic antimicrobial prophylaxis, immunoglobulin replacement therapy (IgRT), and hematopoietic stem cell transplantation (HSCT) (Table V).[52] Furthermore, it includes recommendations on vaccinations for special populations with immunodeficiencies. The IgRT effectively reduces infections and related complications, especially in patients with humoral immunodeficiency, CIDs, and some forms of immune dysregulation.[53-55] All patients receiving IgRT should be subjected to regular evaluation for efficacy and adverse reactions. According to the marketing availability, subcutaneously delivered immunoglobulin products can be considered to address patient preferences and improve their compliance. For those with the unavailability of IgRT in the MENA region, cyclic use of prophylactic antibiotics continues to be the main treatment regimen.

Other therapeutic aspects, including antimicrobial prophylaxis and specific therapies for unique IEI, are presented in Tables V and VI. Diagnosis of different phenotypes (severe, Omenn, and atypical forms—Tables III and IV) of SCIDs is critical and the institution of HSCT as a definitive therapy should be a medical emergency. In this regard, a full-time contact number for an immunology specialist is a must in the IEI third-level care.[56] SCIDs have a diverse genetic etiology, and to date there are 18 known SCID-related genes.[13] They can vary in their prevalence across different populations depending on genetic founder effects and the prevailing frequency of consanguinity. The latter factor is

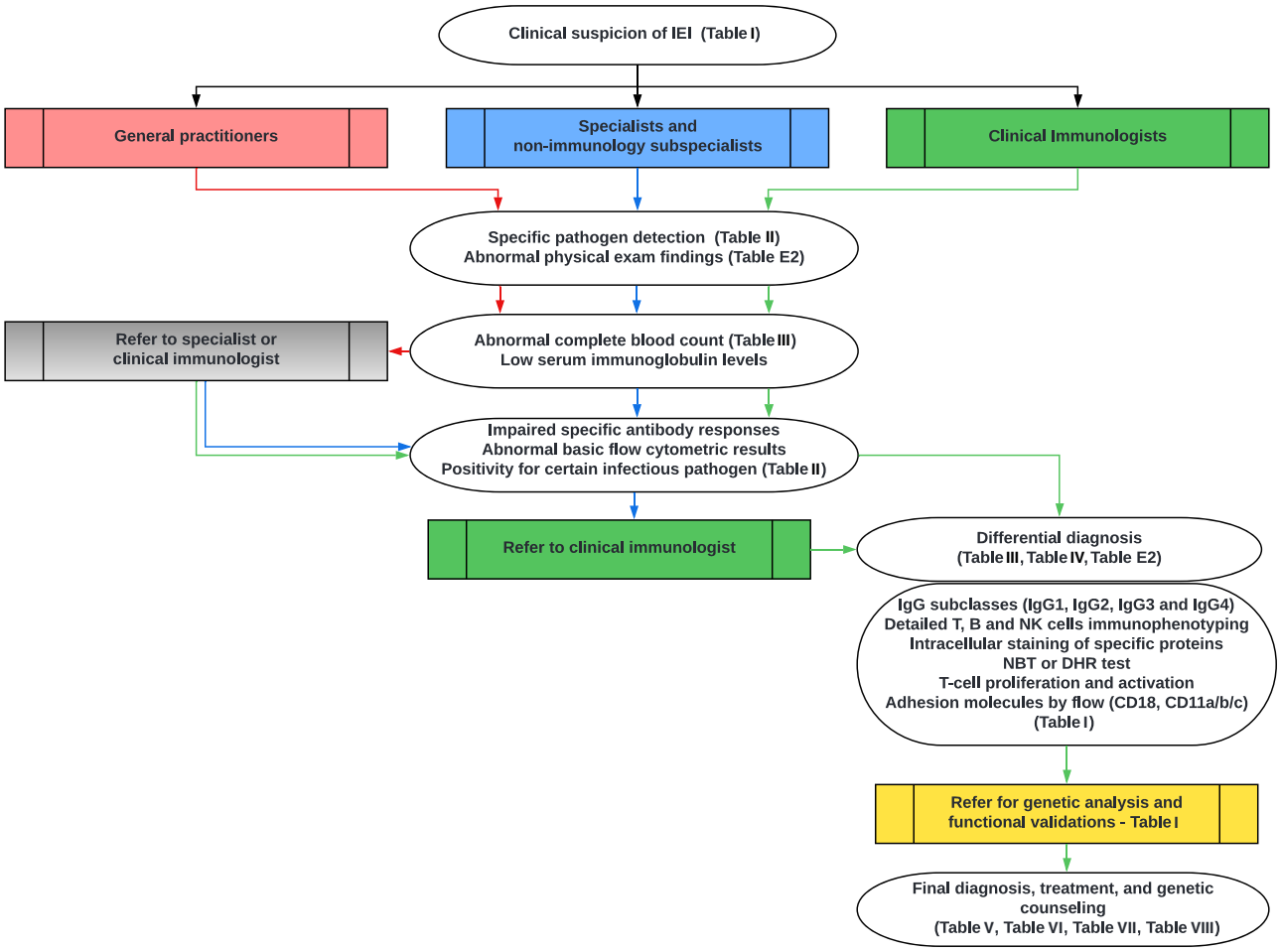

FIGURE 2. A flowchart for diagnosis and treatment of IEI. Each color shows the consecutive task steps of the physicians. General practitioners—red, specialists and nonimmunology subspecialists—blue, clinical immunologist—green. *DHR*, Dihydrorhodamine, *IEI*, inborn errors of immunity; *NBT*, nitro blue tetrazolium.

particularly relevant to the AR forms of SCIDs in the MENA region.[2,28,57-59] In this respect, the most common immune phenotype in MENA is $T^{-}B^{-}NK^{+}$ due to *RAG1* and *RAG2* mutations.[3,45,57,60,61] In general, diagnostic delay and pre-existing infections adversely affect the survival rate of patients with SCID after HSCT.[21,58,62] Notable findings related to SCID in several reports from the MENA area studies are the late age of diagnosis with a high incidence of lung infections, sepsis, and cytomegalovirus (CMV) disease, which are known as negative predictors of favorable prognosis.[58,59,63,64] Viral infections cause significant morbidity and mortality in SCID; thus, routine screening for CMV, Epstein-Barr virus (EBV), herpes simplex virus, adenovirus, influenza, and respiratory syncytial virus is recommended.[65] However, a special issue is the unreliability of serological tests in this patient group. Therefore, polymerase chain reaction—based analysis should be preferred and ordered as early as possible for the diagnosis and monitorization of viral loads.[56] In all patients with SCID, prophylaxis should be started for *Pneumocystis jirovecii* and fungal pathogens. In terms of viral prophylaxis, there is no consensus among centers; however, valganciclovir is a less toxic antiviral agent and can be considered in some patients with SCID with a high risk of CMV infection (Table VI).

BCG vaccination, a live attenuated vaccine form of *Mycobacterium bovis*, is a part of the routine childhood vaccination program in the MENA region due to the endemic *Mycobacterium tuberculosis* infection.[25,28,57] It is administered in early infancy (within the first few days or months from birth) before IEI is diagnosed. Therefore, when compared with the ESID and the Primary Immune Deficiency Treatment Consortium data, BCG complications are more frequently reported in patients with SCID in the MENA region.[66-69] Other patients with other IEI such as phagocytosis defects (chronic granulomatous disease [CGD]) and mendelian susceptibility to mycobacterial disease are also prone to BCG-related complications.[70] For these reasons, patients with SCID or CID who received BCG before transplantation should be commenced on antituberculosis prophylaxis, ideally including isoniazid and rifampicin (Table VI). The chance of BCG-related complications can be reduced by instating newborn screening programs for SCID or by deferring

TABLE IV. MENA-IEI criteria for diagnostic approaches

Approach to cellular immune deficiencies
Severe combined immunodeficiencies
Patients with all the following:
I Life-threatening infections at infancy: severe/disseminated viral and bacterial infections (CMV, EBV, HSV, MC, HPV, *Pseudomonas*), opportunistic infections (PJ, BCG, *Candida*, *Aspergillus*, *Cryptosporidium*, and Giardiasis)
II Absence or a very low number of T cells ($CD3^+$ T cells $<300/mm^3$) and no or very low T-cell proliferation (<10% of lower limit of normal)
III Absence or very low naive $CD4^+$ ($CD3^+CD4^+CD45RA^+$) and/or $CD8^+$ ($CD3^+CD8^+CD45RA^+$) T cells, and recent thymic emigrants
IV Presence of maternal T cells engraftment (if available to analyze)
Atypical SCID
Patients with all the following:
I Severe/disseminated viral and bacterial infections (CMV, EBV, HSV, MC, HPV, varicella, and *Pseudomonas*), opportunistic infections (PJ, BCG, *Candida*, *Aspergillus*, *Cryptosporidium*, and Giardiasis)
II Decreased number of $CD3^+$ T cells (<2 y: $<1000/mm^3$; 2-4 y $<800/mm^3$; >4 y $<600/mm^3$)
III Reduced naive $CD4^+$ ($CD3^+CD4^+CD45RA^+$) and/or $CD8^+$ ($CD3^+CD8^+CD45RA^+$) T cells, elevated $CD3^+$ $TCR^{\gamma/\delta}$ T cells (in some cases)
IV Reduced T-cell proliferation (<30% of the normal control)
V Absence of maternal T cells engraftment (if available to analyze)
Omenn syndrome
Patients with all the following:
I Exfoliative dermatitis and recurrent infections within the first year of life
II Alopecia, hepatosplenomegaly, lymphadenopathy, diarrhea, and failure to thrive
III High eosinophil number and serum IgE level
IV Reduced number of T cells (usually $CD3^+$ T cells $\geq 300/mm^3$) with memory phenotype ($CD45RO^+$), and decreased T-cell proliferation
V Absence of maternal T cells engraftment (if available to analyze)
Combined immunodeficiencies
Required criteria:
I Reduced number of T cells (compared with age-matched reference values, but usually $CD3^+$ T cell is $>300/mm^3$) and decreased T-cell proliferation
II Reduced naive $CD4^+$ ($CD3^+CD4^+CD45RA^+$) and/or $CD8^+$ ($CD3^+CD8^+CD45RA^+$) T cells, elevated $CD3^+$ $TCR^{\gamma/\delta}$ T cells (in some cases)
At least one of the following:
I Severe/disseminated viral and bacterial infections (CMV, EBV, HSV, MC, HPV, varicella, and *Pseudomonas*), opportunistic infections (PJ, BCG, *Candida*, *Aspergillus*, *Cryptosporidium*, and Giardiasis)
II Autoimmunities (mainly immune-mediated cytopenias)
III Chronic diarrhea
IV Failure to thrive
V Lymphoproliferation
VI Malignancies (mainly leukemia and lymphoma)
Hyper-IgM syndrome (CD40 and CD40 ligand deficiencies)
Patients with all the following:
I Recurrent infections and/or opportunistic infections like cryptosporidium and PJ, autoimmunities (neutropenia, hemolytic anemia), liver disease (hepatitis, sclerosing cholangitis), and malignancy (lymphoma, carcinomas affecting the liver, pancreas, biliary tree)
II Normal or elevated IgM (measured at least twice) with low IgG, IgA, and IgE
III Impaired memory B-cell formation
IV Normal T-cell count (in majority of patients)
Approach to B-cell defects
Common variable immune deficiency
Patients with all the following:
I The onset of immunodeficiency at greater than 4 y of age
II Recurrent sinopulmonary infections with encapsulated bacteria, recurrent gastrointestinal infections, autoimmunity, and lymphoproliferation
III Low IgG and IgA and/or IgM with impaired memory B-cell formation and antibody responses (at least to 1 T-dependent or T-independent antigens)
IV Exclusion of severe T-cell deficiency ($CD4^+$ T-cell count $>200/mm^3$)
V Exclusion of secondary causes of hypogammaglobulinemia
Selective IgA deficiency
Patients with all the following:
I Increased susceptibility to infection and/or autoimmune manifestations but most of patients are asymptomatic
II Very low serum IgA level (<7 mg/dL after 4 y of age)
III Normal IgG and IgM levels
IV Normal antibody responses and immunophenotyping
V Exclude secondary causes of hypogammaglobulinemia
VI Intact cellular immunity

