

Chronic Diarrhea

And Inborn Errors of Immunity

Presentation

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Allergist & Clinical Immunologist

Date May 28th - Khordad 7th **Time** 11 – 11:30 am

[Skyroom.online/ch/aveedme.com/ispgh](https://skyroom.online/ch/aveedme.com/ispgh)



- An important component of the clinical picture in many IEI

Note	Date
Highlighting the link between immune dysfunction and the GI tract	

Gastroenterological Disorders in Inborn Errors of Immunity



GI involvement

- In up to 50% of patients with selected IEI subtypes
- May represent the initial clinical presentation

- Chronic diarrhea
- Malabsorption
- Enteropathy
- Immune mediated colitis
- Recurrent infectious colitis

Several IEIs are increasingly recognized to predispose to chronic IBD–like phenotypes:

- Crohn's disease
- Ulcerative colitis
- Indeterminate colitis

Case presentation

- A 10 m/o infant with chronic diarrhea and FTT
- Consanguineous parents
- Recurrent otitis media
- Hypotonia

**High
stool calprotectin**

Sweat chloride test ?

WBC	24660
Neut	7870
Lymph	12670
Mono	3830
Hb	9
MCV	86
Plt	1,185,000
CRP	100



Case presentation

- A 10 m/o infant with chronic diarrhea and FTT
- Consanguineous parents
- Recurrent otitis media
- Hypotonia

IgG 1580

IgM 167

Anti tetanus ab 1.2

CD45	100%
CD3	70%
CD4	54%
CD8	13%
CD19	20%
CD20	20%
CD16	10%
CD56	10%



Colonoscopy

Colitis

CMV +
Mycobacterium + (TB)

CMV viral load

7,000,000 IU/ml

WES

Mutation in ORAI 1 gene

Combined
immunodeficiency
(CID) syndrome

Ca^{2+} is an important second messenger required for activation of lymphocytes and other cell types within and outside the immune system.

- Ganciclovir
- Anti TB
- Dipyridamole

Colonoscopy

Colitis

CMV +
Mycobacterium + (TB)

CMV viral load

7,000,000 IU/ml

WES

**Mutation in
ORAI 1 gene**

Combined
immunodeficiency
(CID) syndrome



EMG

Myopathy

ORAI 1 deficiency



WES

**Mutation in
ORAI 1 gene**

Combined
immunodeficiency
(CID) syndrome



Ectodermal
Dysplasia
Anhidrosis

Introduction

Human Inborn Errors of Immunity

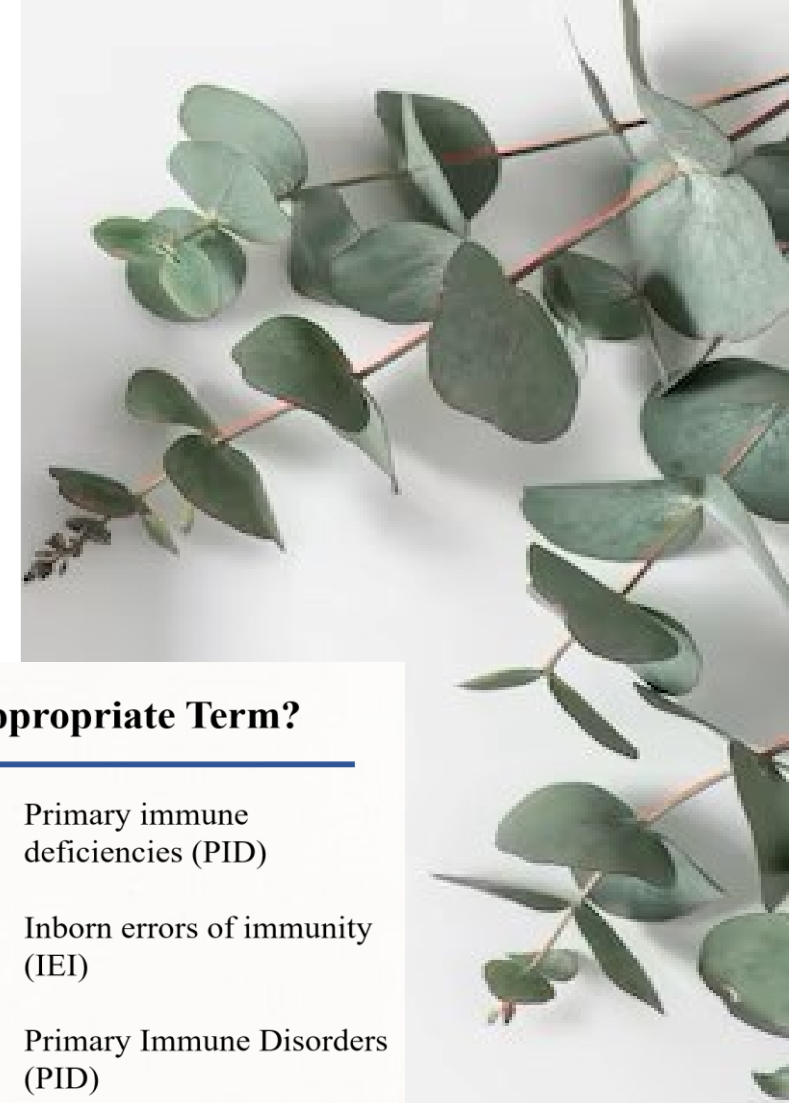
- Large and heterogeneous group of diseases resulting from molecular alterations in genes related to the immune system

