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Review

Social determinants of health and primary immunodeficiency

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Key Messages

- Infectious presentation of inborn errors of immunity (IEI) can be different in various regions of the world, depending on the local distribution of infectious organism and the local vaccine protocols.
- The distribution and severity of IEI are affected by rates of consanguinity in the population.
- Prevention of IEI can be achieved by premarital, pregestational, or prenatal genetic counseling and diagnosis, which must be tailored to the genetic predisposition and ethical code of a patient.
- Access to treatment for IEI is scarce in certain regions of the world, most notably the access to timely hematopoietic stem cell transplantation and newer treatment modalities.
- Collaboration between low- and medium-income countries with increased rates of IEI and Western countries with improved research and diagnosis modalities has improved our diagnosis and understanding of IEI.

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ABSTRACT

Objective: Inborn errors of immunity (IEI) are rare genetic conditions affecting the immune system. The rate of IEI and their presentation, course, and treatment are all affected by a multitude of social determinants, eventually affecting prognosis. This review summarizes the current knowledge of the social determinants affecting infectious susceptibility, genetic predisposition, diagnosis, and treatment of IEI.
Data Sources: PubMed.
Study Selections: Search terms included "consanguinity," "social determinants," and "founder effect." Further studies were selected based on relevant citations.
Results: Changes in climate and human behavior have modulated the spread of disease vectors and infectious organisms. Consanguinity increases the rate of autosomal recessive conditions, changes the distribution, and affects the severity of IEI. Access to sophisticated genetic and immunologic diagnostic modalities affects genetic counseling and timely diagnosis. Effective genetic counseling should address to the patient's genetic background and ethical code. Access to appropriate and timely treatment of immunodeficiencies is scarce in some regions of the world.
Conclusion: High consanguinity rate and reduced access to prophylactic measures increase the burden of immunodeficiencies in many low- and medium-income countries. Furthermore, poor access to diagnostic and treatment modalities in these regions adversely affects patients' prognosis. Increased awareness among health care professionals and the public and increased collaboration with Western countries aid in diagnosis of these conditions. Further advancements require improved public funding to the prevention, diagnosis, and treatment of IEI.

Introduction

Globalization and increased migration have made our world smaller. The advent of global communication has improved access of patients and caregivers to world-leading, specialized, tertiary care centers. Cultural and religious differences and governmental policies are however slower to change. The recent coronavirus disease 2019

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(COVID-19) pandemic demonstrates the effect of world travel in spreading previously regionally contained infectious organisms. In view of this new globalized world, it is important for the clinical immunologist to recognize the social context of a patient.

Inborn errors of immunity (IEI) are rare, monogenic defects in various pathways of the immune system, affecting ability of patients to manage infections, tolerate self-antigens, and regulate inflammation. There are more than 400 known IEI[1] with autosomal dominant, recessive or X-linked (XL) mode of inheritance. Most of the IEI, however, follow an autosomal recessive (AR) mode of inheritance, which accounts for their increased prevalence in communities in which consanguinity is common practice. Vaccine and perinatal screening policies, cultural and religious practices, and access to advanced diagnostic and treatment modalities all influence the prognosis of a patient. This review will address the social determinants that affect the care and prognosis of patients with primary immunodeficiency.

Social Determinants of Infectious Risks

Emerging infections and their associated morbidity and mortality rates are affected by a myriad of intricately linked factors, including climate, hygiene, population density, vaccine policies and acceptance, prevalence of predisposing conditions, and access to medical care.

The effect of climate and climate changes over the expansion of many vector-borne diseases is well recognized. Climate changes include increased temperatures, changes in precipitation, wind, and humidity, and location and rate of extreme weather events, such as floods, droughts, and hurricanes.[2] Changes in temperature, humidity, and precipitation primarily affect the rate of vector-borne diseases by affecting the reproduction, viability, and behavior of a vector and the incubation period of a pathogen.[2,3] The mosquito genus *Anopheles* transmits *Plasmodium* protozoan, responsible for malaria. Malaria transmission has been associated with increased humidity and temperature and standing water. Global warming has been associated with spreading of the vector to higher latitude and altitude regions, leading to shift of the disease.[3] Similarly, *Aedes* species are responsible for transmission of yellow fever, dengue, chikungunya, and Zika. Rainfall is a key factor in vector expansion, whereas temperature change plays a more complex role.[3,4] The effect of climate change on infectious diseases is portrayed in its extremes during extreme weather conditions, such as hurricanes, tornados, droughts, and floods. In this way, both El Niño and La Niña events have been associated with outbreaks of malaria and increased incidence of diarrhea in South America, an outbreak of West Nile fever after a heatwave in Israel,[5] an outbreak of necrotizing cutaneous mucormycosis after a tornado in Missouri,[6] and many more. A recent and sad reminder of the devastating synergism between natural disasters and infections is given in the case of Honduras, wherein many suffered hurricanes along with the COVID-19 pandemic, resulting in a humanitarian crisis.[7]