(continued)

TABLE IV. *(Continued)*

Approach to cellular immune deficiencies
Transient hypogammaglobulinemia
Patients with all the following:
I Recurrent sinopulmonary infections
II At least 2 times age-related low IgG (<-2 SD of normal reference values), could be accompanied by low IgA and/or IgM
III Recovery at 5 y of age (can delay in some patients)
IV Normal antibody responses and immunophenotyping
V Intact cellular immunity
VI Exclude secondary causes of hypogammaglobulinemia
Unclassified hypogammaglobulinemia
Patients with all the following:
I Recurrent sinopulmonary infections
II Persistent low serum IgG levels could be accompanied by low IgA and/or IgM levels (after 5 y of age)
III Normal antibody responses and immunophenotyping
IV Intact cellular immunity
V Exclude secondary causes of hypogammaglobulinemia
Unclassified antibody deficiency
Patients with all the following:
I Recurrent sinopulmonary and gastrointestinal infections, autoimmunity, and lymphoproliferation
II Persistent low serum IgG or IgA or IgM levels (after 2 yr of age)
III Impaired antibody responses
IV Intact cellular immunity
V Exclude secondary causes of hypogammaglobulinemia
Agammaglobulinemia
Patients with all the following:
I Recurrent sinopulmonary and gastrointestinal infections, serious infections in the bloodstream, central nervous system, internal organs, vaccine-associated paralytic poliomyelitis
II Extremely low levels of all types of immunoglobulins
III Low numbers of B cells (<2%)
IV Impaired antibody responses
V Intact cellular immunity
IgG subclass deficiency
Patients with all the following:
I Recurrent sinopulmonary and gastrointestinal infections
II Normal serum IgG, A and M levels
III Low levels of one or more IgG subclass (< -2 standard deviation of mean age levels)
IV Impaired antibody responses to antigens in some patients (especially polysaccharide antigens)
V Intact cellular immunity
Approach to phagocytosis defects
Congenital neutropenia
Patients with all the following:
I Early-onset recurrent bacterial and fungal infections
II Abscesses (skin and deep-seated), oral ulcers, gingivitis, cutaneous infections, omphalitis, otitis, pneumonia
III Absolute neutrophil count less than 500/mm^3, measured at least twice
IV Exclusion of secondary causes of neutropenia (including immune-mediated neutropenia)
Leukocyte adhesion deficiency
Patients with at least 3 of the following:
I Recurrent, life-threatening bacterial infections
II Delayed umbilical cord separation and omphalitis
III Nonpurulent, necrotizing infections of the skin and mucus membranes
IV Severe gingivitis and chronic periodontitis
V Persistent leukocytosis and neutrophilia
VI Defective expression of CD18 on granulocytes (less than 5% of normal) (LAD-1)
VII Short stature, mental retardation and facial dysmorphisms (LAD-2)
VIII Bleeding tendency (LAD-3)

(continued)

TABLE IV. *(Continued)*

Approach to cellular immune deficiencies
Chronic granulomatous disease
Patients with at least 2 of the following:
I Severe infections such as pneumonia, cutaneous and deep tissue abscesses, lymphadenitis, osteomyelitis, and septicemia
II Bacterial (*Burkholderia, Nocardia, Staphylococcus aureus, Serratia, Klebsiella, Salmonella,* mycobacteria) and fungal infections (*Candida, Aspergillus*)
III Inflammatory manifestations (colitis, skin, and deep-seated granulomata-gastrointestinal or urogenital)
IV Autoimmune manifestations (discoid and systemic lupus erythematosus, idiopathic thrombocytopenic purpura, juvenile idiopathic arthritis)
V Abnormal nitroblue tetrazolium or dihydrorhodamine tests in activated neutrophils
Approach to immune dysregulation disorders
Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX)
Patients with at least 2 of the following:
I Male patients with autoimmune enteropathy, early-onset diabetes, eczema, multiple autoimmunities (thyroiditis, cytopenias, hepatitis), failure to thrive
II Early-onset recurrent bacterial and viral infections
III High serum IgE and IgA levels
IV Lack/reduced number or impaired function of $CD4^+CD25^+FOXP^+$ regulatory T cells (in some cases Treg number can be normal)
Lipopolysaccharide-responsive beige-like anchor (LRBA) deficiency (autosomal recessive inheritance)
Patients with at least one of the following:
I Recurrent infections
II Autoimmunities (cytopenias, type 1 DM, arthritis)
III Enteropathy
IV Interstitial lung disease
V Lymphoproliferation
Laboratory criteria (all of the following):
I Low $CD4^+FOXP3^+$ regulatory T cells
II Both low LRBA and CTLA4 expressions
Cytotoxic T lymphocyte–associated antigen-4 (CTLA-4) insufficiency (autosomal dominant inheritance)
Patients with at least one of the following:
I Recurrent infections
II Autoimmunities (cytopenias, type 1 DM, arthritis)
III Enteropathy
IV Interstitial lung disease
V Lymphoproliferation
Laboratory criteria (all of the following):
I Low $CD4^+FOXP3^+$ regulatory T cells
II Low CTLA-4 but normal LRBA protein expression (some patients with missense mutation can exhibit normal CTLA-4 expression)

BCG, Bacillus Calmette-Guerin; *CMV*, cytomegalovirus; *DM*, diabetes mellitus; *EBV*, Epstein-Barr virus; *HPV*, human papilloma virus; *HSV*, herpes simplex virus; *IEI*, inborn errors of immunity; *LAD*, leukocyte adhesion deficiency; *MC*, molluscum contagiosum; *PJ*, *Pneumocystis jirovecii*.

the age of vaccine administration until performing a complete immunological assessment by a specialist, especially in families with a history of IEI.

DNA repair defects including Artemis, NHEJ1, DNA ligase IV deficiencies, Nijmegen breakage syndrome, Bloom syndrome, Ataxia-telangiectasia, and Riddle syndrome are associated with radiosensitivity; therefore, radiation exposure should be avoided as much as possible in this group.

TARGETED THERAPIES AND SPECIAL TIPS IN IEI MANAGEMENT

Granulocyte colony-stimulating factor (G-CSF) and interferon-gamma (IFN-γ) therapies are 2 main cytokines essentially used to treat phagocytic defects.[71-74] G-CSF is regularly administered to patients suffering from severe neutropenia. For most patients, G-CSF is administered on a daily dosage of 5-20 μg/kg by subcutaneous injection, adjusted according to the neutrophil blood levels. Clinical immunologists should also consider using G-CSF to treat patients with resistant candidiasis (eg, in cases with signal transducer and activator of transcription 1 gain-of-function) and invasive fungal infections (caspase recruitment domain containing protein 9 deficiency). G-CSF positively regulates IL-17 levels and thus enhances neutrophil recruitment and function requiring for fungal immunity.[74]

In addition to antibacterial and antifungal prophylaxis, IFN-γ can be used in the treatment of CGD, which is common in the MENA region, particularly the p47-deficient AR form.[20,73] IFN-γ acts on macrophages and other cells and activates them, causing an increase of macrophage killing and antigen-presenting abilities. As a potent activator, IFN-γ has side effects such as fever, weight loss, fatigue, and gastrointestinal complications. The average required dose is 50 $\mu g/m^2$ of body surface area. The drug is usually administrated by subcutaneous injection as 3 times a week. Higher doses of IFN-γ (200 $\mu g/m^2$) can be used for mycobacterial infections in the partial forms of IFN-γ receptor deficiency and in autosomal recessive IL-12Rβ1 deficiency.[75,76]

The curative treatment of some IEI can be achieved by HSCT, especially in CIDs, phagocytosis disorders, and some immune dysregulation disorders (familial hemophagocytic lymphohistiocytosis, immunodysregulation polyendocrinopathy

TABLE V. MENA guidelines for different IEI management

Disease	Immunoglobulin replacement	Hematopoietic stem cell transplantation	Vaccination	Special treatment
Severe combined immunodeficiency (SCID)	Yes	Yes	Avoid live vaccines†	Antimicrobial treatment and prophylaxis§ PJP prophylaxis CMV(−) irradiated blood products with a leukocyte filter Breastfeeding avoidance to prevent CMV transmission (more details in Table VI) Immunosuppressive as required to control autoimmunities (Omenn syndrome and atypical SCID)‖ Recombinant ADA enzyme Gene therapy for IL2RG and ADA deficiencies¶ Avoid radiation exposure in radiosensitive SCIDs
Combined immunodeficiency	Yes	Yes	Avoid live vaccines†	Antimicrobial treatment and prophylaxis PJP prophylaxis CMV(−) irradiated blood products with a leukocyte filter G-CSF for CD40/CD40L deficiency with neutropenia Gene therapy for Wiskott-Aldrich syndrome¶
Wiskott-Aldrich syndrome	Yes	Yes	Avoid live vaccines†	Antimicrobial treatment and prophylaxis PJP prophylaxis Platelet transfusions to treat severe bleeding episodes Thrombopoietin receptor agonist therapy Immunosuppressive as required to control autoimmunities‖
Ataxia telangiectasia	Some*	No	Avoid live vaccines†	Multidisciplinary care Antimicrobial treatment and prophylaxis§ Avoid radiation exposure
DiGeorge syndrome	Some*	No	Avoid live vaccines† In partial DiGeorge live vaccines can be applied‡	Multidisciplinary care Antimicrobial treatment and prophylaxis§ Vitamin D or calcium supplementation Surgical for Cleft palate and heart defects Thymus transplantation (complete form)¶
Hyper-IgE syndrome	Some*	Rare (DOCK8 deficiency)	Avoid live bacterial vaccines† Consider avoidance of all live vaccines in DOCK8 deficiency‡	Antimicrobial treatment and prophylaxis§ Multidisciplinary care Immunosuppressive as required to control autoimmunities‖