IUIS Classification

The International Union of Immunological Societies (IUIS) 2020 classifies IEI into **10 distinct groups** according to the main immune compartments and functions affected.

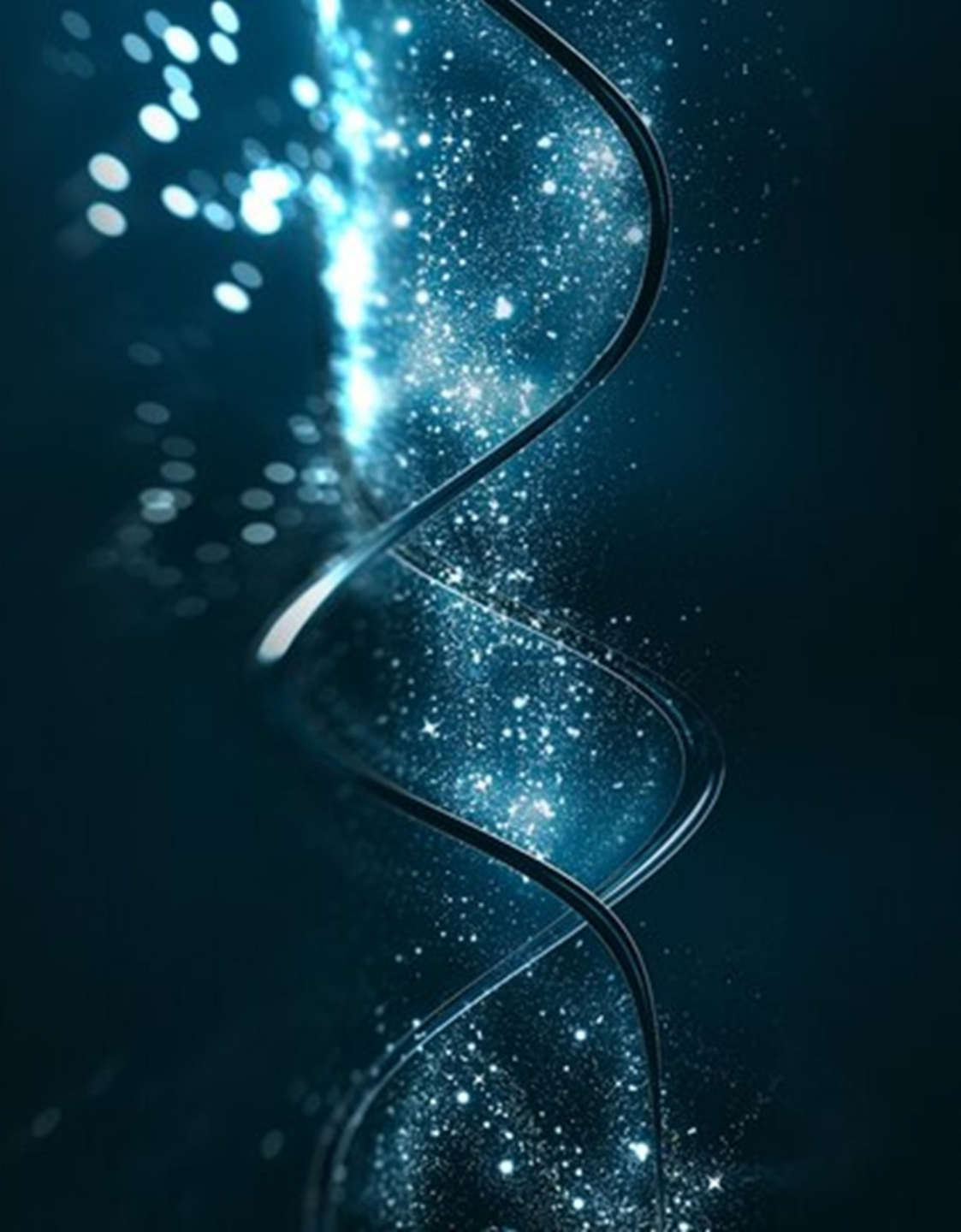
Appropriate Term?