Apart from climate changes, human behavior influences vector spreading considerably. Globalization and increased trade resulted in introduction of disease vectors and pathogens, such as *Aedes aegypti* (a vector of dengue, yellow fever, and chikungunya), *Culex pipiens* (a vector of West Nile fever), and *Plasmodium vivax* (which causes malaria) to new continents. *Borrelia recurrentis*, the spirochete responsible for Louse-born relapsing fever, is another example of a pathogen imported to Europe along with East-African immigrants.[8] Furthermore, air travel accelerates this process by allowing the spread of pathogens and vector-borne disease.[4] Another such example is given in the epidemics of *Neisseria meningitidis* associated with the Hajj in Saudi Arabia.[9]

Changes in land use have also contributed to changes in vector habitats. Deforestation contributed to the expansion of *Anopheles* species through the increase of sunlight and standing water, while eliminating *Aedes* species.[10,11] Reforestation in Northeast America has allowed the expansion of *Ixodes scapularis* ticks and emergence of Lyme disease.[10] The effect of farming practices and drainage of wetland is well documented in the case of malaria: although outbreaks of malaria have been documented in Europe until the beginning of the 20th century, improved farming and construction have resulted in decline of this disease. Such changes were delayed in the Soviet Union, which resulted in the high incidence of the disease until the 1930s, despite having a similar climate to the neighboring Scandinavian countries. The advent of dichloro-diphenyl-trichloroethane and antimalarial therapy finally eliminated this disease from Europe.[11]

The ongoing COVID-19 pandemic has given us the amplest example of the effect of globalization and the impact of social determinants on the spread of infection and its control. Although international travel resulted in the uncontrollable worldwide spread of severe acute respiratory syndrome coronavirus 2 in the winter of 2020, globalization has also enabled the collaborative effort to better understand and fight the disease, with shared reporting on monitoring and management, and the race toward developing and disseminating safe and effective vaccines. COVID-19–related mortality rates are complex to dissect, as they depend not only on governmental policies regarding social distancing, testing, and vaccination but also on the density of the population, rate of elderly people in the population, and health care system resilience.[7,12] COVID-19 also provides an example for the disproportionate impact of disease on minority groups. Higher mortality rates in African American, Native American, and Latin communities in the United States have been linked to higher rates of comorbidities, lower access to health care, higher levels of stress, increased crowdedness, and increased rates of workers who are designated essential and therefore are at increased risk of exposure to the disease.[13,14]

Perhaps the most significant development in the history of human health care has been the advent of vaccination. A key parameter affecting the health of a population is access to vaccines and the efficient widespread implementation of vaccine programs. Governmental policies and public opinion regarding vaccinations are varied. In rural and underprivileged regions, poor health care access and lack of awareness often play a part in low immunization coverage.[15]

Addressing infectious risk is ever more important in the immune-compromised patients. These patients have a unique infectious phenotype and are at risk of increased severity of infections and infections with unusual pathogens. Clinical presentation of IEI can be affected by the prevalence of infectious organisms in their environment. For example, *Paracoccidioides brasiliensis*, a cause of paracoccidioidomycosis, is common in Latin America. Disseminated paracoccidioidomycosis has been described in patients with CD40L and IL12/23R deficiencies in this area.[16] In Southeast Asia, *Mycobacterium tuberculosis, Chromobacterium violaceum, Burkholderia pseudomallei*, and *Penicillium marneffei* have been described as unusual presenting infection in patients with IEI.[17]

Patients with IEI often have poor response to vaccines. This both increases their vulnerability to infections and makes serology testing an unreliable marker for diagnosis. Moreover, these patients are susceptible to complications from the typically used live viral vaccines, including Bacille Calmette-Guérin (BCG),[18] varicella-zoster virus,[19] measles, mumps and rubella,[20] rotavirus,[21] and oral polio vaccine.[16] Unfortunately, these complications are often the presenting symptom of their disease.

