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Consensus of the Italian Primary Immunodeficiency Network on transition management from pediatric to adult care in patients affected with childhood-onset inborn errors of immunity

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Medical advances have dramatically improved the long-term prognosis of children and adolescents with inborn errors of immunity (IEIs). Transfer of the medical care of individuals with pediatric IEIs to adult facilities is also a complex task because of the large number of distinct disorders, which requires involvement of patients and both pediatric and adult care providers. To date, there is no consensus on the optimal pathway of the transitional care process and no specific data are available in the literature regarding patients with IEIs. We aimed to develop a consensus statement on the transition process to adult health care services for patients with IEIs. Physicians from major Italian Primary Immunodeficiency Network centers formulated and answered questions after examining the currently published literature on the transition from childhood to adulthood. The authors voted on each recommendation. The most frequent IEIs sharing common main clinical problems requiring full attention during the transitional phase were categorized into different groups of clinically related disorders. For each group of clinically related disorders, physicians from major Italian Primary Immunodeficiency Network institutions focused on selected clinical issues representing the clinical hallmark during early adulthood. (J Allergy Clin Immunol 2020;■■■:■■■-■■■.)

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Inborn errors of immunity (IEIs) are a group of more than 400 rare inherited disorders due to immune system impairment, the overall estimated prevalence of which is approximately 1 in 1000 to 1 in 5000.[1] The development of recommendations for good clinical practice in management of these disorders is hampered by the low number of patients affected with each single disorder. The spectrum of clinical features may be very wide. The issue of how to manage and treat young adults with severe chronic conditions that were often lethal in childhood until a few decades ago is being raised in many clinical settings. IEIs are usually diagnosed in pediatric age. However, thanks to the increased scientific knowledge of these disorders and the recent advances in innovative therapeutic options and

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Abbreviations used
AML: Acute myeloid leukemia
A-T: Ataxia-telangiectasia
CGD: Chronic granulomatous disease
CID: Combined immunodeficiency
CMC: Chronic mucocutaneous candidiasis
CN: Congenital neutropenia
CRD: Clinically related disorder
CVID: Common variable immunodeficiency
DGS: DiGeorge syndrome
DKC: Dyskeratosis congenita
DRS: DNA repair syndrome
G-CSF: Granulocyte–colony-stimulating factor
GOF: Gain-of-function
GT: Gene therapy
HIES: Hyper-IgE syndrome
HSC: Hematopoietic stem cell
HSCT: Hematopoietic stem cell transplantation
ID: Intellectual disability
IEI: Inborn error of immunity
IPINet: Italian Network of Primary Immunodeficiencies
IRT: Immunoglobulin replacement therapy
LAD: Leukocyte adhesion defect
LTFU: Long-term follow-up
MRI: Magnetic resonance imaging
NASH: Nonalcoholic steatohepatitis
QoL: Quality of life
SCID: Severe combined immunodeficiency
STAT1: Signal transducer and activator of transcription 1
XLA: X-linked agammaglobulinemia

medical care, the cohort of patients entering adulthood is growing year by year.[2]

According to Blum et al, transition is defined as "the purposeful, planned movement of adolescents and young adults with chronic physical and medical conditions from child-centered to adult-oriented health care systems."[3] To date, specific literature on IEIs transition of care is not available. Peculiarities of the adolescent affected with IEIs, such as worsening of chronic lung disease, progressive increase in tumor risk, immune dysregulation and related clinical issues, recently identified phenotypes, and psychological issues, make the transitional care for these patients a unique task.

The transitional process to a dedicated adult team is critical to maintaining a high quality of care during long-term follow-up (LTFU). Synergy between the pediatric and adult teams should be ensured during the period of transition to make the process less stressful for the patient and the family.[4,5] A key element in the transition is the training of adult specialists from different medical branches (gastroenterologist, hematologist, pulmonologist, etc) in the peculiarities of patients with IEIs. To ensure the best management, their medical approach should be tailored to the patient's comorbidities, either related to the preexisting IEIs or secondary to therapies. This also requires an in-depth knowledge of the pathogenic mechanism underlying the specific IEI.

The aim of this work is to propose recommendations on transition of care for the main phenotypes of IEIs categorized into different groups of clinically related disorders (CRDs). Each group of CRDs consists of IEIs sharing common main clinical problems that require full attention during the transitional phase. We have focused on the individual peculiarities of each group of CRDs in an attempt to identify the optimal multidisciplinary teams, by analogy with similar disease models, showing partial clinical overlap with IEIs.

METHODS

The participants were physicians of the main clinical Centers of the Italian Network of Primary Immunodeficiencies (IPINet) who are experts in the management of IEIs. IEIs that share common clinical hallmarks requiring careful attention during the transition phase from adolescence to adulthood were grouped as distinct sets of CRDs. Currently, IPINet centers have approximately 3100 patients with IEIs in follow-up. A steering committee was set up to develop a general questionnaire for each group of CRDs, eventually resulting in a variable number of statements about transitional care key points, which have been rated by all the authors. Each statement is based on evidence drawn from (1) studies involving cases and case series of patients with IEIs, (2) management of other rare diseases with clinical similarities to each group of CRDs, (3) rules of clinical good practice derived from expert-based opinions, and (4) review of the literature from databases such as PubMed and Google Scholar. The literature review was carried out by using the following key words: *transition of care* or *transition of management* or *continuity of care* AND *adolescence* or *pediatrics* or *young adults* or *pediatric patient* AND *primary immunodeficiency* or *inborn errors of immunity*. The literature regarding transitional care in various other pediatric disorders sharing similarities with the clinical hallmarks of each group of CRDs was reviewed as well. Recommendations were rated from –1 (total disagreement) to +1 (total agreement). Agreement was defined as the sum of percentages of the ratings of strongly agree (rated +1) and agree (rated +0.5). Disagreement was defined as the sum of the ratings of strongly disagree (rated –1) and agree (rated –0.5). If at least 75% of the raters agreed with the statement and a mean score of 0.75 or higher was reached, that specific recommendation was assumed to have reached consensus. Furthermore, statements that reached a 75% level of agreement and a mean score between 0.65 and 0.74 were assumed to have reached only partial consensus. No consensus was defined as a mean score lower than 0.64 and agreement by less than 75% of the raters. According to Delphi methodology, after the third round of opinions, the consensus was approved.

RESULTS

General principles for transitional care for IEIs have been summarized in Table I. The majority of raters agreed with the statement that transition of care is critical to ensure appropriate LTFU for patients with IEIs (rate of agreement 96%), for the best management of major clinical issues persisting since childhood and those emerging over time (rate of agreement 100%). Regardless of the specific CRD group, the process should include shared patient-centred and family-centred decision making with the multidisciplinary team (rate of agreement 100%). Patients must learn how to cope with the long-term psychological effects of having a chronic disease. Thus, psychological support or stress management should be offered to the patients to help them deal with their condition in different phases of disease and, in particular, during transition (rate of agreement 100%). To facilitate the transitional process, an adolescent with an undiagnosed condition should not leave the pediatric facility without a diagnostic reevaluation (rate of agreement 86%). Transition should start at the age of 14 years and end by the age of 25 years, but no time limit should be mandated (rate of agreement 96%). The accompaniment, defined as a period when the patient is followed-up simultaneously by pediatricians and adult specialists, should last at least 3 years before the final transfer (rate of agreement 96%). Preliminarily (as shown in Table II), the committee has identified 6 groups of CRDs consisting of IEIs sharing common clinical hallmarks that deserve particular attention during transition. A few general statements were common to all CRDs. In Table III, these statements are indicated

TABLE I. Overarching principles for transitional care for patients with IEIs

Overarching principles	Level	Strength	Level of agreement (%)
Transition of care is critical to ensure appropriate long-term follow-up for patients with IEIs	4	D	96
Transition of care is warranted to ensure best management of clinical issues persisting from childhood and those emerging over time	4	D	100
The care of patients with IEIs should include shared patient-centered and family-centered decision making with the multidisciplinary team	4	D	100
In patients with IEIs, psychosocial support is recommended during the transition phase	4	D	100
Adolescents with an undiagnosed condition should not leave the pediatric facility without a diagnostic reevaluation	4	D	86
Transitional care should be planned during adolescence, preferably starting at the age of 14 years and should end by the age of 25 years; however, no time limit should be mandated	4	D	96
The accompaniment should last at least 3 years before the final transfer	4	D	96
Key documentation and records should be included in the transition package	4	D	100

Level of evidence for chronic pediatric diseases sharing similarities with IEIs. The numeral *4* indicates expert opinion; the uppercase *D* indicates maximal strength based on level 4 evidence. Level of agreement is the percentage of experts who agreed on the recommendation during the final voting round of the consensus.

along with the level of consensus for each CRD group. It should be noted that all the experts agreed that the transitional team should be multidisciplinary even though the composition of the team relied on the clinical peculiarities of the CRD.