(continued)

TABLE V. *(Continued)*

Disease	Immunoglobulin replacement	Hematopoietic stem cell transplantation	Vaccination	Special treatment
Other well-defined syndromes (NBS, ICF, Bloom, cartilage hair hypoplasia, Tricho-hepato-enteric syndrome)	Some*	Some	Administer live vaccines in some patients‡	Multidisciplinary care Antimicrobial treatment and prophylaxis§ Immunosuppressive as required to control autoimmunities‖ Avoid radiation exposure (NBS, Bloom)
Agammaglobulinemia	Yes	No	Avoid live vaccines†	Antimicrobial treatment and prophylaxis§
Common variable immunodeficiency	Yes	Rare	Avoid live vaccines† Recommended vaccination against Pneumococcal strains	Antimicrobial treatment and prophylaxis§ Immunosuppressive as required to control autoimmunities‖ Multidisciplinary care
Other antibody deficiencies (less profound-selective IgA deficiency and IgG subclass deficiency)	Some*	No	Routine vaccination Recommended vaccination against pneumococcal strains Avoid OPV, BCG, YF vaccines; other live vaccines can to be safe	Antimicrobial treatment and prophylaxis§
Familial hemophagocytic lymphohistiocytosis	No	Yes	Routine vaccination	Antimicrobial treatment and prophylaxis§ Chemotherapy per protocol Immunosuppressive as required to control disease activity‖
Autoimmune lymphoproliferative syndrome	No	Some	Routine vaccination	Antimicrobial treatment as required Immunosuppressive as required to control autoimmunities‖
Immunodysregulation polyendocrinopathy enteropathy X-linked syndrome	No	Yes	Routine vaccination	Antimicrobial treatment and prophylaxis§ Immunosuppressive as required to control autoimmunities‖ Targeted therapies#
Autoimmune polyendocrine syndrome	No	No	Routine vaccination	Antifungal treatment and prophylaxis§ Immunosuppressive as required to control autoimmunities‖
Other immune dysregulatory disorders	Some*	Some	Routine vaccination	Antimicrobial treatment and prophylaxis§ Immunosuppressive as required to control autoimmunities‖ Targeted therapies#
Congenital neutropenia	No	Some	Avoid live bacterial vaccines† (BCG and *Salmonella*)	Antimicrobial treatment and prophylaxis§ G-CSF treatment

(continued)

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TABLE V. *(Continued)*

Disease	Immunoglobulin replacement	Hematopoietic stem cell transplantation	Vaccination	Special treatment
Chronic granulomatous disease	No	Yes	Avoid live bacterial vaccines† (BCG and *Salmonella*)	Antimicrobial treatment and prophylaxis§ IFN-γ treatment Granulocyte transfusion Surgical resection of infected tissue Immunosuppressive as required to control autoimmunities‖ Gene therapy¶
Leukocyte adhesion deficiency (LAD)	No	Yes	Avoid live bacterial vaccines† (BCG and *Salmonella*)	Antimicrobial treatment and prophylaxis§ Surgical resection of infected tissue Granulocyte transfusion Ustekinumab for periodontitis and sacral ulcers in LAD-1 Fucose in LAD-2
NEMO deficiency	Yes	Yes	Avoid live vaccines† vaccination against *S. pneumonia*, *H. influenza,* and *N. meningitides*	PJP prophylaxis Antimicrobial treatment and prophylaxis§ Anti-TNF-α (severe colitis)
Mendelian susceptibility to mycobacterial diseases	No	Some (in severe cases)	Avoid live bacterial vaccines† (BCG and *Salmonella*)	Long-term antituberculosis and IFN-γ treatment Azole prophylaxis for candida infection *Salmonella* treatment and prophylaxis Surgical resection of infected tissue
Chronic mucocutaneous candidiasis	No	Some (STAT1-GOF severe cases)	Avoid live vaccines†	Antibacterial, antifungal treatment and prophylaxis§ G-CSF treatment JAK inhibitors (STAT1-GOF)#
Warts, hypogammaglobulinemia, infections, and myelokathexis	Yes	Some	Avoid live vaccines† Recommended vaccination against human papilloma virus	Antimicrobial treatment and prophylaxis§ Wart treatment (5-Fluorouracil, imiquimod, IFN-α, cryotherapy) G-CSF treatment Plerixafor (CXCR4 antagonist)#
TLR signaling pathway deficiency with bacterial susceptibility (IRAK4, MyD88)	Yes (during childhood)	No	Avoid live vaccines† Recommended vaccination against *S. pneumonia*, *H. influenza,* and *N. meningitidis*	Antibacterial treatment and prophylaxis§
TLR signaling pathway deficiency with herpes simplex susceptibility	No	No	Avoid live vaccines†	Treatment with acyclovir and possible recombinant IFN-α during acute HSE episode Long-term acyclovir prophylaxis
Autoinflammatory disorders	No	No	Routine vaccination	Cytokine (IL-1, TNF) inhibitors# Colchicine for TRAPS and FMF Immunosuppressive as required to control autoimmunities‖

(continued)

TABLE V. *(Continued)*

Disease	Immunoglobulin replacement	Hematopoietic stem cell transplantation	Vaccination	Special treatment
Complement deficiency	No	No	Recommended vaccination against *S. pneumonia*, *H. influenza,* and *N. meningitidis*	Antimicrobial treatment and prophylaxis§ C1q inhibitor for hereditary angioedema Immunosuppressive for autoimmunity (C1, C2, C4) Eculizumab for CD55 deficiency and aHUS¶

ADA, Adenosine deaminase; *aHUS*, atypical hemolytic uremic syndrome; *DOCK8*, dedicator of cytogenesis 8; *FMF*, familial Mediterranean fever; *G-CSF*, granulocyte-colony stimulator factor; *GOF*, gain-of-function; *HSE*, herpes simplex encephalitis; *ICF*, immunodeficiency centromeric instability facial dysmorphism; *NBS*, Nijmegen breakage syndrome; *NEMO*, nuclear factor-kappa B essential modulator; *PJ*, *Pneumocystis jirovecii*; *STAT*, signal transducer and activator of transcription; *TLR*, toll-like receptor; *TNF*, tumor necrosis factor; *TRAPS*, tumor necrosis factor receptor-associated periodic syndrome.

*Patients with impaired antibody responses.

†Live vaccines: Measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV), herpes zoster, oral polio vaccine (OPV), varicella, yellow fever (YF), smallpox, rotavirus, live attenuated influenza, and bacterial strains (Bacillus Calmette-Guerin-BCG and Ty21a *Salmonella* typhi).

‡Can be administered only if <1 y: $CD4^+$ T cells >1500 cells/μL; between 1 and 6 y: $CD4^+$T cells >1000 cells/μL; >6 y: $CD4^+$T cells >500 cells/μL with normal T-cell response to mitogen. Adopted from the paper by Shearer et al.[52]

§Table VI for more detail.

‖Common immunosuppressive drugs used in IEI: corticosteroids, cyclosporine A, mycophenolate mofetil, rapamycin, azathioprine, methotrexate, and cyclophosphamide.

¶Not yet available in the MENA region.

#Table VII for more detail.

enteropathy X-linked, CD25 deficiency, lipopolysaccharide-responsive beige-like anchor and cytotoxic T lymphocyte–associated antigen 4 deficiencies, IL-10 deficiency, monogenic IEI with susceptibility to EBV). In general, identifying the patients before the occurrence of significant infections and/or organ damage improves the outcome of HSCT. However, considering the costs of the procedure and the need of advanced human leukocyte antigen (HLA) testing for recipients and donors, some obstacles to HSCT still exist in the MENA region.[58,77,78] A special note for patients with IL21R, CD40, and CD40L deficiencies is that they may require liver transplantation in addition to HSCT due to the hepatobiliary involvement caused by cryptosporidium.[79,80] Other curative therapies, including thymus transplantation (mainly in patients with complete DiGeorge syndrome, FOXN1, and PAX1 deficiencies) and gene therapy (in patients with adenosine deaminase deficiency, IL2RG deficiency, X-linked CGD, and Wiskott-Aldrich syndrome), are currently not available in the MENA region.

In recent years, mechanism-based directed therapeutic approaches have been implemented to improve clinical conditions and prevent infections in patients with IEI.[81-85] This targeted or precision therapy represents a new area in medicine in which medical treatment is tailored for each patient based on the affected pathway in the disease. The most recent targeted therapies with their mechanisms of action and indications are summarized in Tables VII and VIII. A multidisciplinary approach using directed therapies can provide better disease control and outcomes by restoring immune function. It is well known that the great majority of examples of targeted therapies originate from case studies of small sample sizes, often anecdotal reports from few patients or even a single subject. Moreover, a lack of standard in reporting the treatment outcomes in IEI subjects often precludes comparison of different studies and limits a combined analysis of multiple observations or metanalysis. It should also be noted that the experience with gene- or pathway-specific therapies stems from a medical practice setting where the drug is used as an off-license therapy. These facts should be discussed on different platforms, including the policymakers, insurance agencies, scientists, and the broader community. As a result, long-term data regarding targeted therapies are needed to understand the full efficacy of these therapies in controlling the disease symptoms compared with curative treatments such as HSCT and gene therapy.

To further improve the care of patients with IEI in the MENA region, several measures should be taken in the coming years. These include: (1) increasing the awareness of IEI in the general population, health care providers, and physicians by conducting educational campaigns and meetings, and improving training in basic and clinical immunology;[32-34] (2) empowering the infrastructure of immunology laboratories that will improve the diagnosis of IEI by developing faster and more accurate screening for these defects; (3) establishing and updating national policies regarding newborn screening of IEI; (4) providing timely and appropriate therapeutic agents for IEI; (5) revising the vaccination schedule in patients with IEI; and (6) implementing genetic tests for diagnosis, which also include prenatal screening and carrier identification.[86] In addition, health care authorities should facilitate setting up stem cell banks, which will be a resource for patients with no HLA-matched related donors. Foundation of HSCT services in many MENA countries with expansion of the existing ones can be achieved; however, it needs major effort and governmental support. Finally, encouraging regional collaborations and improving networks between established centers and less experienced centers will improve the diagnosis and treatment of IEI in the MENA region.