Social Determinants of the Genetic Predisposition for Primary Immune Deficiency

In the Middle East and North Africa (MENA) region and west Asia, consanguinity is customary and constitutes 20% to 50% of all

marriages.[22] It is practiced among Muslims, Christians, and Hindu alike.[23-25] Intrafamilial unions are often preferred for their advantage in preserving family structure and property and strengthening the intrafamilial relationships.[22,26,27] Emigrants from these regions to Western countries continue to practice these social traditions, thus bringing new health concerns into their adoptive countries.[28] Rates of consanguinity are ever changing,[27,29] with reduction noticed in association with increase in women's education levels, increased social status, urbanization, and in cases of immigration, a gradual transition to the adopting country's culture.[22,29,30] Consanguinity has serious health risks and is associated with increased morbidity and mortality owing to monogenic and polygenic conditions.[26,31]

In the most common form of consanguineous unions, marriage between first cousins, each offspring is autozygous in 6.26% of their genetic loci. In many cases, multiple loops of consanguinity result in a higher level of autozygosity which is difficult to predict.[32] Understandably, this may result in more than one homozygous genetic defect in a given family or patient,[33] thus complicating the clinical picture and genetic workup.[29]

Another phenomenon observed in traditional Middle Eastern and North African societies is endogamy (ie, marriage within the community), which results in intracommunity genetic homogeneity. This phenomenon is well known in many culturally, religiously, or geographically secluded societies in South India,[24,34] Southeast Asia,[35] the Gitano population in Spain,[32] the Amish community, certain regions in Switzerland, La Reunion Island,[33] the Adriatic islands in Croatia,[36] and many more.[33,37-42]

IEI are traditionally considered rare diseases, with a global incidence of 1 per 10,000 to 1 per 50,000 live births. Nevertheless, with advancements in diagnosis and changes in definition, the prevalence of these conditions is now considered to be 10 times higher.[1,43] Owing to the predominance of AR conditions, the prevalence of some IEI is disproportionally increased in communities with high rates of consanguinity and endogeny,[44,45] leading to a unique distribution of IEI and increased disease severity.[46-48] Although predominantly antibody deficiencies are the most common type of disorders in North and Latin America, South Africa, Southeast Asia, and Europe,[17,49-54] combined T- and B-cell deficiencies, other syndromes, and phagocytic defects predominate in North Africa[55-57] and the Middle East[44,46,58-60] (Fig 1). Furthermore, the most prevalent genetic conditions within each category differ in regions most affected by consanguinity and endogeny. In this way, although pathogenic variants in IL2RG (an XL trait) are the most common cause for severe combined immune deficiency (SCID) worldwide, MHC class II, *RAG1*, and *RAG2* deficiencies predominate in the MENA region.[55,56,61] Likewise, *CYBB* mutations are the most common worldwide cause of chronic granulomatous disease, whereas AR defects predominate in the MENA region.[56] In addition, *CD40L* mutations are the predominant worldwide cause of hyperimmunoglobulin M syndrome, whereas *AICDA* defects are typically found in North Africa.[56] Founder effects are responsible for local surges of increased prevalence of otherwise rare conditions in many secluded populations worldwide. In this way, *CD18* deficiency, the cause for leukocyte adhesion defect(LAD) type I, and *IL12B* defect, which causes Mendelian susceptibility to mycobacterial disease, are both common in North Africa.[55,56] Other examples include *SLC35C1*, the cause of LAD type II in Israeli Arabs,[62] *NCF1* mutations causing chronic granulomatous disease among Kavkazi Jews,[63] *NSB1* mutations causing Nijmegen breakage syndrome in people of Slavonic origin,[64] *RAB27A* mutations causing Griscelli type II syndrome in Qatar,[65] Bloom syndrome among Ashkenazi Jews,[66] adenosine deaminase deficiency in Somalians,[67] *ZAP70* in Mennonites,[68] *IKBKB* mutations among First Nation of Northern Cree ancestry,[68] and pathogenic variants in *RMRP*, the cause of cartilage–hair hypoplasia among Finns and Old Order Amish in the United States.[69] This partial list emphasizes the need for the immunologist and geneticist caring for patients with immunodeficiency to be aware of the conditions associated with ethnic and cultural background of every patient.