Common clinical hallmarks of the humoral immune defects group of CRDs during transition

More than half of all patients with an IEI have disorders characterized by a predominant impairment in antibody production. The International Union of Immunological Societies (IUIS) classification of IEIs provided a current overview of this group of diseases.[1] In this consensus article, we have focused on common variable immunodeficiency (CVID) and other B-cell deficiencies impairing 2 or more immunoglobulin classes; we have done so because selective antibody deficiencies, even though more frequent, are usually less severe and only rarely share clinical manifestations with more severe B-cell disorders.

The increased susceptibility to infections, usually from encapsulated bacteria mainly involves respiratory tract, but all organs may potentially be affected (Table II). X-linked agammaglobulinemia (XLA) has been associated with life-threatening infections caused by viruses of the genus *Enterovirus*, thus resulting in neurologic sequelae. A reduced risk of severe infections and an improved long-term quality of life (QoL) is achieved under adequate immunoglobulin replacement therapy (IRT) through intravenous IgG or subcutaneous IgG and antibiotic prophylaxis, even though less severe infections can persist during the follow-up.[6-11] Antibiotic therapy requires an appropriate stewardship, in particular, during adulthood. Live attenuated vaccines are not recommended in patients receiving IRT, whereas inactivated vaccines may be administered because they could elicit T-cell–mediated responses. Yearly influenza vaccination is recommended for patients with B-cell defects and household contacts.[12-15]

Respiratory complications are the lifelong hallmark of this group of CRDs.[10,11] Chronic lung disease has a prevalence higher than 50% in almost all adult age groups with CVID, and it may affect almost half of patients with XLA by their 40s to 50s despite adequate levels of IRT.[8-10,16-18] Granulomatous lymphocytic interstitial lymphocytic disease (GLILD) has a severe impact on the outcome. The extent of lung damage should be evaluated at baseline and during the follow-up through extensive lung functional tests, imaging techniques (such as high-resolution computed tomography and magnetic resonance imaging [MRI]), and other tests, depending on clinical features. Prevention, through early diagnosis and regular monitoring, can reduce the morbidity associated with chronic lung disease. A personalized respiratory physiotherapy program is often required. Gastrointestinal manifestations are among the most frequent clinical problems during LTFU. Adult patients usually report abdominal pain, bloating, nausea, vomiting, diarrhea and weight loss. Affected individuals may also experience impaired ability to absorb nutrients.[19] Moreover, chronic gastrointestinal inflammatory disease is frequent, particularly in CVID in early adulthood. Along with chronic enteropathy, manifestations can also include gastritis and pernicious anemia. A risk of *Helicobacter pylori* infection has also been reported.[20,21] Liver nodular regenerative hyperplasia has been documented in up to 5% of adult patients with CVID,[19,22,23] and it may quickly progress to hepatitis, portal hypertension, and hepatic failure. Thus, it should be managed aggressively: biopsy is often required to assess the inflammatory infiltrate, which can benefit of immunosuppressive treatment.[22]

The prevalence of autoimmunity in patients with CVID varies from 7% to 33% in different studies.[9,24-29] Fischer et al showed that autoimmune manifestations occur throughout the patient's lifetime and that the overall survival time was significantly reduced in patients with autoimmune manifestations.[30] Treatment of noninfectious complications benefits from tailored approaches, including immunosuppressive treatment.

Malignancy is a major cause of early mortality in cohorts of adults with CVID. Up to 20% of adult patients with CVID develop cancer,[21,31-34] including malignancies of lymphatic tissue, such as non-Hodgkin lymphoma and gastrointestinal cancer, which is almost 50 times more frequent than in the healthy population.[21,35-37] Gastrointestinal tract malignancies (eg, gastric adenocarcinoma, liver carcinoma, colon adenocarcinoma) have been reported in patients with XLA.[11,38,39]

Group–specific consensus. As reported in Table IV, an agreement for 6 group-specific statements was reached and assumed as IPINet consensus. Thus, lifelong care of patients with confirmed B-cell defects should be led by a clinical immunologist as the case manager (rate of agreement 96%; score 0.76 ± 0.25). The continuity of IRT adherence and periodic

TABLE II. Common hallmarks of the clinical entities within each group CRDs during adolescence and transitional age

CRD	Main disorders included	Hallmarks	Main issues
Humoral defects	XLA or AR-agammaglobulinemia, CVID	Susceptibility to infections	Encapsulated bacteria
		Chronic lung disease	Bronchiectasis, GLILD, otitis, sinusopathy
		Chronic gastrointestinal involvement	Chronic enteropathy, malnutrition, primary biliary cirrhosis, hepatitis, and nodular regenerative hyperplasia, *Giardia lamblia* and/or bacterial or viral recurrent infections
		Long-lasting autoimmunity and autoinflammation	Thrombocytopenia, hemolytic anemia, arthritis, IBD, granuloma
		Lymphoproliferative disorders and malignancy	Lymphadenopathy, splenomegaly, lymphoma, solid cancer
		Susceptibility to infections	Osteomyelitis, meningitis
DGS spectrum	22q11.2 deletion syndrome, DiGeorge-like syndromes	Congenital and acquired cardiovascular anomalies	Postsurgery lifelong FUP, bacterial endocarditis, arrhythmia, ventricular dysfunction, and aortic root dilatation
		Neuropsychiatric disorders	Neurodevelopment decline, psychotic disorder, schizophrenia, anxiety, autism spectrum disorder, ADHD, depressive and mood disorders, brain abnormalities
		Immunologic features	Susceptibility to infections
			Autoimmune cytopenia and cancer susceptibility
		Endocrine aspects	Hypoparathyroidism/hypocalcemia, hypothyroidism, hyperthyroidism, obesity
		Orthopedic alterations	Cervical spine anomalies, severe scoliosis
		Genetic counseling	Reproductive genetic counseling and contraception
		Genitourinary anomalies	Unilateral renal agenesis, multicystic dysplastic kidney
CID	CID, late-onset CID and untreated SCID, syndromic CID, *CD40*, *CD40L* deficiency	Immunologic features	Progressive lymphopenia, severe/ atypical infections
		Immune dysregulation and autoimmunity	Cytopenia, vasculitis, HLH, granulomata, IBD, diabetes, thyroiditis, neuropathy
		Dermatologic issues	Severe eczema, CMC, warts
		Lymphoproliferative disorders and malignancy	Lymphoma, EBV-related lymphoproliferation, solid cancer
		Extraimmunologic manifestations	Involvement of several organs and systems
		Drug-related side effects	Drug toxicity, antibiotic resistance
Innate immunity defects	CGD, SCN, LAD, CMC, HIES	Susceptibility to infection	Fungi, *Staphylococcus aureus, Serratia marcescens, Nocardia* spp, *Salmonella*, and bacillus Calmette-Guérin infections
		Inflammation and autoimmunity	CGD colitis, systemic autoimmune disorders
		Malignancy	Hematopoietic and solid cancer
		Extraimmunologic manifestations	ID, growth retardation, skeletal and skin defects, albinism, metabolic diseases, vascular abnormalities
DRSs, Inborn errors with malignancies	A-T, A-T–like disorders, NBS, BS DKC, telomeropathies	Neurologic features	Progressive neurologic degeneration, extrapyramidal involvement
		Immunologic features	T- and B-lymphocyte deficiency, low Ig levels, susceptibility to infections
		Respiratory manifestations	Chronic bronchopneumopathy, ILD, pharyngeal incoordination, and respiratory muscles insufficiency
		Nutritional problems	Malnutrition, metabolic disorder
		Endocrine system and metabolic status	IGF-1 deficiency; pubertal delay; gonadal, thyroid, and adrenal gland dysfunction; insulin resistance; NASH; cardiovascular risk
		Immune dysregulation and cancer	Granuloma, lymphoid and solid tumors
		Hematologic features and malignancy	Bone marrow failure and cancer susceptibility
		Skin and annexa features	Oral leukoplakia, dystrophic nails, and reticular skin pigmentation
		Premature aging	Graying hair, liver fibrosis, portal hypertension, osteopenia

(Continued)

TABLE II. *(Continued)*

CRD	Main disorders included	Hallmarks	Main issues
HSCT or GT	Severe forms of IEIs (SCID, IPEX, CGD, HLH, WAS)	End-organ damage Long-term side effects of conditioning regimen Uncorrected disease manifestations Incomplete immune reconstitution Secondary cancer Chronic graft-versus-host disease Genetic counseling and sterility treatment	Infectious and noninfectious sequelae Cataract, endocrine dysfunction, liver and lung disease, metabolic syndrome Extraimmunologic manifestations Recurrent infections, autoimmune manifestations, immunoglobulin substitution, antimicrobial prophylaxis, immunosuppression Intrafamilial recurrence, drug-related sterility

AR, Autosomal recessive; *BS*, Bloom syndrome; *CMC,* chronic mucocutaneous candidiasis; *DKC*, dyskeratosis congenita; *FUP,* follow-up; *GLILD*, granulomatous lymphocytic interstitial lymphocytic disease; *HLH*, hemophagocytic lymphohistiocytosis; *IBD*, inflammatory bowel disease; IGF-1, insulin-like growth factor-1; *ILD*, interstitial lung disease; *IPEX*, immunodysregulation polyendocrinopathy enteropathy X-linked; *LAD,* leukocyte adhesion defect; *NASH*, nonalcoholic steatohepatitis; *NBS*, Nijmegen breakage syndrome; *SCN*, severe congenital neutropenia; *WAS*, Wiskott-Aldrich syndrome.