In conclusion, developing well-defined diagnostic and therapeutic guidelines for medical practitioners in the MENA region

TABLE VI. Commonly used antimicrobial prophylaxis and immunoglobulin replacement therapy in IEI

Drugs	Dose	Special notes
Antibacterial prophylaxis		
Trimethoprim-sulfamethoxazole (TMP-SMX)	3-5 mg/kg, PO, once or twice daily (component of trimethoprim) Adult: 160 mg once or twice daily	Can cause cytopenia and skin rash. First choice especially for cellular, humoral immune deficiencies, and phagocytic defects. Used for PJP, *Salmonella,* and toxoplasmosis prophylaxis. Pentamidine is an alternative drug and can be used in patients with PJP who are resistant to TMP-SMZ
Amoxicillin	20 mg/kg, PO, once or twice daily Adult: 500-1000 mg once or twice daily	Cellular, humoral, and innate defects, patients with salmonella (MSMD)
Azithromycin	5 mg/kg every other day or 10 mg/kg weekly, PO, single dose Adult: 250 mg every other day or 500 mg weekly, single dose	Can be selected in patients with chronic lung disease due to its immunomodulatory effects
Clarithromycin	7.5 mg/kg, PO, once daily Adult: 500 mg, PO, once daily	Can be used as an alternative to azithromycin
Isoniazid (INH)	10-15 mg/kg, PO, once daily, up to 300 mg daily	In patients with combined immunodeficiencies who received BCG vaccination, INH and RIF should be started. In the case of signs of BCGitis, antituberculosis treatment with INH, RIF, and ethambutol is necessary. *Mycobacterium bovis* is naturally resistant to pyrazinamide. Numbness and tingling in the extremities, nausea, vomiting, and hepatitis are the most common side effects of INH
Rifampicin (RIF)	10-15 mg/kg, PO, once daily, up to 600 mg daily	Side effects: abdominal pain, loss of appetite, nausea, vomiting, yellowing skin and eyes, elevated liver function tests, flu-like symptoms
Antifungal prophylaxis		
Fluconazole	6 to 12 mg/kg, PO, once daily, maximum dose 400 mg/d	First choice in patients with SCID and CMC. Elevated liver function tests can be observed. Fluconazole does not offer *Aspergillus* coverage
Itraconazole	100 mg/daily, PO, once daily (aged 5-12 y) 200 mg/daily, PO, once daily (age ≥13 y)	First choice in CGD. In the case of itraconazole-resistant fungal infections, voriconazole or posaconazole can be considered. Common side effects: diarrhea and nausea
Antiviral prophylaxis		
Valganciclovir	Infant dose (≤4 mo): 16 mg/kg/dose, PO, twice daily Pediatric dose (>4 mo): 7 × BSA × CrCl, PO, once daily (maximum daily dose: 900 mg/dose) Adult: 900 mg/once a day	Use for CMV prophylaxis in patients with SCID. There is no clear consensus among experts, but general recommendations are summarized below: • Consider stopping breastfeeding and starting infant formula until maternal CMV status is established. • If the patient is healthy and the mother is CMV IgG (−), follow-up without prophylaxis. • Consider starting valganciclovir immediately if there are clinical indications of CMV, like lung or liver involvement. • If the mother is CMV IgG (+), consider starting valganciclovir for at least 2 negative blood PCR CMV (measured weekly) and cut breastfeeding. • Because of the myelotoxicity, ganciclovir should not be preferred for CMV prophylaxis. Common side effects: fever, nausea, vomiting, diarrhea, and cytopenia
Aciclovir	<40 kg: 60-90 mg/kg/d in 2 to 3 divided PO doses; maximum dose: 800 mg/dose ≥40 kg: 400-800 mg PO twice daily	Use for HSV and VZV prophylaxis, mainly in patients with CIDs and herpes simplex encephalitis. Side effects: nausea, vomiting, diarrhea, headache, and acute kidney injury

(continued)

TABLE VI. *(Continued)*

Drugs	Dose	Special notes
Interferon-gamma (IFN-γ)	50 mcg/m^2, subcutaneously 3 times weekly	Recommended in CGD and MSMD. Fever and myalgias are the most common adverse events but can be minimized by the use of acetaminophen. Higher doses of IFN-γ (200 μg/m^2) can be used for mycobacterial infections in the partial forms of IFN-γ receptor deficiency and in recessive IL12Rβ1 deficiency
Immunoglobulin replacement therapy (IgRT)	400-600 mg/kg every 4 wk for intravenous route 100-150 mg/kg weekly for the subcutaneous route	Maintain IgG trough >800 mg/dL. Tailor trough level based on the patient condition and response. IgRT products and batches are not interchangeable

BCG, Bacillus Calmette-Guerin; *BSA*, body surface area; *CGD*, chronic granulomatous disease; *CID*, combined immunodeficiency; *CMC*, chronic mucocutaneous candidiasis; *CMV*, cytomegalovirus; *CrCl*, creatinine clearance (based on the modified Schwartz formula); *HSV*, herpes simplex virus; *MSMD*, Mendelian susceptibility to mycobacterial disease; *PCR*, polymerase chain reaction; *PJP*, *Pneumocystis jirovecii* pneumonia; *PO*, per oral; *SCID*, severe combined immunodeficiency; *VZV*, varicella-zoster virus.

TABLE VII. Current available targeted therapies for specific IEI

Targeted protein	Molecule	Diseases
mTOR inhibitor	Sirolimus, everolimus	ALPS, LRBA deficiency, CTLA4 insufficiency, NLRC4-GOF
B7-1 (CD80) binding B7-2 (CD86) binding	Abatacept	LRBA deficiency, CTLA4 insufficiency
B7-1 (CD80) binding B7-2 (CD86) binding	Belatacept	CTLA4 insufficiency
JAK1 and JAK2 inhibitor	Ruxolitinib	STAT1/3-GOF, HLH, STAT6-GOF, AGS, SAVI, STAT2 R148-LOF, HCK-GOF, STAT5B-GOF, COPA deficiency, SOCS1 haploinsufficiency
	Baricitinib	STAT1-GOF, CANDLE, STAT6-GOF, AGS, SAVI, COPA deficiency, SOCS1 haploinsufficiency
JAK1 and JAK3 inhibitor	Tofacitinib	STAT3-GOF, CANDLE, STAT6-GOF, AGS, SAVI, PSMB9-GOF, SOCS1 haploinsufficiency
P110delta inhibitor	Leniolisib	APDS
TNF-α inhibitor	Etanercept	DADA2, CANDLE, NEMO deficiency, IKBKG (NEMO exon 5 deletion), TBK1 deficiency
	Infliximab	
	Adalimumab	
CD20 inhibitor	Rituximab	CVID/CID/APDS
IL-12/IL-23 inhibitor	Ustekinumab	CGD/LAD-1
IL-1R inhibitor	Anakinra	CAPS (MWS, NOMID, FACS), FMF, TRAPS, HIDS, DIRA, CGD, CDC42 deficiency, C2orf69 deficiency
IL-1β inhibitor	Canakinumab	CAPS (MWS, NOMID, FACS), DIRA, CDC42 deficiency
	Rilonacept	
CD52 inhibitor	Alemtuzumab	HLH
IFN-γ inhibitor	Emapalumab	HLH
IL-6R inhibitor	Tocilizumab	STAT3-GOF, RIPK1 deficiency
C5 inhibitor	Eculizumab	CD55 deficiency
IL-18 binding protein	Tadekinig-α	NLRC4-GOF
CXCR4 antagonist	Plerixafor	WHIM
α4β7 integrin antagonist	Vedolizumab	XLA

AGS, Aicardi-Goutieres syndrome; *ALPS*, autoimmune lymphoproliferative syndrome; *APDS*, activated phosphoinositide 3-kinase delta syndrome; *CANDLE*, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; *CAPS*, cryopyrin-associated periodic syndrome; *CDC42*, cell division cycle 42; *CGD*, chronic granulomatous disease; *CID*, combined immunodeficiency; *COPA*, coatomer protein subunit α; *C2orf69*, chromosome 2 open reading frame 69; *CTLA-4*, cytotoxic T lymphocyte antigen-4; *DADA2*, deficiency of adenosine deaminase; *DIRA*, deficiency of IL-1 receptor antagonist (IL-1RA); *FACS*, familial cold autoinflammatory syndrome; *FMF*, familial Mediterranean fever; *HCK-GOF*, hematopoietic cell kinase-gain-of-function; *HIDS*, hyper-IgD syndrome; *HLH*, hemophagocytic lymphohistiocytosis; *IEI*, inborn errors of immunity; *IKBKG (NEMO exon 5 deletion)*, inhibitor of kappa polypeptide gene enhancer in B cells, kinase γ/nuclear factor κB, essential modulator; *IL-1R*, interleukin-1 receptor; *IL-1β*, interleukin-1 β; *IL-6R*, interleukin-6 receptor; *JAK*, Janus kinase; *LAD-1*, leukocyte adhesion defect type 1; *LOF*, loss-of-function; *LRBA*, lipopolysaccharide-responsive and beige-like anchor protein; *mTOR*, mammalian target of rapamycin; *NEMO*, nuclear factor-kappa B essential modulator; *NLRC4-GOF*, NLR family CARD domain containing 4 gain-of-function; *NOMID*, neonatal-onset multisystem inflammatory disease; *PSMB9-GOF*, proteasome subunit β type-9-gain-of-function; *RIPK1*, receptor interacting serine/threonine protein kinase 1; *SAVI*, STING-associated vasculopathy with onset in infancy; *SOCS1*, suppressors of cytokine signaling; *STAT1-GOF*, signal transducer and activator of transcription 1 gain-of-function; *STAT3-GOF*, signal transducer and activator of transcription 3 gain-of-function; *STAT6-GOF*, signal transducer and activator of transcription 6; *TBK1*, TANK binding kinase 1; *TNF-α*, tumor necrosis factor α, *TRAPS*, tumor necrosis factor receptor-associated periodic syndrome; *XLA*, X-lined agammaglobulinemia; *WHIM*, warts, hypogammaglobulinemia, infections, and myelokathexis.

will increase awareness of IEI, thus promoting early diagnosis and appropriate therapies, resulting in favorable outcomes with better survival of patients.