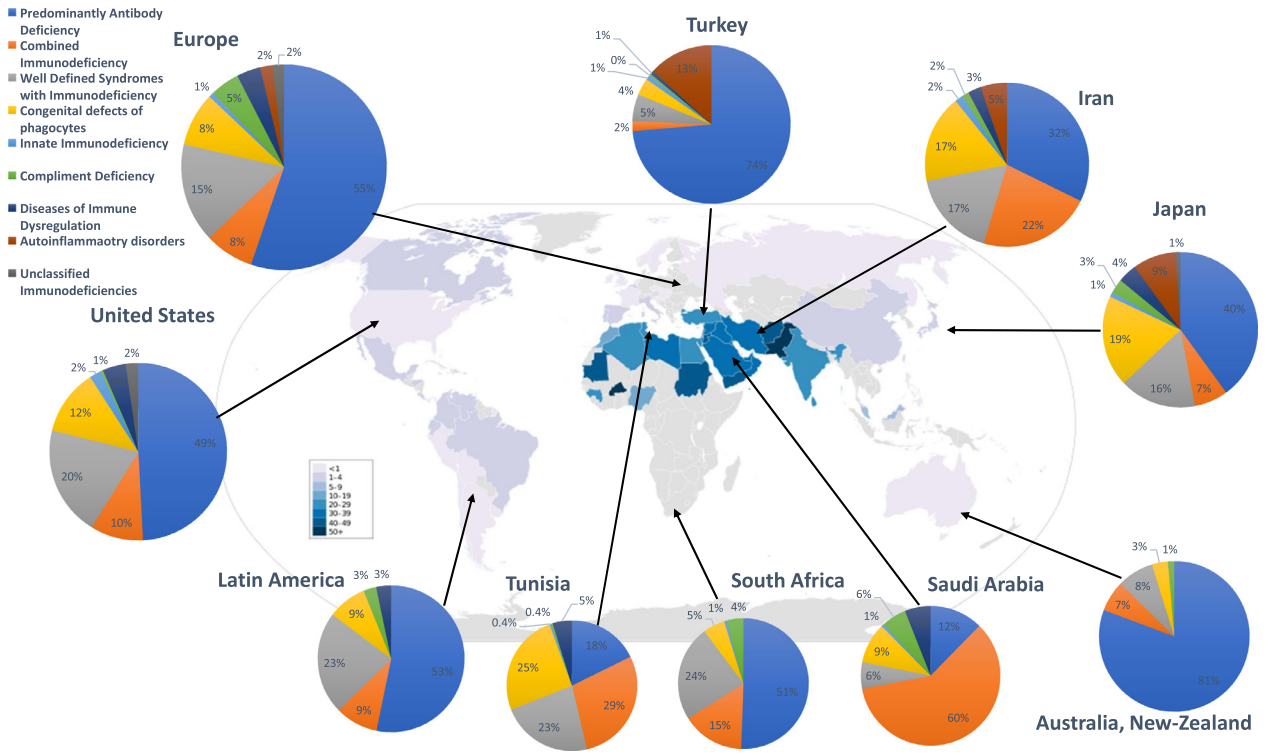

Figure 1. Distribution of IEI in association to rate of consanguinity. Distribution of different categories of IEI[1] in selected countries is presented. Countries are color coded based on rate of consanguinity in the population.[88] IEI, inborn errors of immunity.

Social Determinants of Prevention and Diagnosis of Primary Immune Deficiency

For many severe forms of immune deficiency, early diagnosis and treatment are of extreme importance. Such is the case for the profound combined T- and B-cell deficiencies, requiring early hematopoietic stem cell transplantation (HSCT).[70] In many Western countries, early diagnosis of SCID is possible through newborn screening (NBS) programs using T-cell excision circles (TREC), and has been proven to be both cost-effective and beneficial for patient prognosis.[71] Unfortunately, NBS for SCID is not yet available in many countries with increased incidence of this condition,[45,72] and in fact, Israel is the only country in the MENA region with an established NBS program for SCID.[44] A NBS study in Saudi Arabia has confirmed the increase incidence of SCID (approximately 1 per 3000 live births) and has proven the yield of performing NBS in this population.[45] A similar study confirmed the reliability of TREC testing in Brazil,[73] and the test is available through a private company.[74] Unfortunately, NBS for SCID is still not publicly available in Latin America. The need for early diagnosis of SCID is further emphasized by the routine protocol for early BCG vaccination in many countries, which may adversely affect undiagnosed patients with SCID.[16,18]