TABLE III. General statements for all CRDs with or without consensus

	Level of agreement (%) (mean score ± SD)					
Statement	Humoral immune defects	DGS	CID or untreated SCID	Innate immune disorders	DRSs and IEIs with malignancies	HSCT or GT
How should the transitional team be composed?						
A pediatric immunologist and an adult immunologist in a multidisciplinary setting, as required	92* (0.76 ± 0.35)	100† (0.81 ± 0.24)	100‡ (0.87 ± 0.22)	100§ (0.87 ± 0.22)	100‖ (0.83 ± 0.24)	96¶ (0.73 ± 0.25)
What are the process outcomes?						
Patient and family satisfaction	92 (0.75 ± 0.35)	92 (0.75 ± 0.35)	88 (0.68 ± 0.35)	74 (0.69 ± 0.37)	92 (0.76 ± 0.25)	96 (0.58 ± 0.30)
Adherence to therapies	92 (0.88 ± 0.21)	96 (0.73 ± 0.25)	92 (0.70 ± 0.25)	77 (0.69 ± 0.37)	76 (0.56 ± 0.47)	NA
Adherence to follow-up	92 (0.90 ± 0.20)	96 (0.73 ± 0.25)	92 (0.57 ± 0.38)	81 (0.67 ± 0.35)	89 (0.68 ± 0.35)	100 (0.73 ± 0.25)
Patient and family empowerment	96 (0.66 ± 0.24)	96 (0.84 ± 0.23)	NA	77 (0.78 ± 0.25)	89 (0.77 ± 0.25)	96 (0.68 ± 0.24)
Disease activity status#	NA	96 (0.80 ± 0.24)	96 (0.80 ± 0.24)	78 (0.68 ± 0.36)	92 (0.76 ± 0.25)	100 (0.69 ± 0.24)

NA, Not applicable.

Level of agreement is the sum of the percentage of strong agreement (rated +1) and level of agreement (rated +0.5); consensus is defined as a 75% or higher rate of agreement and a mean score of 0.75 or higher. Partial consensus is defined as a 75% or higher rate of agreement and a mean ranging from 0.65 to 0.74.

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†Psychiatrist, neurologist, endocrinologist, cardiologist, hematologist, and psychologist.

‡Infectiologist, endocrinologist, gastroenterologist, nutritionist, pulmonologist, gynecologist, dermatologist, and psychologist.

§Pulmonologist, gastroenterologist, cardiologist, dermatologist, oncologist, and orthopedist.

‖Neurologist, pulmonologist, gastroenterologist, cardiologist, dermatologist, oncologist, orthopedist, and psychologist.

¶Medical professional experienced in HSCT for adult patients with IEIs.

#Infection rate, admissions in emergency unit, extraimmunologic. complications, including neurologic, endocrine, malnutrition, abnormal liver and heart function, and joint deformities.

monitoring of serum IgG levels should be assessed (rate of agreement 92%; score 0.84 ± 0.33), making the patient aware of the potential complications of not adhering to IRT and for better self-regulation. The adherence to lung physiotherapy (rate of agreement 92%; score 0.88 ± 0.21) should be periodically evaluated, and monitoring of hematologic (eg, malignancy and cytopenia), gastrointestinal (eg, granulomatous diseases), and pulmonary complications must be ensured (rate of agreement 100%; score 0.94 ± 0.16). An adapted vaccination course should also be planned during adulthood in consideration of IRT (partial consensus; rate of agreement 96%; score 0.69 ± 0.34), and an annual complete follow-up should be guaranteed (partial consensus; score 0.72 ± 0.25). There was no consensus on the contraindications to starting the transition.

Common clinical hallmarks of the DGS group of CRDs during transition

22q11.2 deletion syndrome is the most frequent chromosomal microdeletion disorder underlying DiGeorge syndrome (DGS), occurring in up to 1 in 4000 live births.[40] In a few cases, cytogenetic abnormalities other than 22q11.2 or *TBX1* haploinsufficiency have been found in patients with a DGS clinical phenotype, including velocardiofacial syndrome or conotruncal anomaly face syndrome. Clinical features deserving maximal attention during adolescence and adulthood may be variable among different subjects.[40] The multitude of clinical manifestations associated with the syndrome and the high variability of the clinical phenotype complicate the transition of care in this syndrome.[40] It should be noted that in addition to the predominant

TABLE IV. Recommendation on transitional care for patients with humoral immune defects

Statement	Level of agreement (%)	Level of disagreement (%)	Mean score ± SD
Which clinical conditions mean that it is not appropriate to start the transition?			
No consensus			
Unstable clinical condition (eg, autoimmune flares, acute infection)	74	26	0.46 ± 0.66
Who should be the case manager within the adult team?			
Consensus			
Clinical immunologist	96	4	0.76 ± 0.25
No consensus			
Pulmonologist	29	71	–0.06 ± 0.61
Internist	89	11	0.62 ± 0.41
Any health care professional who assumes full responsibility for care coordination and planning	44	56	–0.01 ± 0.61
What are the peculiarities to focus on in this specific CRD?			
Consensus			
To ensure continuity of IRT adherence and monitoring	92	8	0.84 ± 0.33
To evaluate periodically adherence to lung physiotherapy	92	8	0.88 ± 0.21
To focus on hematologic, gastrointestinal, and lung complications	100	0	0.94 ± 0.16
Partial consensus			
To sensitize and monitor an adapted vaccination course	96	4	0.69 ± 0.34
To guarantee annual complete follow-up	89	11	0.72 ± 0.25

Level of agreement is the sum of the percentage of strong agreement (rated +1) and the percentage of agreement (rated +0.5); level of disagreement is the sum of percentage of strong disagreement (rated –1) and percentage of disagreement (rated –0.5). Consensus is defined as a 75% or higher level of agreement and a mean score of 0.75 or higher. Partial consensus is defined as a 75% or higher level of agreement and a mean score ranging from 0.65 to 0.74.

features summarized in Table II, the clinical phenotype may also encompass other manifestations, including dysmorphic features, which profoundly affect the self-confidence and social life, thus requiring special attention during adolescence.[27,41] A successful transfer to adult services is a very complicated process, especially in those patients with various organ and intellectual or developmental disabilities. Practical guidelines for managing pediatric and adult patients with 22q11.2 deletion syndrome have been proposed.

The specificity and critical issues of transition of care in this condition are summarized in the Table II.

Of note, several congenital heart disorders require lesion-specific management and lifetime surveillance, even after corrective surgery.[27,42] Furthermore, patients with DGS may develop cardiac manifestations during the follow-up as a result of comorbidities such as chronic kidney disease, leading to hypertension, endocrine dysfunction (parathyroid or thyroid disorders) causing arrhythmias, low physical activity, and side effects of antipsychotic therapies resulting in metabolic syndrome.[42]

As for neuropsychiatric disorders, intellectual disability (ID) and subsequent impaired social processing are common in DGS, with variable degrees of severity. A gradual decline in neurodevelopment throughout the lifespan has been reported, and a link between ID and psychiatric disease has been hypothesized.[27,43-45] Overall, the neuropsychiatric phenotype may evolve over time, with earlier symptoms persisting or being replaced by others with the transition from childhood to adulthood, thus entailing a strong need for continuous follow-up. Autism spectrum disorder and attention-deficit/hyperactivity disorder emerge during childhood and can have an impact on adult life as an independent issue. There is no apparent correlation between these disorders and the subsequent development of schizophrenia.[46] Interestingly, risk factors for the development of schizophrenia include the aforementioned early cognitive decline, social and executive dysfunction, and depressive and anxiety disorders,[47] which are common in adult patients. Among the other factors that may affect neuropsychiatric outcome and its interindividual variability are lower parental socioeconomic status and intrusive parenting style, which have been shown to be related to worse social functioning.[48] Special attention should also be placed on environmental demands: tracing a thorough outline of the individual's intellectual and psychiatric phenotype is mandatory to plan the required social adaptations to avoid the stress deriving from a mismatch.[27,47] Ear and palatal anomalies may be associated with hearing loss (found in 30%-40% of patients) and speech disorders,[40] which may often interfere with social functioning.[27,49]