S. Baris, H. Abolhassani, W. Al-Herz, and R. S. Geha conceptualized and designed the study, drafted the article, critically revised the content and provided scientific contribution,

TABLE VIII. Selected IEI with targeted therapies

Immune dysregulation disorders	Laboratory findings	Clinical findings	Targeted molecular pathway	Targeted treatment
IPEX syndrome (XL)	Elevated IgE and eosinophils, normal or low circulating FOXP3 Treg cells and FOXP3 expression	Enteropathy, failure to thrive, endocrinopathies (type 1 diabetes, thyroiditis, hepatitis, and cytopenia), dermatitis	Impairment in Treg cells, increased Teff cells	Tacrolimus Cyclosporine A mTOR inhibitor (rapamycin)
CD25 deficiency (AR)	Circulating Tregs normal/low, impaired T-cell proliferation	Enteropathy, eczema, recurrent respiratory infections, and lymphoproliferation	Impairment in Treg cells, increased Teff cells	Cyclosporine A
CTLA4 deficiency (AD)	Hypogammaglobulinemia, low T and B cells, low class-switched memory B cells, low, normal or high Tregs, reduced FOXP3 expression	Recurrent infections, autoimmune cytopenias, multiorgan lymphocytic infiltration, enteropathy, interstitial lung disease, and lymphoproliferation	Upregulation of T-cell costimulatory pathway	mTOR inhibitor (sirolimus) CTLA-4-Fc fusion protein (abatacept, belatacept)
LRBA deficiency (AR)	Low IgG and IgA, low switched-memory B cells, low memory T cells, low, normal or high Tregs	Recurrent infections autoimmune cytopenias, multiorgan lymphocytic infiltration, enteropathy, and interstitial lung disease	Increased CTLA-4 degradation leading to upregulation of T-cell costimulatory pathway	mTOR inhibitor (sirolimus) CTLA-4-Fc fusion protein (abatacept) Hydroxychloroquine
APDS (PIK3CD-GOF/PIK3R1-LOF) (AD)	Normal/low IgG, IgA, normal/elevated IgM, poor antibody responses, low switched-memory B cells, decreased T cells, increased exhausted effector T cells	Respiratory tract infections autoimmunity, lymphoproliferation, CMV and EBV infections, and susceptibility to malignancies	PI3K pathway hyperactivation	mTOR inhibitor (sirolimus) PI3K inhibition (leniolisib, nemiralisib, seletalisib)
STAT1 GOF (AD)	Abnormal STAT1 phosphorylation and impaired dephosphorylation, decreased T_H17 cells	Mucocutaneous candidiasis, susceptibility to fungal, bacterial, and viral infections, autoimmune cytopenias, diabetes, thyroiditis, and enteropathy	Enhanced transcriptional activity of STAT1	JAK inhibition (ruxolitinib, tofacitinib, baricitinib) Anti-CD20 (rituximab)
STAT3 GOF (AD)	Low T and B cells, decreased Tregs and memory B cells	Increased infections, lymphoproliferation, and solid organ autoimmunity	Enhanced transcriptional activity of STAT3	JAK inhibition (ruxolitinib, tofacitinib) IL-6R inhibition (tocilizumab) Anti-CD20 (rituximab)
CD122 deficiency (AR)	Decreased Tregs, hypergammaglobulinemia, increased NK cells but impaired NK cell development, increased memory T and B cells	Lymphoproliferation, autoimmune hemolytic anemia, enteropathy, eczema, recurrent EBV and CMV infections	Defective IL-2 induced STAT3 and STAT5 in T cells, dysregulated NK cells	mTOR inhibitor (sirolimus)
DEF6 deficiency (AR)	Low T cells, normal/low B cells, slightly reduced Tregs	Recurrent infections, enteropathy, hepatosplenomegaly, cardiomyopathy, and dermatitis	Defective CTLA4 expression	CTLA-4-Fc fusion protein (abatacept)
CD55 deficiency (AR)	Lack of CD55 expression	Protein-losing enteropathy, hypogammaglobulinemia, and thrombosis	Enhanced complement activity	C5 inhibitor (eculizumab)

AD, Autosomal dominant; *APDS*, activated phosphoinositide 3-kinase delta syndrome; *AR*, autosomal recessive; *CMV*, cytomegalovirus; *CTLA*, cytotoxic T lymphocyte−associated protein; *EBV*, Epstein-Barr virus; *FOXP3*, forkhead box P3; *GOF*, gain-of-function; *IPEX*, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; *JAK*, Janus kinase; *LOF*, loss-of-function; *LRBA*, LPS-responsive beige-like protein; *mTOR*, mammalian target of rapamycin; *PI3K*, phosphoinositide 3-kinase; *STAT*, signal transducer and activator of transcription; *Teff cells*, effector T cells; *Tregs*, regulatory T cells; *XL*, X-linked.

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ONLINE REPOSITORY

TABLE E1. Novel inborn errors of immunity described by studying patients from the MENA region

	Disease	Gene	Origin in MENA	Consanguinity	Year of publication	References
1.	Immunodeficiencies affecting cellular and humoral immunity					
1.	MHC class I deficiency	*TAP2*	Morocco	1	1994	PMID: 7517574
2.	CD45 deficiency	*PTPRC*	Turkey	1	1997	PMID: 9068311
3.	CD40 deficiency	*CD40*	Saudi Arabia	1	2001	PMID: 11675497
4.	Cernunnos/XLF deficiency	*NHEJ1*	Turkey	1	2006	PMID: 16439204
5.	DNA PKcs deficiency	*PRKDC*	Turkey	1	2009	PMID: 19075392
6.	DOCK8 deficiency	*DOCK8*	Turkey	1	2009	PMID: 19776401
7.	ITK deficiency	*ITK*	Turkish	1	2009	PMID: 19425169
8.	TCRα deficiency	*TRAC*	Pakistan	1	2011	PMID: 21206088
9.	STK4 deficiency	*STK4*	Turkey	1	2012	PMID: 22174160
10.	MALT1 deficiency	*MALT1*	Lebanon	1	2013	PMID: 23727036
11.	IL-21R deficiency	*IL21R*	Lebanon	1	2013	PMID: 23440042
12.	PAX1 deficiency	*PAX1*	Turkey	1	2013	PMID: 23851939
13.	OX40 deficiency	*TNFRSF4*	Turkey	1	2013	PMID: 23897980
14.	IL-21 deficiency	*IL21*	Turkey	1	2014	PMID: 24746753
15.	NIK deficiency	*MAP3K14*	Turkey	1	2014	PMID: 25406581
16.	DOCK2 deficiency	*DOCK2*	Lebanon/Turkey/ Kuwait	1	2015	PMID: 26083206
17.	LAT deficiency	*LAT*	Arab (origin not specified)	1	2016	PMID: 27242165
18.	TFRC deficiency	*TFRC*	Kuwait/Saudi Arabia	1	2016	PMID: 26642240
19.	c-Rel deficiency	*REL*	Kuwait	1	2019	PMID: 31103457
20.	FCHO1 deficiency	*FCHO1*	Turkey/Algeria	Unknown	2019	PMID: 30822429
21.	ITPKB deficiency	*ITPKB*	Egypt	1	2020	PMID: 31987846
22.	MAN2B2 deficiency	*MAN2B2*	Saudi Arabia	1	2020	PMID: 31775018
23.	γ1-COP deficiency	*γ1-COP*	Oman	1	2021	PMID: 33529166
24.	CD28 deficiency	*CD28*	Iran	1	2021	PMID: 34214472
25.	GIMAP6 deficiency	*GIMAP6*	Palestinian family	1	2021	PMID: 33328581
26.	HELIOS deficiency	*IKZF2*	Iran	1	2021	PMID: 34826259
27.	SLP76 deficiency	*LCP2*	Palestinian family	1	2022	PMID: 33231617
2.	Combined immunodeficiencies with associated or syndromic features					
28.	Ataxia-telangiectasia	*ATM*	Arab (origin not specified)	Unknown	1992	PMID: 1551665
29.	Comel-Netherton syndrome	*SPINK5*	Pakistan/Turkey	1	2002	PMID: 11841556
30.	Hepatic veno-occlusive disease with immunodeficiency (VODI)	*SP110*	Lebanon	1	2006	PMID: 16648851
31.	Hereditary folate malabsorption	*SLC46A1*	Turkey	1	2007	PMID: 17446347
32.	Transcobalamin 2 deficiency	*TCN2*	Lebanon/Turkey	1	2009	PMID: 19373259
33.	Hennekam lymphangiectasia-lymphedema syndrome	*CCBE1*	Oman/Iraq	1	2009	PMID: 19935664
34.	Tricho-hepato-enteric syndrome (THES)	*TTC37*	Pakistan/Kurdish	1	2010	PMID: 20176027
35.	MOPD1 deficiency (Roifman syndrome)	*RNU4ATAC*	Lebanon	0	2011	PMID: 21977988
36.	Immunodeficiency with centromeric instability and facial anomalies (ICF 2)	*ZBTB24*	Turkey	1	2011	PMID: 21596365
37.	WIP deficiency	*WIPF1*	Morocco	1	2012	PMID: 22231303
38.	Tricho-hepato-enteric syndrome (THES)	*SKIV2L*	North Africa/Turkey	1	2012	PMID: 22444670
39.	EPG5 deficiency (Vici syndrome)	*EPG5*	Saudi Arabia/Turkey	1	2013	PMID: 23222957
40.	MYSM1 deficiency	*MYSM1*	Saudi Arabia	1	2013	PMID: 24288411

(continued)