Many IEI, including combined immunodeficiencies,[68,75] and non–T-cell defects are not detected by NBS using TREC. Population-specific NBS programs have been proven effective in regions with known founder effects. Such is the case for next generation-based screening of 202 pathogenic variants among old order Amish and Mennonites in Pennsylvania,[76] screening for *ZAP70* among Canadian Mennonites and for *IKBKB* among First Nations of Northern Cree ancestry in Manitoba, Canada.[68]

Premarital and preconception genetic counseling are important ways to reduce genetic diseases, including IEI. Prophylactic measures include prevention of at-risk marriages, pregestation diagnosis (PGD), or prenatal diagnosis (PND) by amniocentesis or chorionic villous sampling. In many countries with high prevalence of consanguinity, genetic counseling is aimed at educating the population regarding the possible health risks of consanguineous unions and addressing family- and community-specific genetic risks.[77] In Saudi Arabia[78] and Tunisia,[79] obligatory genetic testing and counseling programs have been implemented for premarital couples. Most couples, however, are reluctant to cancel their weddings even when advised of an increased risk for a genetic condition[22,78,79] because of fear of social stigmata and wedding arrangements already being made. Another concern is the fear of possible stigmatization associated with a genetic diagnosis for the patient and the family.[27] A private organization[80] has addressed these issues among religious Jewish people in offering early (school age) anonymous testing to common AR conditions in this population. In this way, potential at-risk unions are prevented at an early stage. This approach, if implemented on a larger scale in countries with high rates of consanguinity, can potentially prevent the birth of many severely affected children.

Other than preventing at-risk marriages, possible benefits of genetic counseling include the option of PGD which will prevent the conception of an affected fetus, and the opportunity for PND, which may help early diagnosis and presymptomatic treatment, or the possibility of selective termination of an affected fetus. PGD and PND are both acceptable in the Islamic world.[81-85] Both, however, require the collaborative effort of geneticists, gynecologists, and specialized laboratories, which are costly and not widely available. Islamic religious advice (fatwa) issued in 1990 allows abortion in the presence of severe fetal malformations not amenable to treatment or leading to poor quality of life for patients and their relatives.[27] Abortion in the Islamic world should be carried out before 120 days postfertilization. Termination of pregnancy for medical reasons is debated by other religions as well. Although most Catholics and Buddhists oppose abortions, maintaining the sanctity of life in any form, views by Protestants, Jewish, and Hindu vary with the severity of the genetic condition, the stage of pregnancy, and the effect on the mother and society.[86] Whether premarital, pregestational, prenatal, or postnatal, when providing genetic counseling, extreme care must be given with a professional and compassionate attitude, respect for religious and ethical beliefs of the patient, and patient confidentiality and informed consent.

Diagnosis of IEI requires specialized laboratories and medical personnel to perform highly specialized immunologic and genetic tests and interpret the results in their clinical context. In the MENA region, countries such as Saudi Arabia, Turkey, Iran, and Israel perform extensive genetic testing, including whole-exome sequencing (WES). Other countries in the region have tertiary care centers that diagnose and treat the major types of immune deficiencies, whereas complex immunologic and genetic workup are managed in collaboration with specialized centers in Europe and United States[44] (Fig 2). Latin America and Southeast Asia both are affected with paucity of specialized centers for immunodeficiency, affecting the access of patients to advanced diagnostic and therapeutic facilities.[16,17] In Latin America, an effort has been made by the Latin American Society for Immunodeficiencies to increase awareness of IEI and improve diagnosis and treatment. An online registry was developed, and educational programs were set in place, with considerable increase in diagnosis and reporting of these conditions.[16] Many challenges, however, remain. Specialized immunology laboratory facilities such as T- and B-cell immunophenotyping, pneumococcal antibody titer test, and dihydrorhodamine test are scarce and restricted to large cities. Certain tests, such as fluorescence in situ hybridization, are expensive, resulting in underdiagnosis of conditions, such as DiGeorge syndrome.[16] Similar initiatives have helped increase awareness among physicians and improve access to advanced immunologic and genetic workup in Central and Eastern Europe,[87] Western Asia,[88] and Africa.[89] Still, availability of advanced genetic workup through public health care systems is low, leaving many patients without a genetic diagnosis. In most countries, access to WES or whole-genome sequencing is curtailed by high costs and perceived lack of clinical utility by public and private insurers, and disparities exist based on the health coverage of individual patient.[90] This is despite the proven yield and clinical relevance of WES and whole-genome sequencing.[91,92]