Immune alterations may be very variable, ranging from partial DGS (characterized by normal or mild reduction of T-cell number and function) to complete DGS, in which the T-cell defect is more profound, resembling a severe combined immunodeficiency (SCID)-like phenotype associated with atypical infections.[50-52] Velopharyngeal insufficiency, gastroesophageal reflux, and asthma/rhinitis also may contribute to susceptibility to infection.[53] The incidence of infections tends to decrease with age. However, a few patients may require that prophylactic treatment with broad-spectrum antibiotics and, rarely, intravenous IgG or subcutaneous IgG also be continued in adulthood.[50] In this scenario, immunoglobulin levels, T-cell counts, and vaccine-specific antibody titers should be controlled over time, along with the frequency of infections. Counts of T cells, which show a senescent and memory phenotype, tend to increase with age.[54,55] Patients with DGS may also develop autoimmunity and immune dysregulation later in life, especially autoimmune cytopenias.[56] Notably, peculiar immunophenotypic alterations, such as decreased numbers of naive $CD4^+$ cells and class-switched B cells, have been identified early after diagnosis of DGS in patients who developed such complications; therefore, closer monitoring is warranted for these subgroups of patients.[56]

A higher overall rate of malignancies (eg, thyroid cancer, leukemia, lymphoma) has also been reported.[57]

Genetic counseling. Reproductive genetic counseling should be offered to patients, starting from adolescence and continuing throughout adulthood. Future parents should be informed about recurrence risk, even in the absence of causative deletion in their genotype, because of the potential germline mosaicism, and they should also be informed about broad interfamilial and intrafamilial variability in clinical phenotype.[40,49,50] They should be offered diagnostic testing by chorionic villus sampling or amniocentesis.[53] Gynecologic counseling during adolescence should be offered to prevent unplanned pregnancies.

Group-specific consensus. As reported in Table V, agreement regarding 6 group-specific statements was reached and assumed as IPINet consensus. Because of the wide spectrum of manifestations of this group of diseases, the case manager within the adult team should be identified with consideration for the prominent phenotypic feature of each patient (rate of agreement 96%; score 0.78 ± 0.25). Particular attention should be paid to cardiovascular (rate of agreement 100%; score 0.76 ± 0.25), neuropsychiatric (rate of agreement 96%; score 0.81 ± 0.34), and orthopedic (rate of agreement 96%; score 0.75 ± 0.25) issues, and genetic counseling (rate of agreement 96; score 0.78 ± 0.25) should be planned. Even though immunodeficiency may be more attenuated in adult patients, the raters agreed that attention should be paid to immune-related manifestations (partial consensus; rate of agreement 96%; score 0.70 ± 0.34).

In contrast, there was no consensus on conditions that contraindicate the transition. In all, 89% of raters agreed on the need to identify subspecialists who must be trained on the specificity of the peculiar features in the DiGeorge spectrum syndrome; however, a definitive consensus on this issue was not reached (score 0.62 ± 0.33). Furthermore, the majority of raters (37% and 45%, respectively) believed that a diagnosis close to the age of transition or the presence of smaller affected siblings may be not a significant obstacle to transition.

Common clinical hallmarks of the CID and untreated SCID group of CRDs during transition

SCIDs and late-onset combined immunodeficiencies are a group of heterogeneous genetic disorders characterized by severe recurrent infections, and impaired cellular and humoral functionality.[58,59] Because most patients with SCIDs are successfully treated with hematopoietic stem cell transplantation (HSCT), the transition of care is guided mainly by hematologists with expertise in HSCT who ensure LTFU of HSCT survivors. On the other hand, patients with milder phenotypes characterized by a late onset of the disease need to be closely evaluated for progression of the disease, including lymphopenia, and possible complications. Within this group, patients with profound combined immunodeficiency (CID) associated with severe infections and/or immune dysregulation often have an uncertain indication for HSCT, and its timing is debated on account of transplantation risks.[60] Moreover, patients who carry hypomorphic mutations of known SCID-causing genes can be diagnosed in adolescence or adulthood when they have a milder clinical presentation or are even clinically asymptomatic.[61] In such cases a potential progressive immunologic deterioration may be expected.[62-64] The specificity and critical issues of transition of care of patients with this condition are summarized in Table II.

Increased susceptibility to bacterial, fungal, or viral infections frequently results in chronic obstructive lung disease and/or bronchiectasis and chronic organs damage.[58,59] An atypical course of some infections (such as *Helicobacter* bacteremia, adenovirus/cytomegalovirus, EBV infections and, rarely, mycobacteriosis), chronic candidiasis, warts caused by human papilloma virus, or recurrent molluscum contagiosum, is also frequent in these patients. Moreover, patients undergoing lifelong prophylactic treatments should be regularly checked for the occurrence of drug-related side effects.

In some patients, the phenotype is predominated by immune dysregulation and autoimmunity, which can be triggered by infections. The prototype of the late-onset subgroup is recombination-activating gene hypomorphic deficiency, in which autoimmunity and hyperinflammation are common.[60,65] These patients should be regularly checked for the occurrence of EBV-related lymphoma or Hodgkin-like features. Uncontrolled hyperinflammation, as life-threatening hemophagocytic lymphohistiocytosis, may occur in all forms when proper clearance of an infectious agent fails to be achieved. Attention should also be paid to the transitional care of patients affected with radiosensitive disorders due to defects of nonhomologous end joining factors such as DNA ligase IV, which are associated with increased risk of developing leukemia and other lymphoproliferative disorders.[66]

CIDs with extraimmunologic manifestations (CIDs with associated or syndromic features), according to the phenotypic classification by IUIS, were also included within this group.[1] Several organs and systems may be involved, displaying microcephaly, dysmorphic facies, and developmental delay or skeletal, endocrine, and hematologic (eg, microthrombocytopenia) abnormalities. Malabsorption is a frequent issue.

CRD group–specific consensus. After a literature review and scoring, IPINet consensus was reached concerning a number of critical issues regarding transitional care for patients with CIDs and untreated patients with the clinical spectrum of SCIDs (Table VI). For patients with very rare untreated SCIDs, transition should be avoided if the adult center is not fully equipped to handle the potential severe progression and frequent clinical instability of these patients (rate of agreement 96%; score 0.75 ± 0.35), and transition should be postponed if the patient is critically ill (partial consensus; rate of agreement 100%; score 0.66 ± 0.33). The case manager within the adult team should preferentially be the clinical immunologist (rate of agreement 92%; score 0.78 ± 0.35). Attention should be paid to management of chronic end-organ damage and several extraimmunologic manifestations (rate of agreement 100%; score 0.83 ± 0.24), and new disease therapeutic strategies (rate of agreement 100%; score 0.86 ± 0.22) and indications for HSCT (rate of agreement 100%; score 0.81 ± 0.24) should be periodically discussed. Multidisciplinary discussion of diagnosis and further tests to improve the work-up of undiagnosed patients should be encouraged (rate of agreement 100%; score 0.81 ± 0.24), and drug-related side effects should be evaluated (rate of agreement 100%; score 0.79 ± 0.35). Even though high-efficiency particle air filtration rooms or laminar flow units are in general not mandatory, the adult center should ensure immediate medical care when necessary and the patient should be admitted to a single room (rate of agreement 96%; score 0.79 ± 0.34). In addition, monitoring of the progression of immunologic deterioration (partial consensus; rate of agreement 96%; score 0.72 ± 0.36), end-stage disease (partial consensus; rate of agreement 96%; score 0.68 ± 0.34), endocrine complications

TABLE V. Recommendation on transitional care for patients with DiGeorge spectrum syndrome

Statement	Level of agreement (%)	Level of disagreement (%)	Mean score ± SD
Which clinical conditions mean that it is not appropriate to start the transition?			
No consensus			
Lack of subspecialist experts in the specific aspects of the disease	89	11	0.62 ± 0.33
Recent diagnosis close to the age of transition	63	37	0.28 ± 0.61
Younger siblings affected	55	45	0.13 ± 0.62
Who should be the case manager within the adult team?			
Consensus			
The choice should take into account the prominent phenotypic feature	96	4	0.78 ± 0.25
No consensus			
Clinical immunologist	81	19	0.62 ± 0.48
Geneticist	51	49	0.09 ± 0.63
Internist	89	11	0.58 ± 0.40
Any health care professional who assumes full responsibility for care coordination and planning	74	26	0.35 ± 0.64
What are the peculiarities to focus on in this specific CRD?			
Consensus			
To manage cardiovascular anomalies, including congenital and acquired conditions (eg, congenital heart disorders, bacterial endocarditis, rhythm disturbances, ventricular dysfunction and aortic root dilatation, metabolic syndrome)	100	0	0.76 ± 0.25
To monitor the evolution of neuropsychiatric disorders	96	4	0.81 ± 0.34
To evaluate the progression of orthopedic impairment (ie, scoliosis, club foot)	96	4	0.75 ± 0.25
Genetic counseling	96	4	0.78 ± 0.25
Partial consensus			
To evaluate immune functionality and immune-related manifestations	96	4	0.70 ± 0.34
No consensus			
To guarantee complete follow-up biannually	76	24	0.45 ± 0.55

Level of agreement is the sum of the percentage of strong agreement (rated +1) and the percentage of agreement (rated +0.5); level of disagreement is the sum of the percentage of strong disagreement (rated –1) and the percentage of disagreement (rated –0.5). Consensus is defined as a 75% of higher level of agreement and a mean score of 0.75 or higher. Partial consensus is defined as a 75% or higher level of agreement and a mean score ranging from 0.65 to 0.74.