TABLE E1. *(Continued)*

	Disease	Gene	Origin in MENA	Consanguinity	Year of publication	References
41.	PGM3 deficiency	*PGM3*	Morocco/Tunisia/ Turkey	1	2014	PMID: 24589341
42.	ERCC6L2 (Hebo deficiency)	*ERCC6L2*	Pakistan	1	2014	PMID: 24507776
43.	Immunodeficiency with centromeric instability and facial anomalies (ICF 3)	*CDCA7*	Turkey	1	2015	PMID: 26216346
44.	Immunodeficiency with centromeric instability and facial anomalies (ICF type 4)	*HELLS*	Turkey	1	2015	PMID: 26216346
45.	HOIP deficiency	*RNF31*	Kuwait	1	2015	PMID: 26008899
46.	POLE2 (polymerase ε subunit 2) deficiency	*POLE2*	Saudi Arabia	1	2017	PMID: 26365386
47.	Activating *de novo* mutations in nuclear factor erythroid 2−like (NFE2L2)	*NFE2L2*	Qatar	0	2017	PMID: 29018201
48.	ZNF341 deficiency AR-HIES	*ZNF341*	Morocco/Iran/Turkey/ Lebanon/Arab-Israeli families	1	2018	PMID: 29907690 PMID: 29907691
49.	IL6ST deficiency (complete deficiency)	*IL6ST-AR*	Saudi Arabia	1	2019	PMID: 31130284
50.	POLD2 deficiency	*POLD2*	Turkey	1	2019	PMID: 31449058
51.	POLD1 deficiency	*POLD1*	Turkey	1	2020	PMID: 31629014
52.	IL6ST deficiency (dominant negative)	*IL6ST-AD*	Turkey	0	2020	PMID: 32207811
3.	Predominantly antibody deficiencies					
53.	μ heavy chain deficiency	*IGHM*	Turkey	1	1996	PMID: 8890099
54.	Igα deficiency	*CD79A*	Turkey	0	1999	PMID: 10525050
55.	AID deficiency	*AICDA*	Morocco/Turkey	1	2000	PMID: 11007475
56.	CD19 deficiency	*CD19*	Turkey	1	2006	PMID: 16672701
57.	CD81 deficiency	*CD81*	Morocco	1	2010	PMID: 20237408
58.	CD20 deficiency	*CD20*	Turkey	1	2010	PMID: 20038800
59.	TRNT1 deficiency	*TRNT1*	Pakistan	1	2014	PMID: 25193871
60.	ATP6AP1 deficiency	*ATP6AP1*	Tunisia	1	2016	PMID: 27231034
61.	FNIP1 deficiency	*FNIP1*	Turkey/Kurdish	1	2020	PMID: 32181500
4.	Diseases of immune dysregulation					
62.	Prolidase deficiency	*PEPD*	Middle East	0	1990	PMID: 2365824
63.	Chediak-Higashi syndrome	*LYST*	Kuwait/Turkey	1	1997	PMID: 9215679
64.	Griscelli syndrome type 2	*RAB27A*	Turkey	1	2000	PMID: 10835631
65.	FERMT1 deficiency	*FERMT1*	North African	1	2003	PMID: 12668616
66.	UNC13D/Munc13-4 deficiency (FHL3)	*UNC13D*	Morocco	1	2003	PMID: 14622600
67.	Syntaxin 11 deficiency (FHL4)	*STX11*	Kurdish	1	2005	PMID: 15703195
68.	STXBP2/Munc18-2 deficiency (FHL5)	*STXBP2*	Saudi Arabia/Turkey	1	2009	PMID: 19804848
69.	IL-10R deficiency	*IL10RA*	Lebanon/Turkey	1	2009	PMID: 19890111
70.	FADD deficiency	*FADD*	Pakistan	1	2010	PMID: 21109225
71.	LRBA deficiency	*LRBA*	Iran/Arab (origin not specified)	1	2012	PMID: 22608502
72.	CD27 deficiency	*CD27*	Morocco	1	2012	PMID: 22197273
73.	PRKCD deficiency	*PRKCD*	Turkey	1	2013	PMID: 23319571
74.	Hermansky-Pudlak syndrome type 10	*AP3D1*	Turkey	1	2016	PMID: 26744459
75.	RASGRP1 deficiency	*RASGRP1*	Turkey	1	2016	PMID: 27776107
76.	RLTPR deficiency	*CARMIL2*	Morocco/Tunisia/ Turkey	1	2016	PMID: 27647349
77.	CD70 deficiency	*CD70*	Egypt/Turkey/Iran	1	2017	PMID: 28011863
78.	TGFB1 deficiency	*TGFB1*	Pakistan	1	2018	PMID: 29483653
79.	RIPK1 deficiency	*RIPK1*	Pakistan	1	2018	PMID: 30026316
80.	DEF6 deficiency	*DEF6*	Pakistan/Iraq	1	2019	PMID: 31308374
81.	IL37 deficiency	*IL37*	Turkey	1	2021	PMID: 33674380
82.	iRHOM2 deficiency	*RHBDF2*	Turkey	1	2022	PMID: 34937930
83.	ST6 deficiency	*ST6*	Turkey	1	2022	PMID: 35303419
84.	IKZF1 gain of function	*IKZF1*	Turkey	Unknown	2022	PMID: 35333544

(continued)

TABLE E1. *(Continued)*

	Disease	Gene	Origin in MENA	Consanguinity	Year of publication	References
5.	Congenital defects of phagocyte number or function					
85.	Papillon-Lefèvre syndrome	*CTSC*	Egypt/Pakistan/ Lebanon	1	1999	PMID: 10581027
86.	Leukocyte adhesion deficiency type 2 (LAD2)	*SLC35C1*	Turkey/Arab-Israeli families	Unknown	2001	PMID: 11326279
87.	HAX1 deficiency (Kostmann disease) (SCN3)	*HAX1*	Turkey/Iran/Lebanon/ Kurdish	1	2007	PMID: 17187068
88.	Leukocyte adhesion deficiency type 3 (LAD3)	*FERMT3*	Turkey	1	2007	PMID: 17185466
89.	G6PC3 deficiency (SCN4)	*G6PC3*	Turkey	1	2009	PMID: 19118303
90.	VPS45 deficiency (SCN5)	*VPS45*	Palestinian families	1	2013	PMID: 23738510
91.	JAGN1 deficiency	*JAGN1*	Algeria/Iran/Turkey/ Morocco/ Pakistan	1	2014	PMID: 25129144
92.	3-Methylglutaconic aciduria	*CLPB*	Turkey	0	2015	PMID: 25597510 PMID: 25597511 PMID: 25650066
93.	Shwachman-Diamond syndrome	*DNAJC21*	Algeria/Pakistan	1	2016	PMID: 12496757
94.	WDR1 deficiency	*WDR1*	Qatar	1	2016	PMID: 27557945
95.	SMARCD2 deficiency	*SMARCD2*	Pakistan/Lebanon	1	2017	PMID: 28369036
96.	Shwachman-Diamond syndrome	*EFL1*	Palestinian families	1	2017	PMID: 28331068
6.	Defects in intrinsic and innate immunity					
97.	IL-12 and IL-23 receptor β1 chain deficiency	*IL12RB1*	Turkey	1	1998	PMID: 9603733
98.	IL-12p40 (IL-12 and IL-23) deficiency	*IL12B*	Pakistan	1	1998	PMID: 9854038
99.	Osteopetrosis	*TCIRG1*	Turkey	1	2000	PMID: 10942435
100.	EVER1 deficiency	*TMC6*	Algeria	1	2002	PMID: 12426567
101.	EVER2 deficiency	*TMC8*	Algeria	1	2002	PMID: 12426567
102.	IRAK4 deficiency	*IRAK4*	Saudi Arabia	1	2003	PMID: 12637671
103.	Osteopetrosis	*TNFSF11*	Tunisia/Kurdish	1	2007	PMID: 17632511
104.	MyD88 deficiency	*MYD88*	Turkey	1	2008	PMID: 18669862
105.	CARD9 deficiency	*CARD9*	Iran	1	2009	PMID: 19864672
106.	TRIF deficiency	*TICAM1*	Saudi Arabia	1	2011	PMID: 22105173
107.	Osteopetrosis	*SNX10*	Palestinian families	1	2012	PMID: 22499339
108.	ISG15 deficiency	*ISG15*	Turkey/Iran	1	2012	PMID: 22859821
109.	RORγt deficiency	*RORC*	Saudi Arabia	1	2015	PMID: 26160376
110.	IL-17RC deficiency	*IL17RC*	Turkey	1	2015	PMID: 25918342
111.	CIB1 deficiency	*CIB1*	Iran	1	2018	PMID: 30068544
112.	IRF9 deficiency	*IRF9*	Algeria	1	2018	PMID: 30143481
113.	DBR1 deficiency	*DBR1*	Arab (origin not specified)	1	2018	PMID: 29474921
114.	IFNAR1 deficiency	*IFNAR1*	Iran	1	2019	PMID: 31270247
115.	IL-18BP deficiency	*IL18BP*	Algeria	1	2019	PMID: 31213488
116.	SNORA31 deficiency	*SNORA31*	Morocco/Saudi Arabia	1	2019	PMID: 31806906
117.	IFN-γ deficiency	*IFNG*	Kuwait	1	2020	PMID: 32163377
118.	T-bet deficiency	*TBX21*	Morocco/Qatar	1	2020	PMID: 33296702
119.	NOS2 deficiency	*NOS2*	Iran	1	2020	PMID: 31995689
120.	IFN-γ deficiency	*IFNG*	Lebanon	1	2020	PMID: 32163377
121.	ZNFX1 deficiency	ZNFX1	Iran/Morocco/Saudi Arabia/Egypt	1	2021	PMID: 33876776
122.	PD-1 deficiency	*PDCD1*	Turkey	1	2021	PMID: 34183838
123.	TLR7 deficiency	*TLR7*	Iran/Turkey	0	2021	PMID: 34413140
7.	Autoinflammatory disorders					
124.	Familial Mediterranean fever	*MEFV*	Iraq/North African	Unknown	1997	PMID: 9288758

(continued)

TABLE E1. *(Continued)*

	Disease	Gene	Origin in MENA	Consanguinity	Year of publication	References
125.	Chronic recurrent multifocal osteomyelitis and congenital dyserythropoietic anemia (Majeed syndrome)	*LPIN2*	Jordan	1	2005	PMID: 15994876
126.	TREX1 deficiency Aicardi-Goutieres syndrome 1 (AGS1)	*TREX1*	Pakistan/Turkey	1	2006	PMID: 16845398
127.	RNASEH2B deficiency AGS2	*RNASEH2B*	Morocco/Algeria/ Tunisia	1	2006	PMID: 16845400
128.	RNASEH2C deficiency AGS3	*RNASEH2C*	Pakistan	1	2006	PMID: 16845400
129.	Histiocytosis-lymphadenopathy plus syndrome	*SLC29A3*	Arab (origin not specified)	1	2008	PMID: 18940313
130.	DIRA (deficiency of the interleukin-1 receptor antagonist)	*IL1RN*	Lebanon	1	2009	PMID: 19494218
131.	SAMHD1 deficiency AGS5	*SAMHD1*	Pakistan/Morocco/ Arab (origin not specified)	1	2009	PMID: 19525956
132.	ADAM17 deficiency	*ADAM17*	Lebanon	1	2011	PMID: 22010916
133.	DITRA (deficiency of IL-36 receptor antagonist)	*IL36RN*	Tunisia	1	2011	PMID: 21848462
134.	Pediatric systemic lupus erythematosus due to DNASE1L3 deficiency	*DNASE1L3*	Saudi Arabia	1	2011	PMID: 22019780
135.	Spondyloenchondrodysplasia with immune dysregulation (SPENCD)	*ACP5*	Turkey/Pakistan/ Egypt	1	2011	PMID: 21217755
136.	STING-associated vasculopathy infantile-onset (SAVI)	*TMEM173*	Turkey	Unknown	2014	PMID: 25029335
137.	USP18 deficiency	*USP18*	Turkey	1	2016	PMID: 27325888
138.	NLRP1 deficiency	*NLRP1*	Algeria	1	2016	PMID: 27965258
139.	Otulipenia/ORAS	*OTULIN*	Pakistan	1	2016	PMID: 27523608
140.	A20 deficiency	*TNFAIP3*	Turkey	Unknown	2016	PMID: 26642243
141.	T-cell lymphoma subcutaneous panniculitis-like (TIM3 deficiency)	*HAVCR2*	North African	Unknown	2018	PMID: 30374066
142.	STAT2 gain of function	*STAT2*	Morocco	1	2020	PMID: 32092142
143.	HEM1 deficiency	*NCKAP1L*	Iran/UAE/Saudi Arabia	1	2020	PMID: 32647003 PMID: 32646852 PMID: 32766723
144.	C2orf69 deficiency	*C2orf69*	Turkey/Iran/Saudi Arabia/Tunisia	1	2021	PMID: 34038740
8.	Complement deficiencies					
145.	Membrane cofactor protein (CD46) deficiency	*CD46*	Turkey	1	2003	PMID: 14566051
146.	C1q deficiency due to defects	*C1QA*	Iraq/Turkey/Sudan	1	2011	PMID: 21654842
147.	C1q deficiency due to defects	*C1QB*	Morocco	1	2011	PMID: 21654842
148.	C1q deficiency due to defects	*C1QC*	Saudi Arabia/ Pakistan/Turkey	1	2011	PMID: 21654842
149.	CD55 deficiency (CHAPLE disease)	*CD55*	Turkey/Morocco/ Syria/Palestinian family	1	2017	PMID: 28657829 PMID: 28657861
9.	Bone marrow failure					
150.	Fanconi anemia type G	*XRCC9*	Lebanon	1	1998	PMID: 9806548
151.	Fanconi anemia type E	*FANCE*	Turkey	Unknown	2000	PMID: 11001585
152.	Dyskeratosis congenita, DKCB1	*NOLA3*	Saudi Arabia	1	2007	PMID: 17507419
153.	Fanconi anemia type I	*FANCI*	Turkey	1	2007	PMID: 17452773
154.	Fanconi anemia type N	*PALB2*	Morocco	Unknown	2007	PMID: 17200671
155.	Dyskeratosis congenita, DKCB4	*TERT*	Iran/Libya	1	2007	PMID: 17785587
156.	Dyskeratosis congenita, DKCB2	*NOLA2*	Turkey	1	2008	PMID: 18523010
157.	Fanconi anemia type O	*RAD51C*	Pakistan	1	2010	PMID: 20400963
158.	Fanconi anemia type U	*XRCC2*	Saudi Arabia	1	2012	PMID: 22232082