Social Determinants of Treatment of Primary Immune Deficiency

HSCT is a complex, high-risk procedure. It requires great expertise and experience and should only be performed in highly specialized tertiary care centers. HSCT is often the only curative treatment for a variety of combined and phagocytic immune deficiencies. In the most severe cases, it is performed as an emergency procedure. In the MENA regions, HSCT is performed in several centers in Saudi Arabia, Iran, Jordan, Turkey, Tunis, and Israel.[44] In other countries, such as Egypt, Algeria, and Morocco, experience with HSCT is lacking. In many of these countries, the demand far exceeds the supply, and timely access to HSCT is problematic. In a report from Latin America,[93] an estimate of less than 10% of required transplants are carried out. Challenges include cost, donor availability, number of transplant centers, and lack of expertise. Donor selection is based on published guidelines[94] and center preferences. When available, a matched sibling donor or matched related donor is almost always preferable. In case of lack of such a donor, donor selection is determined by the availability of unrelated donors in international registries, which is affected by the ethnic background of the patient.[95] The lack in local registries, additional costs of unrelated donor search, and graft shipment, and in some regions, the abundance of large, consanguineous families, all result in the increased use of matched sibling donor and matched related donor in the MENA region and Latin America.[16,53]

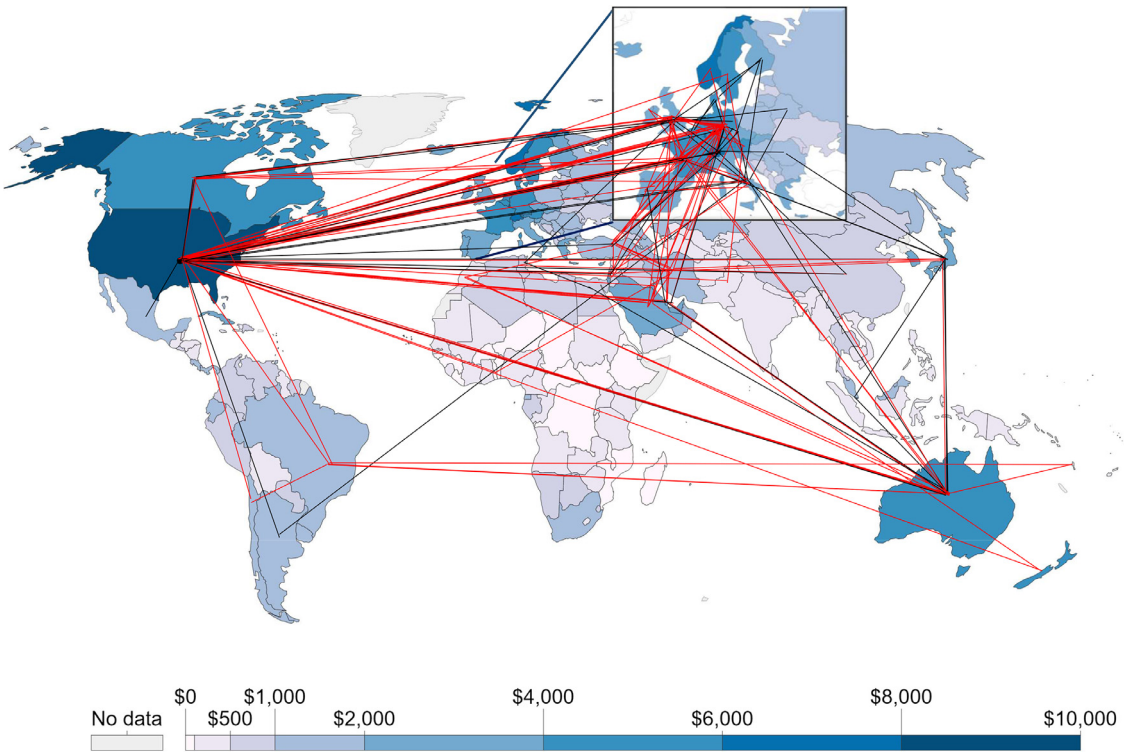

Figure 2. International collaborations in the diagnosis of new IEIs. The world map color code represents health expenditure per person in each country.[89] Lines represent international collaborations in the diagnosis of new genes responsible for IEI as identified in the 2019 IUIS update.[1] Red lines represent AR conditions and black lines represent AD and XL conditions. AD, autosomal dominant; AR, autosomal recessive; IEI, inborn errors of immunity; IUIS, International Union of Immunological Societies; XL, X-linked.