(partial consensus; rate of agreement 100%; score 0.72 ± 0.25), and QoL (partial consensus; rate of agreement 96%; score 0.66 ± 0.33) should be performed.

No consensus was reached regarding the follow-up intervals that should be adapted for each subject or regarding nutritional issues.

Common clinical hallmarks of the innate and intrinsic immunity defects group of CRDs during transition

Defects in innate and intrinsic immunity encompass a heterogeneous group of inherited diseases associated with invasive, life-threatening infections characterized mainly by increased susceptibility to a single or narrow group of microorganisms and immune dysregulation leading to autoimmune and autoinflammatory disorders**.** Within this CRD group, particular attention in the transitional care process must be paid to congenital defects of phagocyte function and number, such as chronic granulomatous disease (CGD), leukocyte adhesion deficiency (LAD), congenital neutropenias (CNs), chronic mucocutaneous candidiasis (CMC) due to signal transducer and activator of transcription 1 (*STAT1*) gain-of-function (GOF) mutations, and hyper-IgE syndrome (HIES).[1,67] All these disorders, although profoundly different in their pathogenic mechanism, share similarities in the major clinical problems that may characterize patients during adolescence and early adulthood.

The main common clinical hallmark of patients with innate and intrinsic immunity includes an increased risk of bacterial and fungal infections. In particular, patients affected with CGD, or with CNs, may develop severe recurrent infections mainly due to *Aspergillus* spp and *Staphylococcus aureus*.[68-70] A recent study documented that one-third of all infectious events occurred in patients with CGD after the age of 16 years. Similarly, noninfectious granuloma or inflammatory granulomatous bowel disease in patients with CGD occurred during the same period in 46% of patients. The prognosis of CGD has greatly improved since it was first described thanks to earlier diagnosis, better management of infectious and inflammatory complications, antibacterial and antifungal prophylaxis, and good outcome after HSCT.[71,72] The aging process of the population of individuals with CGD, as a paradigm of the whole CRD group, poses new challenging problems because of the lifetime recurrence of pulmonary manifestations and sequelae; growth failure; and noninfectious liver disease, including toxic drug–induced hepatitis, nodular regenerative hyperplasia, noncirrhotic portal hypertension, and several autoimmune manifestations. Although the frequency of inflammatory episodes tends to increase slightly after the age of 16 years, infectious events tend to decrease over time.[73] Thus, although infections remain the first cause of death, inflammatory complications, mainly pulmonary or digestive, seem to predominate during adulthood. For patients with CN, the availability of granulocyte–colony-stimulating factor (G-CSF) therapy drastically changed the QoL and their overall survival is now estimated at approximately 80%. However, about 10% of patients (mainly G-CSF nonresponders) still die from severe bacterial infections.[74] *STAT1* GOF mutation accounts for half of the cases of CMC. Affected patients are at risk of invasive candidiasis (sepsis,

TABLE VI. Recommendation on transitional care for patients with CID or untreated SCID

Statement	Level of agreement (%)	Level of disagreement (%)	Mean score ± SD
Which clinical conditions mean that it is not appropriate to start the transition?			
Consensus			
For untreated patients with SCID, transition may be not feasible if the adult center is not fully equipped	96	4	0.75 ± 0.35
Partial consensus			
Critical illness (eg, active opportunistic infections or severe invasive/systemic infections or uncontrolled immune dysregulation manifestations)	100	0	0.66 ± 0.33
Who should be the case manager within the adult team?			
Consensus			
Clinical immunologist	92	8	0.78 ± 0.35
No consensus			
Hematologist	63	37	0.23 ± 0.57
Pulmonologist	19	81	–0.38 ± 0.41
Internist	78	22	0.42 ± 0.51
Any health care professional who assumes full responsibility for care coordination and planning	41	59	–0.12 ± 0.54
What are the peculiarities to focus on in this specific CRD?			
Consensus			
To manage each chronic end-organ damage	100	0	0.83 ± 0.24
To manage several extraimmunologic features	100	0	0.83 ± 0.24
To periodically discuss new disease therapeutic strategies	100	0	0.86 ± 0.22
Periodic multidisciplinary discussion of diagnosis and further tests to improve the work-up in undiagnosed patients	100	0	0.81 ± 0.24
Periodic discussion of indication to HSCT (especially in late-onset and evolving diseases)	100	0	0.81 ± 0.24
To monitor drug-related side effects	100	0	0.79 ± 0.35
The adult center should ensure immediate medical care when necessary and isolation of the patient in a single room	96	4	0.79 ± 0.34
Partial consensus			
To monitor the progression of functional immunologic deterioration	96	4	0.72 ± 0.36
To manage the progression to end-stage disease	96	4	0.68 ± 0.34
To monitor endocrine complications (primary or secondary to therapies)	100	0	0.72 ± 0.25
To evaluate QoL index	96	4	0.66 ± 0.33
No consensus			
To guarantee complete follow-up biannually	92	8	0.57 ± 0.38
To provide exclusive or partial enteral nutrition	92	8	0.62 ± 0.40

Level of agreement is the sum of the percentage of strong agreement (rated +1) and the percentage of agreement (rated +0.5); level of disagreement is the sum of the percentage of strong disagreement (rated –1) and the percentage of disagreement (rated –0.5). Consensus is defined as a 75% or higher rate of agreement and a mean score of 0.75 or higher. Partial consensus is defined as a 75% or higher rate of agreement and a mean ranging from 0.65 to 0.74.

nephritis), or other fungal infections, which may manifest in adulthood also.[75,76] As CMC may be the cause of impairment in activities of daily living or social barriers, long-term prophylaxis should be continued for these patients. Autoimmune manifestations, including thyroiditis, type 1 diabetes, cytopenia, and enteropathy, may occur in the whole CRD group during the second decade of life.[77]

The risk of malignancies in CMC, HIES, and CN is high. Most patients with CN are at increased risk of progression to myelodysplasia and acute myeloid leukemia (AML). The cumulative incidence of myelodysplasia and/or AML is estimated at 11% at 20 years of age and at 22% after 15 years of G-CSF therapy. Although it has been clearly demonstrated that G-CSF dramatically improves survival of patients with CN, it is also likely that G-CSF itself affects clonal evolution. The risk of developing AML or myelodysplasia varies considerably across the spectrum of genetic etiologies: by 30 years of age, this rate is estimated to be roughly 60% in patients with *GATA2* mutations, 30% in patients with *SBDS* mutations, and 15% in patients with *ELANE* mutations. Chromosomal abnormalities, including monosomy 7 and gain of chromosome 21, as well as additional acquired somatic mutations in *CSF3R* and *RUNX1* genes, are frequently detected before AML transformation and should be checked.[61] Oral squamous cell carcinoma and esophageal cancer constitute the most common cause of death due to malignancy in patients with *STAT1* GOF mutations. Other cancers have also been reported in affected patients: cutaneous, gastrointestinal, or laryngeal carcinoma; melanoma; or even leukemia. About 7% of patients with HIES also develop malignancies, especially various types of lymphoma.[78]

As for extraimmunologic manifestations, severe mental and growth retardation in late childhood as a consequence of defect in fucose metabolism have been reported in patients with LAD-2. The risk of bleeding is also an important issue in LAD-3 on account of mutation in the kindlin-3 gene, affecting the integrin activation cascade. CNs are sometimes associated with a multiplicity of syndromic features that may include oculocutaneous albinism, metabolic diseases, and bone marrow failure syndromes. When compared with children without CGD, children with CGD exhibit higher rates of difficulty acquiring social and/or school skills, difficulty establishing peer relationships, and conduct and/or emotional problems.[79] In contrast, adults with CGD report greater

TABLE VII. Recommendation on transitional care for patients with innate immune disorders