(continued)

TABLE E1. *(Continued)*

	Disease	Gene	Origin in MENA	Consanguinity	Year of publication	References
159.	Coats plus syndrome	*CTC1*	Egypt	1	2012	PMID: 22267198
160.	Dyskeratosis congenita, DKCB6	*PARN*	Pakistan	1	2015	PMID: 25893599
161.	Coats plus syndrome	*STN1*	Pakistan	1	2016	PMID: 27432940

0: nonconsanguineous marriage; 1: consanguineous marriage.

TABLE E2. MENA guideline for diagnostic evaluation of IEI

First-line approach/general practitioners	Second-line approach/specialists and nonimmunology subspecialists	Third-line approach/immunologists	Differential diagnosis of IEI
Autoimmunity, lymphoproliferation, and immune dysregulation			
Lymphopenia Isolated or accompanied by other cell line abnormalities	Evaluation by hematologist and immunologist	Approach to T-cell defects, B-cell defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	SCID, CID, B-cell deficiency, and immune dysregulation disorders
Anemia Isolated or accompanied by other cell line abnormalities	Bone marrow production defects or autoimmune cytopenia (isolated or with thrombocytopenia/ neutropenia): evaluation by hematologist	Approach to T-cell defects, B-cell defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	B-cell defects, CID, immune dysregulation disorders, and complement defects
Thrombocytopenia Isolated or accompanied by other cell line abnormalities	Bone marrow production defects or autoimmune cytopenia (isolated or with thrombocytopenia/ neutropenia): evaluation by hematologist	Approach to T-cell defects, B-cell defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	SCID, CID, B-cell deficiency, immune dysregulation disorders. Special disorders related to low platelet: WAS: thrombocytopenia with small size platelets WIP deficiency: thrombocytopenia with or without small platelets Arp2/3-mediated filament branching defect: thrombocytopenia with normal size platelets
Neutropenia Isolated or accompanied by other cell line abnormalities	Bone marrow production defects or autoimmune cytopenia (isolated or with anemia/ thrombocytopenia): evaluation by hematologist	Approach to phagocytosis defects, T-cell defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	Congenital neutropenia, myeloperoxidase deficiency, iso-immune neonatal neutropenia, chronic autoimmune neutropenia, chronic idiopathic neutropenia, CD40L/CD40 deficiency, STK4 deficiency, moesin deficiency, WAS, GINS1 deficiency, MTHFD1 deficiency, TWEAK deficiency, Chediak Higashi, Griscelli syndrome, Hermansky-Pudlak syndrome, and WHIM
Signs/symptoms of autoimmune endocrine disorders Family history of autoimmune disorders	Evaluation by endocrinologist	Approach to T-cell defects, B-cell defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	ALPS, IPEX, CVID, CID, CTLA4 insufficiency, LRBA deficiency, CD25 deficiency, APECED, Calcium channel defects, STAT1 and STAT3 GOF disorders, ITCH deficiency
Failure to thrive Anal fissures or perianal abscesses Signs/symptoms of inflammatory bowel disease and autoimmune enteropathy Family history of autoimmune disorders	Evaluation by gastroenterologist	Approach to T-cell defects, B-cell defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	IL10 and IL10R deficiencies, ALPS, IPEX, CVID, CID, agammaglobulinemia (X-lined), CGD, LAD, CTLA4 insufficiency, LRBA deficiency, CD25 deficiency, XIAP deficiency, APECED, STAT3 GOF, ITCH deficiency, STAT1 GOF, NFAT5, ELF4 and RIPK1 deficiencies, C1s, r, q, and CD55 deficiencies
Signs/symptoms of autoimmune arthropathy and rheumatologic disorders Family history of autoimmune disorders	Evaluation by rheumatologist	Approach to T-cell defects, B-cell defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	ALPS, CVID, CID, CTLA4 insufficiency, LRBA deficiency, CD25 deficiency, APECED, STAT3 GOF, ITCH deficiency, STAT1 GOF, NLRP1 deficiency, COPA defect, and MASP2 deficiency

(continued)

TABLE E2. *(Continued)*

First-line approach/general practitioners	Second-line approach/specialists and nonimmunology subspecialists	Third-line approach/immunologists	Differential diagnosis of IEI
Signs/symptoms of alopecia, vitiligo, and dermatologic autoimmunity Family history of autoimmune disorders	Evaluation by dermatologist	Approach to T-cell defects, B-cell defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	ALPS, CVID, CID, CTLA4 insufficiency, LRBA deficiency, CD25 deficiency, APECED, Calcium channel defects, ITCH deficiency, and STAT1 GOF
Family history of other autoimmune disorders Signs/symptoms of autoimmune vasculitis	Evaluation by rheumatologist Evaluation by dermatologist	Approach to T-cell defects, B-cell defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	WAS and Arp2/3-mediated filament branching defect, CVID, CID (MHCI), and DNASE1L3 deficiency
Signs/symptoms of autoimmune uveitis Family history of autoimmune disorders	Evaluation by ophthalmologist	Approach to T-cell defects, B-cell defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	ALPS, CVID, CID, A20 deficiency, and Blau syndrome
Signs/symptoms of autoimmune glomerulonephritis	Evaluation by nephrologist	Approach to T-cell defects, B-cell defects, and complement defects Confirmation of MENA diagnostic criteria (Table IV)	WAS and C3 deficiency
Signs/symptoms of adenopathies, lymphadenopathy, splenomegaly, hepatomegaly, granulomatous disease, and hyperinflammation Family history of lymphoproliferative disorders	Evaluation by hematologist/oncologist Evaluation by pulmonologists for GLILD, pulmonary fibrosis, and interstitial lung disorders	Approach to T-cell defects, B-cell defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	STK4 deficiency, CVID, PTEN deficiency, PI3K deficiency, familial hemophagocytic lymphohistiocytosis, CTLA4 insufficiency, LRBA deficiency, CD25 deficiency, IPEX, STAT3 GOF, CD27/70 deficiency, ALPS, SH2D1A deficiency, XIAP deficiency, CTPS1 deficiency, ITK deficiency, MAGT1 deficiency, and PRKCD deficiency
Signs/symptoms of severe allergic reaction, asthma, eczema, urticaria, and atopy	Evaluation by allergist Evaluation by dermatologist	Approach to T-cell defects, B-cell defects, immune dysregulation, and innate immune defects Confirmation of MENA diagnostic criteria (Table IV)	DOCK8 deficiency, WAS, PGM3 deficiency, CARMIL2 deficiency, Muckle-Wells syndrome, NLRP3/12 deficiency, PLCG2 deficiency, CANDLE syndrome, OTULIN deficiency, STAT5b GOF, STAT6 GOF
Other signs and symptoms			
Intrauterine polyhydramnios	Evaluation by neonatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Immunodeficiency with multiple intestinal atresia
Intrauterine growth retardation	Evaluation by neonatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	DKC, Schimke syndrome, and tricho-hepato-enteric syndrome
Poor wound repair	Evaluation by infectious specialists	Approach to phagocytosis defects and B-cell defects Confirmation of MENA diagnostic criteria (Table IV)	LADs, RAC2 and WDR1 deficiencies
Delay in shedding of primary teeth	Evaluation by dentists	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Autosomal dominant HIES
Delayed umbilical cord separation	Evaluation by neonatologist	Approach to phagocytosis defects and B-cell defects Confirmation of MENA diagnostic criteria (Table IV)	LADs, RAC2 deficiency

(continued)