Although immunoglobulin replacement therapy is universally accepted treatment for IEI, access to this treatment modality varies across the world. In addition to barriers in appropriate diagnosis of IEI, disparities exist in reimbursement policies across regions and between different insurance plan options.[96] For example, immunoglobulin replacement therapy is covered by most European national health care programs.[96,97] In contrast, in many MENA countries, access to this treatment is limited.[44] In Latin America, immunoglobulin replacement is available through either governmental or private funding.[16] As most immunoglobulin products are produced in Europe and United States, the antibodies they contain reflect the epidemiology of these regions.[2] As a result, patients may have suboptimal protection against infectious organisms causing local epidemics, such as dengue fever.[16]

Finally, recent advancements in the understanding of IEI have led to development of targeted therapies for several of these conditions, including *CTLA4* and *LRBA* mutations treated with abatacept, activated phosphoinositide 3-kinase δ syndrome treatment with PI3Kδ inhibitors, adenosine deaminase deficiency treatment with gene therapy, and more.[98] Cost issues and the tremendous resources required for clinical trials of new treatments impede their use in low- and medium-income countries.

Although data regarding the impact of socioeconomic and insurance status on the management and prognosis of patients with IEI are lacking, multiple studies have alluded to gaps in unmet health care needs[99,100] and the management and outcome of various conditions.[100-104] The reasons for these disparities are difficult to dissect but are presumably multifaceted, including delays in diagnosis and treatment[101] and an association of less favorable insurance status with household poverty. In the United States, the Patient Protection and Affordable Act of 2010 has allowed for 20 million previously uninsured adults to gain health care insurance coverage, reducing delays in necessary medical care and increasing outpatient visits, access to preventative medical services,[105,106] and patient-reported health.[107,108] In many low- and middle-income countries, mandatory or voluntary universal health care programs were found to have a generally good effect on health care utilization, financial protection, and health status.[109] Even among patients with health insurance coverage, an unresolved health care imbalance continues to exist owing to socioeconomic status.[102] Possible reasons to this could be poor access to advanced medical care in tertiary academic facilities, poor adherence to outpatient follow-up visits and treatments owing to transportation difficulties, need to work,[110] lower health literacy, and more. In a survey of 3749 children undergoing HSCT, overall survival was lower among Medicaid-insured children with malignant diseases (but not those with nonmalignant conditions). Medicaid insurance was postulated to be a proxy to household poverty. The disparity between malignant and nonmalignant conditions is intriguing, and possibly a result of a selection bias in the nonmalignant cohort, in which often HSCT is not the first-line treatment option.[111] In the posttransplant period, 34% of patients with long-term graft-vs-host disease had experienced delayed/denied treatments for their condition contributing to their financial hardship.[112] A multidisciplinary approach including psychosocial and sociodemographic assessments can help mitigate these challenges.[113] Data from the Center for International Blood and Marrow Transplant Research suggest inferior access to transplantation for adult Americans with lymphoproliferative disease who come from disadvantaged areas.[114] Nevertheless, there are no data on the effect of health coverage status on access to transplantation. The rarity of IEI conditions makes it impossible to investigate the access of patients with these conditions to advanced treatments, including HSCT. Further research is needed to address these issues.

Conclusion

As the spectrum of immune deficiency and dysregulation broadens and diagnostic capabilities expand, IEI are increasingly recognized as more common than previously thought. Moreover,

distribution of these conditions is variable, and increased burden of the disease exists in low- and medium-income countries, which is affected by high rates of consanguinity along with reduced access to diagnostic and treatment modalities. To overcome these challenges, continued effort must be made to educate health care professionals in the early diagnosis and treatment of IEI, increase public awareness to the health risks of consanguinity, improve access to genetic counseling and premarital, pregestational, and prenatal testing, and timely treatment. Although the challenges ahead are immense, collaborations with centers in North America, Europe, and Australia have promoted some of these goals tremendously (Fig 2). Further advancement will require changes in governmental policies and public funding.

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