Statement	Level of agreement (%)	Level of disagreement (%)	Mean score ± SD
Which clinical conditions mean that it is not appropriate to start the transition?			
Consensus			
Critical illness (eg, active or severe invasive/systemic infections, uncontrolled inflammatory/autoimmune manifestations)	92	8	0.76 ± 0.42
Recent onset or treatment of myelodysplasia or leukemia or HSCT	92	8	0.76 ± 0.42
Who should be the case manager within the adult team?			
Consensus			
Clinical immunologist	96	4	0.82 ± 0.24
Partial consensus			
Internist	92	8	0.70 ± 0.42
No consensus			
Pulmonologist	34	66	–0.23 ± 0.45
Infectiologist	70	30	0.23 ± 0.51
What are the peculiarities to focus on in this specific CRD?			
Consensus			
To monitor severe and recurrent infections	100	0	0.82 ± 0.24
To monitor recurrence of infections due to a single group of microorganisms	89	11	0.85 ± 0.23
To manage accelerated progression of common infections	89	11	0.87 ± 0.22
To manage inflammatory and autoimmune diseases	96	4	0.84 ± 0.23
To manage progressive and chronic end-organ damage	100	0	0.87 ± 0.22
To manage extraimmunologic condition	92	8	0.76 ± 0.25
Malignancy surveillance	96	4	0.78 ± 0.25
To monitor drug-related side effects/multidrug resistance	81	19	0.84 ± 0.23
To evaluate new disease therapeutic strategies	81	19	0.81 ± 0.24
To manage pregnancy and genetic counseling	77	23	0.78 ± 0.25
To evaluate QoL index	81	19	0.81 ± 0.24
Partial consensus			
To manage malnutrition and growth failure and/or pubertal delay	85	15	0.72 ± 0.36

Level of agreement is the sum of the percentage of strong agreement (rated +1) and the percentage of agreement (rated +0.5); level of disagreement in the sum of the percentage of strong disagreement (rated –1) and the percentage of disagreement (rated –0.5). Consensus is defined as a 75% or higher level of agreement and a mean score of 0.75 or higher. Partial consensus is defined as a 75% or higher level of agreement and a mean score ranging from 0.65 to 0.74.

difficulties in either mental and physical area than adults without CGD do. Clinical status may affect psychological and school dimensions and social networking.[59] Inflammatory symptomatic cerebral and extracerebral aneurysms and aortic calcification have been detected at a higher rate than in the general population and at a younger age (23 vs 50 years) in patients with *STAT1* GOF mutation syndrome than in those without such mutation.[80,81] Cumulative survival rate was significantly lower in patients who developed invasive infections, cancer, and/or symptomatic aneurysms.[77] In patients with HIES, facial abnormalities, retention of the primary teeth, skeletal abnormalities such as osteopenia resulting in multiple fractures for minor traumas and scoliosis, joint hyperextensibility, various vascular malformations, and chronic severe eczema have been described.[52,78,82]

Several genetic defects associated with susceptibility to specific pathogens or a narrow group of pathogens (mycobacteria, pyogenes, human papilloma virus, herpes simplex virus, and other viruses; *Candida* spp, and other fungi) have been recently described, thus requiring a personalized approach.

CRD group–specific consensus. After a literature review and scoring, IPINet consensus was reached concerning a number of critical issues on transitional care for innate and intrinsic immunity defects (Table VII). Active or severe invasive and/or systemic infections, uncontrolled inflammatory or autoimmune manifestations, recent onset or treatment of myelodysplasia or leukemia, or HSCT might contraindicate the transition process (rate of agreement for both 92%; score 0.76 ± 0.42). The case manager within the adult team should be the clinical immunologist (rate of agreement 96%; score 0.82 ± 0.24); alternatively, the internist should be considered (partial consensus; rate of agreement 92%; score; 0.70 ± 0.42). To manage inflammatory, autoimmune (rate of agreement 96%; score 0.84 ± 0.23), chronic end-organ damage (rate of agreement 100%; score 0.87 ± 0.22), and extraimmunologic manifestations (rate of agreement 92%; score 0.76 ± 0.25), including the risk of aneurysm in *STAT1* GOF mutations; special attention should be paid to monitoring recurrence and severity of infections (rate of agreement 100%; score 0.82 ± 0.24), especially those due to a single group of microorganisms (rate of agreement 89%; score 0.85 ± 0.23) or with accelerated progression (rate of agreement 89%; score 0.87 ± 0.22). Malignancy surveillance, including cytogenetic studies, is mandatory in several forms (rate of agreement 96%; score 0.78 ± 0.25). Monitoring of drug-related side effects, multidrug resistance (rate of agreement 81%; score 0.84 ± 0.23), and QoL should be carried out (rate of agreement 81%; score 0.81 ± 0.24). New disease therapeutic strategies should be discussed periodically (rate of agreement 81%; score 0.81 ± 0.24), and pregnancy management and counseling should be offered (rate of agreement 77%; score 0.78 ± 0.25). Attention should be paid to malnutrition risk and to the growth failure and/or pubertal

delay (partial consensus; rate of agreement 85%; score 0.72 ± 0.36).

Common clinical hallmarks of the DNA repair syndromes and IEIs with malignancy susceptibility group of CRDs

DNA repair syndromes (DRSs) are a heterogeneous group of conditions characterized by defects in the process of DNA damage repair and, clinically, mainly by neurologic, immunologic, and systemic involvement. The CRD group includes ataxia-telangiectasia (A-T) and AT-like disorders, Nijmegen breakage syndrome, Bloom syndrome, and other rarer disorders.[24] Other IEIs associated with cancer susceptibility include dyskeratosis congenita, an inherited bone marrow failure syndrome that is typically characterized by skin and annexa features, as illustrated in Table II. To date, several genetic alterations may modify telomere maintenance and function.[83] Bone marrow failure is the primary cause of death in these patients, and therefore, HSCT is the only curative treatment.[84] However, HSCT cannot correct other systemic manifestations of defects of telomere maintenance.[85] In rarer telomeropathies, premature aging, liver fibrosis, and predisposition to myelodysplastic syndrome and myeloid leukemia are reported. All these conditions share a poor prognosis as a result of development of serious complications such as malignancies and bone marrow failure.

A-T (Online Mendelian Inheritance in Man no. 208900), although rare, is the most frequent DRS and will be used as a model for management and surveillance for the whole group; the remaining DRSs, share similar management protocols with A-T.[86] The main causes of death in A-T are respiratory infections, leading to progressive respiratory failure, and cancer.[87] The multiple and different functions played by Ataxia telangiectasia mutated (ATM) protein explain well the wide variety of clinical manifestations in individuals with A-T and the severity of their clinical phenotype (classic vs mild).[86] Affected individuals with classic A-T usually survive until the second or third decade of life, whereas individuals with milder cases can reach their 60s.[24,88]

The improvement in the quality of care has changed the natural history of A-T by lengthening life expectancy and revealing new clinical manifestations typically associated with young adulthood.[89,90] Given the complexity of these heterogeneous conditions, transition of care must be tailored to the individual patient.

A-T is characterized by progressive cerebellar degeneration, extrapyramidal disorders, and oculomotor apraxia.[91,92] Progressive motor dysfunction is responsible for postural anomalies, dysarthria, respiratory failure, and joint contractures that worsen the nutritional aspect. These manifestations are variably represented in the young adult with A-T, who invariably also experiences loss of gait and significant movement disorders.[93] Regarding the neurologic manifestations, which are only transiently controlled by therapies,[12,94,95] adult neurologists (mainly experts in movement disorders), physiatrists, psychologists, and therapists with expertise in motor disability, respiratory, speech, and occupational rehabilitation are required.[24,89]

About two-thirds of patients with A-T have an immune defect with a reduction in T- and B-lymphocyte counts that is often associated with deficiency of 1 or more immunoglobulin classes. About 10% of patients show hyper-IgM syndrome, which together with the IgG2 deficiency, is associated with a worse clinical course. Immunodeficiency leads to increased susceptibility to infections, which affect the lung almost exclusively.[90] Under certain circumstances, antibiotic prophylaxis, IRT, and vaccinations have proved effective in the prevention of infectious diseases.[12,52] HSCT has been used in very few patients, but the results are not encouraging.[2]