TABLE E2. *(Continued)*

First-line approach/general practitioners	Second-line approach/specialists and nonimmunology subspecialists	Third-line approach/immunologists	Differential diagnosis of IEI
Skeletal abnormality Short stature, skeletal dysplasia, and limb dwarfism	Evaluation by neonatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	RNF168, MCM4, β-actin, STAT5B, FILS deficiencies, SPENCD, Schimke, Bloom, NBS, and Vici syndromes, Cartilage hair hypoplasia, Roifman and Kabuki syndromes, PGM3, Cernunnos, DNA ligase IV, and EXTL3 deficiencies
Mental retardation	Evaluation by neurologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	β-Actin deficiency and ICF syndrome
Microcephaly	Evaluation by neonatologist Evaluation by neurologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	NBS, X-linked DKC, DNA ligase IV, Cernunnos, RAD50, RNF168, DNAPKcs, and DIAPH1 deficiencies
Dysmorphic face	Evaluation by neonatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	DiGeorge, CHARGE, ICF, FILS, Bloom, NBS, and Cohen syndromes, XLF, ITCH, STAT5B, and RNF168 deficiencies
Developmental delay	Evaluation by neonatologist Evaluation by neurologist	Approach to T-cell defects, phagocytosis defects, and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	Cohen-Barth and LAD type 2 syndromes, ITCH, ADAR1, and P14 deficiencies
Cognitive defect	Evaluation by neonatologist Evaluation by neurologist	Approach to T-cell defects and phagocytosis defects Confirmation of MENA diagnostic criteria (Table IV)	Kostmann disease, AT, and other syndromic CIDs
Ataxia	Evaluation by neurologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	AT, AT-like disease, RNF168, and purine nucleoside phosphorylase deficiencies
Granulomatous skin lesions	Evaluation by dermatologist Evaluation by hematologist	Approach to T-cell and phagocytosis defects Confirmation of MENA diagnostic criteria (Table IV)	AT, hypomorphic SCIDs, CGD
Telangiectasia	Evaluation by ophthalmologist Evaluation by dermatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	AT, autosomal recessive DKC
Bamboo hair	Evaluation by dermatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Comel-Netherton syndrome
Sparse scalp hair and eyelashes	Evaluation by dermatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	NEMO deficiency, *NFKBIA GOF,* Winged helix deficiency, and autosomal recessive DKC
Livedo like rash	Evaluation by dermatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	FILS syndrome
Hypopigmentation	Evaluation by dermatologist	Approach to phagocytosis defect Confirmation of MENA diagnostic criteria (Table IV)	Chediak Higashi, Hermansky-Pudlak syndrome type 2, Griscelli syndrome type 2, and P14 deficiency
Anhidrotic ectodermal dysplasia	Evaluation by dermatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	NEMO, STIM1, and ORAI1 deficiencies
Hypoplastic nails	Evaluation by dermatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	RTLE1, NOP10, NOLA2, Winged helix, and X-linked DKC deficiencies

(continued)

TABLE E2. *(Continued)*

First-line approach/general practitioners	Second-line approach/specialists and nonimmunology subspecialists	Third-line approach/immunologists	Differential diagnosis of IEI
Café-au-lait spots	Evaluation by dermatologist Evaluation by neurologist	Approach to T-cell defects and B-cell defects Confirmation of MENA diagnostic criteria (Table IV)	WAS, NBS, ICF syndromes, PMS2, and MSH2 deficiencies
Disseminated cutaneous viral infection	Evaluation by infectious specialists Evaluation by dermatologist	Approach to T-cell defects and innate immune defects Confirmation of MENA diagnostic criteria (Table IV)	DOCK8, STK4, CARMIL2, and STAT2 deficiencies
Venous angiectasis	Evaluation by dermatologist Evaluation by hematologist	Approach to phagocytosis defect Confirmation of MENA diagnostic criteria (Table IV)	G6PC3 deficiency
Neonatal onset of rash	Evaluation by dermatologist	Approach to T-cell defects and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	Muckle-Wells, Omenn, WAS, IPEX, and Comel-Netherton syndromes
Inner ear deafness	Evaluation by ENT specialists	Approach to phagocytosis defect Confirmation of MENA diagnostic criteria (Table IV)	G6PC3 deficiency
Coloboma	Evaluation by ophthalmologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	CHARGE syndrome
Dental enamel hypoplasia	Evaluation by dentists	Approach to immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	APECED syndrome, ORAI, and STIM1 deficiencies
Congenital heart disorder	Evaluation by cardiologists	Approach to phagocytosis defect and T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	G6PC3 and STK4 deficiencies, velocardiofacial syndrome, FNIP1 deficiency, Kabuki, and Barth syndromes
Vesico-renal-genital anomaly	Evaluation by urologists	Approach to phagocytosis defect and T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	CHARGE syndrome and G6PC3 deficiency
Joint hypermobility	Evaluation by rheumatologists	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Autosomal dominant HIES
Lipodystrophy	Evaluation by rheumatologists Evaluation by neurologist	Approach to immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	CANDLE syndrome
Chondrodysplasia	Evaluation by rheumatologists	Approach to phagocytosis defect Confirmation of MENA diagnostic criteria (Table IV)	Shwachman−Diamond syndrome
Hypocalcemia and seizure	Evaluation by endocrinologist and neonatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	DiGeorge syndrome and PAX1 deficiency
Cytopenia and steatorrhea	Exocrine pancreatic insufficiency	Approach to phagocytosis defect Confirmation of MENA diagnostic criteria (Table IV)	Shwachman−Diamond syndrome
Absent or hypoplastic thymus	Evaluation by hematologist Evaluation by radiologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	SCID, DiGeorge syndrome, Winged helix deficiency, and PAX1 deficiency
Congenital asplenia	Evaluation by hematologist Evaluation by radiologist	Approach to innate immune defects	Isolated congenital asplenia
Viral encephalitis	Evaluation by neurologist Evaluation by infectious specialists	Approach to innate immune defects	TLR3, UNC93B1, TRAF3, TRIF, and TBK1 deficiencies
Hepatomegaly and veno-occlusive disease	Evaluation by pathologist	Approach to combined immune defects	VODI syndrome
Intracranial calcification	Confirmed by radiologist/neurologist	Approach to immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	Aicardi-Goutières and SPENCD syndromes

(continued)

TABLE E2. *(Continued)*

First-line approach/general practitioners	Second-line approach/specialists and nonimmunology subspecialists	Third-line approach/immunologists	Differential diagnosis of IEI
Aneurysm	Confirmed by cardiologists/ neurologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Autosomal dominant HIES STAT1-GOF
Choanal atresia	Confirmed by neonatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	CHARGE syndrome
Early-onset enteric fistula	Evaluation by gastroenterologist Evaluation by surgeon	Approach to immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	IL10, IL10RA, and IL10RB deficiencies
Palmoplantar keratoderma	Confirmed by dermatologist	Approach to phagocytosis defect Confirmation of MENA diagnostic criteria (Table IV)	Papillon−Lefevre syndrome and USB1 deficiency
Intestinal obstruction and vomiting	Confirmed by gastroenterologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Immunodeficiency with multiple intestinal atresia
Leukoplakia	Premalignant leukokeratosis of mouth mucosa confirmed by a pathologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	DKC
Angioedema	Evaluation by cardiologists Evaluation by dermatologist	Approach to complement defects and immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	C1 inhibitor, factor XII deficiencies
Hypertension	Atypical hemolytic uremic syndrome and pre-eclampsia confirmed by a hematologist	Approach to complement defects	CD46, factor B, factor I, factor H, factor H−related protein, and thrombomodulin deficiencies
Infertility	Impaired spermatogenesis confirmed by urologist/gynecologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Cartilage hair hypoplasia
Coarse facies	Evaluation by dermatologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Autosomal dominant HIES
Scoliosis	Evaluation by rheumatologists Evaluation by orthopedic surgeon	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Autosomal dominant HIES
Osteoporosis	Evaluation by rheumatologists Evaluation by orthopedic surgeon	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Autosomal dominant HIES
Chronic cough Pleurisy	Bronchiectasis confirmed by pneumologist/radiologist	Approach to B-cell defects Confirmation of MENA diagnostic criteria (Table IV)	CVID, IgA deficiency, and XLA
Costochondral junction flaring	Evaluation by rheumatologists Evaluation by orthopedic surgeon	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Adenosine deaminase deficiency
Family history of other malignancies	Lymphoid cancers confirmed by a hematologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	AT, MRE11-RAD50-NBS deficiencies, DNA ligase IV, XLF, and Artemis deficiencies
Family history of other malignancies Early screening tests	Gastric cancers confirmed by hematologist/oncologist	Approach to B-cell defects Confirmation of MENA diagnostic criteria (Table IV)	CVID
Family history of other malignancies Early screening tests	HPV-related papilloma cancer confirmed by hematologist/ oncologist	Approach to innate immune defects	EVER1, EVER2, STK4, RHOH, MAGT1, ITK deficiencies, and WHIM
Family history of other malignancies Early screening tests	EBV-related lymphoma confirmed by hematologist/oncologist	Approach to immune dysregulation Confirmation of MENA diagnostic criteria (Table IV)	CD27, CD70, ITK, XIAP, SH2D1A, PRKCD, STK4, Coronin-1A, CTPS1, CD137, RASGRP1, MAGT1, CARMIL2, TET2, HELIOS, and AIOLOS deficiencies

(continued)

TABLE E2. *(Continued)*

First-line approach/general practitioners	Second-line approach/specialists and nonimmunology subspecialists	Third-line approach/immunologists	Differential diagnosis of IEI
Family history of other malignancies Early screening tests	Colorectal carcinoma confirmed by hematologist/oncologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	PMS2 deficiency
Family history of other malignancies Early screening tests	HHV8-related Kaposi sarcoma confirmed by hematologist/oncologist	Approach to T-cell defects Confirmation of MENA diagnostic criteria (Table IV)	OX40 deficiency
Family history of other malignancies Early screening tests	Thymoma confirmed by hematologist/oncologist	Approach to B-cell defects Confirmation of MENA diagnostic criteria (Table IV)	Good syndrome

ALPS, Autoimmune lymphoproliferative syndrome; *APECED*, autoimmune polyendocrinopathy candidiasis ectodermal dystrophy; *AT*, ataxia-telangiectasia; *CANDLE*, chronic atypical neutrophilic dermatosis with lipodystrophy; *CBC*, complete blood count; *CHARGE*, coloboma, heart defects, atresia choanae, growth retardation, genital and ear abnormalities; *CID*, combined immunodeficiency; *COPA*, coatomer protein complex subunit alpha; *CTLA4*, cytotoxic T lymphocyte−associated protein 4; *CVID*, common variable immune deficiency; *DHR*, dihydrorhodamine; *DIAPH1*, diaphanous-related formin 1; *DKC*, dyskeratosis congenita; *DNT*, double negative T cell; *EVER*, endoplasmic reticulum transmembrane proteins; *EXTL3*, exostosin-like 3; *FILS*, facial dysmorphism, immunodeficiency, livedo, and short stature; *FNIP1*, folliculin-interacting proteins 1; *GLILD*, granulomatous lymphocytic interstitial lung disease; *G6PD*, glucose-6-phosphate dehydrogenase; *GOF*, gain-of-function; *HIES*, hyper-IgE syndrome; *ICF*, immunodeficiency, centromeric instability, facial dysmorphism; *IEI*, inborn errors of immunity; *LAD*, leukocyte adhesion defect; *LRBA*, LPS-responsive beige-like protein; *MENA*, Middle East and North Africa; *NBS*, Nijmegen breakage syndrome; *NEMO*, nuclear factor-kappa B essential modulator; *PGM3*, phosphoglucomutase 3; *RAC2*, Ras-related C3 botulinum toxin substrate 2; *SPENCD*, spondyloenchondrodysplasia; *STK4*, serine/threonine kinase 4; *VODI*, hepatic veno-occlusive disease with immunodeficiency; *XLA*, X-linked agammaglobulinemia.