Respiratory disease progresses with age and includes (1) respiratory chronic disease due to recurrent infections, (2) interstitial lung diseases, and (3) respiratory manifestations due to the neurologic dysfunction.[87,96] Optimal multispecialist respiratory management of young adult patients is necessary owing to the recurrence of respiratory manifestations, pharyngeal incoordination, and insufficiency of the respiratory muscles. Specific guidelines for antibiotic prophylaxis in A-T are not available; however, indirect indications may be obtained from the experience of cystic fibrosis, or as suggested by expert opinions. IRT is generally considered only in the case of frequent respiratory infections and poor antibody response to specific immunizations. IL-6 and IL-8 may serve as potential biomarkers to identify subjects at higher risk of lung failure.[41,89,97] Interstitial lung disease occurs in about 25% of patients with A-T and usually develops during adolescence. Regular functional monitoring of lung airways by means of spirometry and respiratory physiotherapy is required. Chest radiographs and high-resolution computed tomography scan may show different degrees of inflammation and pulmonary fibrosis, but they are not indicated in these patients; MRI should be preferred given the radio sensitivity.[98]

The nutritional status of adolescents with A-T is often compromised, which is, at least in part, explained by swallowing disorders, recurrent infections, respiratory failure, and reduced motor activity. The involvement of the endocrine and skeletal systems, along with frequent metabolic alterations, contributes to malnutrition.[99,100]

The treatment of endocrine abnormalities is mainly based on use of replacement therapies and on control of the nutritional intake.[101] Vitamin D and lipid metabolism may be impaired in a number of cases. Nonalcoholic steatohepatitis (NASH) is a fairly common condition in adults with A-T, and it parallels metabolic syndrome. NASH leads to liver failure with progressive and irreversible liver fibrosis due to accumulation of fats and to the subsequent inflammatory process. FibroScan, MRI, and MRI with elastography are also useful in NASH monitoring. In the absence of a specific therapeutic treatment, adjustments of the nutritional plan on the basis of liver conditions remain the main supportive treatment.[102,103]

Glucose intolerance, alteration of lipid metabolism, metabolic syndrome, and low levels of vitamin E contribute to the risk of acute (myocardial infarction and stroke) and chronic cardiovascular diseases (eg, arterial hypertension). The use of antioxidant drugs, which are also indicated for the treatment of NASH, is supported by evidence of efficacy in small groups of cases so far reported.

Granuloma, a predominantly inflammatory lesion, frequently occurs in A-T; it mainly affects the skin and, less frequently, the bones, joints, or internal organs. It is likely related to previous administration of the rubella vaccine and has a chronic progressive course. Therapeutic options include topical corticosteroids associated with immunoglobulins, TNF inhibitors; more recently, allogenic HSCT has been proposed.[65,104]

Malignancies mainly affect blood and lymphoid organs, with an increase of solid tumors in young adulthood. Surveillance protocols and treatments require strong attention and careful

monitoring, as patients are hypersensitive to radiography, radiomimetic drugs, and chemotherapy, which are often fatal.

CRD group–specific consensus. After a literature review and scoring, IPINet consensus was reached concerning the following critical issues on transitional care for DRSs and IEIs with susceptibility to malignancy (Table VIII): severe respiratory failure, profound malnutrition or cachexia, advanced neurodegeneration, and end-stage cancers in extremely compromised patients might contraindicate the transition process (rate of agreement 96%; score 0.76 ± 0.35). A partial consensus was reached concerning the case manager within the adult team, who in the opinion of many raters should be the clinical immunologist (rate of agreement 92%; score 0.67 ± 0.34). Special attention should be paid to monitoring multisystemic disease, neurologic deterioration, respiratory failure, and endocrine imbalance, as well as to conducting cancer surveillance (rate of agreement 89%; score 0.81 ± 0.24). Close cooperation between pediatric and adult care physicians is mandatory (rate of agreement 89%; score 0.77 ± 0.25); relevant care professionals such as physical, speech, respiratory, and occupational therapists and nutritionists are highly recommended (rate of agreement 100%; score 0.83 ± 0.24), and the support of a psychologist is highly suggested for patients and their families (rate of agreement 100%; score 0.81 ± 0.24). Younger adults may take advantage of assistance from special education teachers in the transition process (rate of agreement 92%; score 0.78 ± 0.25), and periodic discussions aimed at the mitigation of disease-specific barriers, including aspects related to incomplete understanding of disease pathophysiology and at the evaluation of therapeutic opportunities, should be held (partial consensus; rate of agreement 89; score 0.68 ± 0.24).

No consensus was reached regarding the evaluation of QoL because the majority of raters believed that it may be related more to the natural history of the disorder in adolescence rather than to the transition process.

Common clinical hallmarks in the transitional care for patients having undergone HSCT or GT in childhood

Cellular therapy is increasingly being used for patients with IEIs. Treatment approaches include allogeneic HSCT or autologous hematopoietic stem cells (HSCs) with gene therapy (GT).[105] Allogeneic HSCT is a well-established treatment for the most severe forms of IEIs, including SCID, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome, Wiskott-Aldrich syndrome, and CGD.[106-109] The development of less toxic conditioning regimens (eg, use of reduced dose busulfan, treosulfan, and/or fludarabine) and more sophisticated stem cell procurement and *in vitro* manipulation have led to more widespread use of HSCT for patients with IEIs. Thus, it has been proposed as a treatment option for several other IEIs (eg, CID, lypopolysaccharide-responsive beige-like anchor *[LRBA]* protein, or adenosine deaminase 2 deficiency).[60,110,111] The GT approach has been identified as a successful definitive treatment option for several IEIs, with some advantages over allogeneic HSCT, including the use of autologous HSC and a reduced rate of mortality and complications thanks to less intensive chemotherapeutic agents.[112,113] Patients who received HSCT or HSC GT require LTFU, and transition of care to a dedicated adult team is critical to maintain a high quality of care over the long term.

In particular, attention should be paid to the different clinical aspects, as illustrated in Table II. The uncorrected gene defect in nonhematopoietic tissues may be responsible for ongoing extraimmunologic manifestations.[2] Immune function may not be completely restored by cellular therapy on account of incomplete engraftment or rejection in the case of HSCT or insufficient transduction and loss of gene-corrected cells in GT trials. Specific HSCT settings are associated with a high risk of incomplete immune reconstitution (eg, unconditioned HSCT for IL-2 receptor subunit gamma deficiency is associated with absent B-cell engraftment).[114] Patients might require further cell therapy, or they might need lifelong prophylactic measures to control the disease manifestations. In the latter case, monitoring of complications related to the original IEI should be guaranteed over the course of LTFU. Vaccination schedule and the specific antibody response should be carefully monitored over time.[115]

Among patients surviving cellular therapy for IEIs, an increased risk of cancer might exist because of (1) the specific gene defect (eg, DNA instability); (2) long-term effects of the conditioning regimen; or (3) potentially, insertional oncogenesis (GT).[116,117]

Genetic counseling and sterility treatment. Survivors of cellular therapy for IEIs require genetic counseling to assess the risk of transmitting the disease to their offspring. Moreover, drugs used in the conditioning regimen can cause sterility in some patients. Survivors need adequate counseling and treatment for fertility preservation and also regarding the use of cryopreserved ovules, ovarian tissue, or sperm.[118]

CRD group–specific consensus. Only limited data are available to guide the choice of the optimal clinical model to provide such transitional care. As shown in Table IX, agreement was achieved regarding extraimmunologic manifestations, drug toxicity, and risk for the offspring (rate of agreement 92%; score 0.80 ± 0.25), as well as regarding the need for monitoring of uncorrected manifestations and incomplete immune reconstitution (rate of agreement 100%; score 0.78 ± 0.25), severe organ damage, and chronic graft-versus-host disease (rate of agreement 100%; score 0.82 ± 0.24) and evaluation of QoL (partial consensus; rate of agreement 96%; score 0.66 ± 0.24).

No consensus was reached regarding those clinical conditions for which starting the transition is deemed inappropriate or on the evaluation of vaccination status.

The available information is mostly derived from patients receiving HSCT for childhood cancer, and little is known regarding patients undergoing cellular therapy for IEIs.[2,5,119] However, the majority of raters agreed that the adult team needs to incorporate medical personnel specifically trained in HSCT or GT for IEIs. Because only a few centers worldwide perform cellular therapy for adults with IEIs, the capacity of these structures might not suffice to address the need for all patients requiring LTFU. We propose that in a setting in which such professionals are not available, the LTFU might be provided by a hematologist experienced in cellular therapy in close collaboration with an immunologist experienced in IEIs. Second, patients receiving GT are often enrolled in study protocols that require a specific long-term follow-up as required by the competent authorities (US Food and Drug Administration and European Medicines Agency). In such a setting, the transition to another team might cause issues in the compliance with study requirements. The follow-up plan should be clearly stated, and the results of relevant

TABLE VIII. Recommendation on transitional care for patients with DRSs and IEIs with malignancy susceptibility

Statement	Level of agreement (%)	Level of disagreement (%)	Mean score ± SD
Which clinical conditions mean that it is not appropriate to start the transition?			
Consensus			
Severe respiratory failure, profound malnutrition/cachexia	96	4	0.76 ± 0.35
Advanced neurodegeneration	96	4	0.76 ± 0.35
End-stage cancers in extremely compromised patients	96	4	0.76 ± 0.35
Who should be the case manager within the adult team?			
Partial consensus			
Clinical immunologist	92	8	0.67 ± 0.34
No consensus			
Neurologist	56	44	0.13 ± 0.67
Pulmonologist	45	55	0 ± 0.56
Internist	85	15	0.56 ± 0.46
Any health care professional who assumes full responsibility for care coordination and planning	56	44	0.13 ± 0.67
What are the peculiarities to focus on in this specific CRD?			
Consensus			
To monitor several aspects of the multisystemic disease	89	11	0.81 ± 0.24
To monitor neurologic deterioration, respiratory failure, endocrine imbalance, and cancer surveillance	89	11	0.81 ± 0.24
To ensure a solid cooperation between pediatric and adult care physicians	89	11	0.77 ± 0.25
To ensure care by physical, speech, respiratory, occupational therapists and nutritionists	100	0	0.83 ± 0.24
To ensure psychologist support	100	0	0.81 ± 0.24
To ensure educator teacher support	92	8	0.78 ± 0.25
Partial consensus			
To mitigate the presence of disease-specific barriers (eg, incomplete understanding of disease pathophysiology, limitations of information)	89	11	0.68 ± 0.24
To discuss current therapeutic strategies and difficulty of experimental trials	89	11	0.68 ± 0.24
No consensus			
To evaluate QoL index	81	19	0.64 ± 0.42

Level of agreement is the sum of the percentage of strong agreement (rated +1) and the percentage of agreement (rated +0.5); level of disagreement is the percentage of strong disagreement (rated –1) and the percentage of disagreement (rated –0.5). Consensus is defined as a 75% or higher level of agreement and a mean score of 0.75 or higher. Partial consensus is defined as a 75% or higher level of agreement and a mean score ranging from 0.65 to 0.74.

TABLE IX. Recommendation on transitional care for patients with IEIs who underwent HSCT or gene therapy

Statement	Level of agreement (%)	Level of disagreement (%)	Mean score ± SD
Which clinical conditions mean that it is not appropriate to start the transition?			
No consensus			
Enrolment in a study protocol requiring a specific long-term follow-up (mainly after gene therapy)	77	23	0.50 ± 0.54
Unstable chimerism	77	23	0.35 ± 0.49
What are the peculiarities to focus on in this specific DRG?			
Consensus			
To manage several aspects related both to the genetic disease (eg, nonimmunologic disease manifestations, risk for the offspring) and to the treatment (ie, late toxicity of the conditioning regimen and infused products on fertility, endocrinologic, pneumologic, auxologic aspects)	92	8	0.80 ± 0.25
To monitor uncorrected manifestations and incomplete immune reconstitution	100	0	0.78 ± 0.25
To monitor organ damage and cGVHD	100	0	0.82 ± 0.24
Partial consensus			
To evaluate QoL index	96	4	0.66 ± 0.24
No consensus			
To evaluate the response to vaccinations and attendance to the community	92	8	0.59 ± 0.31

cGVHD, Chronic graft versus host disease.
Level of agreement is the sum of percentage of strongly agreement (rated +1) and the percentage of agreement (rated +0.5); level of disagreement is the sum of the percentage of strong disagreement (rated –1) and the percentage of disagreement (rated –0.5). Consensus is defined as a 75% or higher level of agreement and a mean score of 0.75 or higher. Partial consensus is defined as a 75% or higher level of agreement and a mean score ranging from 0.65 to 0.74.

assessments should be transmitted to the original team that treated the patient with GT.

DISCUSSION

Adolescents and young adults affected with IEIs represent a very vulnerable population. In 2011, the American Academy of Pediatrics, with the endorsement of the American Academy of Family Physicians and the American College of Physicians, emphasized the need to plan health care transition for chronic diseases.[4,120] Although programs of transitional care are continuously evolving for patients affected with several pediatric-onset chronic conditions (eg, cystic fibrosis, inflammatory bowel disease, diabetes mellitus, rheumatologic diseases), at present none of them focuses on IEIs. The medical problems at the time of transition of young people with IEIs are often complex and characterized by a marked trend toward progression over time. Thus, transition of care is critical to maintaining high quality of care of patients with IEIs during LTFU, and it should be considered an emerging priority.[5] IEIs are newly identified diseases, with new gene defects continuously discovered, thus implying that time is required to allow a proper overall knowledge among adult health care professionals. Most adult immunologists are dealing mainly with allergy or autoimmunity and not with IEIs, and many adult specialists in gastroenterology, endocrinology, and respiratory diseases have little or no exposure to patients with IEIs during their training. Dynamic programs aimed at improving awareness of physicians to recognize complications, and promoting optimal treatment, should be implemented in each center to break down barriers. Without an established transition program, a significant number of patients may be lost to follow-up during transfer, with consequently higher rates of nonadherence and increased morbidity and mortality.[5,101]

Because of the high number of IEIs, which differ profoundly in terms of clinical phenotypic expression, the transition process may not be a one-size-fits-all undertaking. The IPINet Committee categorized IEIs in different groups of CRDs that share common major clinical hallmarks deserving special attention during the transition. The committee formulated a number of statements for each CRD group to help physicians during the process. Both pediatricians and adult care providers need to screen for, prevent, and treat unique medical and psychosocial comorbidities associated with different IEIs in a tailored approach to health.[60] Adaptation of vaccination schedule, monitoring of the effects of advanced therapies and IRT, cancer surveillance, and promotion of preventive health measures and compliance with care (including lung physiotherapy) are critical to achieve successful clinical management in this population. A few patients with IEIs have different degrees of ID, requiring a personalized approach to transition, including decision-making support and neuropsychiatric evaluations by trained providers.

New technologies, such as chromosome microarray and high-throughput next-generation sequencing, were not available when patients with childhood-onset IEIs were first investigated.[60] Therefore, adolescents without a definite molecular diagnosis should be reevaluated before transition.

One of the main issues that emerged is that the transition may be a very difficult task for those patients with more complex syndromes, mainly when a specialized, fully trained, and well-equipped adult center is not available. Adult specialist physicians should have dedicated expertise in the specific clinical problem within the context of the IEI pathogenic mechanism.

Critical health conditions have been considered by the committee a contraindication to the transition for most IEIs. Nevertheless, to avoid sudden decisions that are forced or imposed under unexpected and rapidly progressive conditions in the context of an intensive care setting health care, providers should carefully plan in advance the transition for patients with severe chronic organ damage. Young adults with IEIs experience psychosocial issues, such as depression, anxiety, suicidal ideation, relational difficulties, and engagement in risky behaviors, which require careful psychological support.

Going forward, improving transitional services will require careful evaluation of several issues through *ad hoc* studies focusing on development of valid measures of quality improvement and implementation and also taking local resources into consideration. Quantification of health-related QoL in IEIs has recently been initiated as an important tool to evaluate patients' health status over time, to assess the effects of therapeutic intervention, and the appropriateness of the transitional process.[59] Unlike for other chronic conditions such as diabetes or cystic fibrosis, for which QoL measures are available, for IEIs, only the CVID-QoL questionnaire has been developed as a disease-specific instrument for adults with CVID.[121] Several variables have been suggested as objective outcome measures for evaluating a successful transition, including reduced attempts to return to child-centered care. It must be emphasized that disease-specific outcome measures are to be preferred. Unfortunately, tools to evaluate the process outcome for IEIs are not available. Instruments validated for other chronic diseases, such as the Karnofsky Performance Status Scale, the Mind the Gap scale or the On Your Own Feet Transfer Experiences Scale, the Hospital Anxiety and Depression Scale, and the Treatment Satisfaction Questionnaire for Medication-9, may be used to evaluate disease activity status, anxiety, depression, or adherence to therapy. Patient and family empowerment should be checked according to the American College of Physicians to evaluate the transition readiness. The frequency of follow-up has not reached universal consensus because data obtained during the transitional age are not available. However, follow-up should be adapted to each IEI, to the peculiarity of each patient, and to center rules. Subspecialty physicians should be involved by the Case Manager on an individual basis.

In Developing Countries with a poor economy, the shortage of health care providers and the difficulty of creating multidisciplinary teams make planning transitional care even more complex, and thus, protocols should be adapted to local environment.

Our scope was aimed at defining a general framework to help the transition process in the group of IEIs, which are extraordinarily complex diseases that invariably challenge physicians, patients, and their families.

Conclusion

We have presented a consensus statement on the transitional care for patients with different IEIs that can serve as a rational basis for future experimental studies and guidance. These guidelines will be updated periodically as more evidence becomes available.

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Clinical implications: A consensus on the transition process to adult health care services for patients with IEIs has been formulated by physicians from the IPINet to improve clinical practice.

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