- Primary immune deficiencies (PID)
- Inborn errors of immunity (IEI)
- Primary Immune Disorders (PID)



The 2024 Update of IUIS Phenotypic Classification of Human Inborn Errors of Immunity

- In this update, 559 IEI are described
 - 67 novel monogenic defects
 - 2 new phenocopies

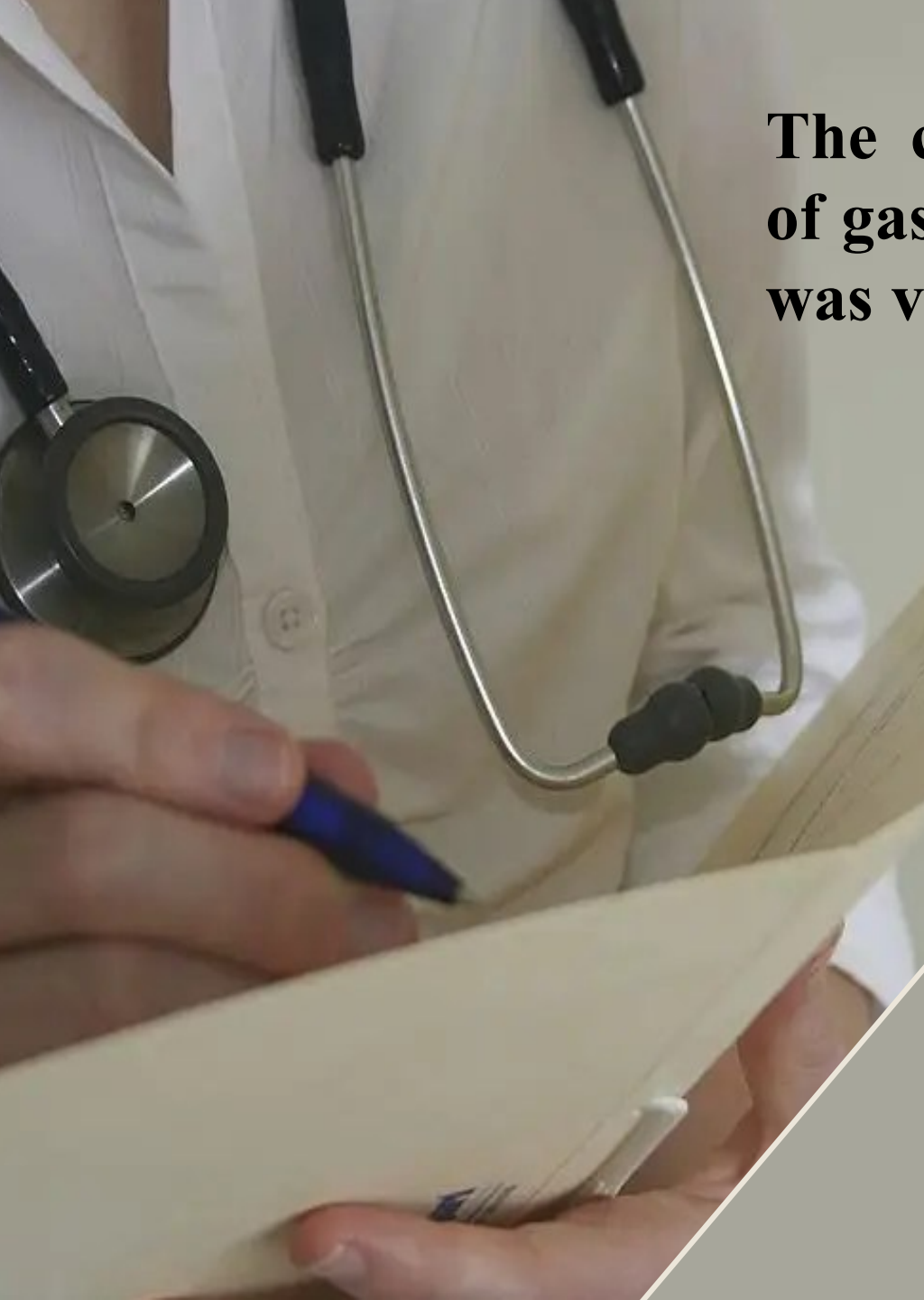


Although recurrent infection represents the classical clinical hallmark...

- Immune dysregulation
- Autoimmunity
- Chronic inflammation
- Organ-specific disease



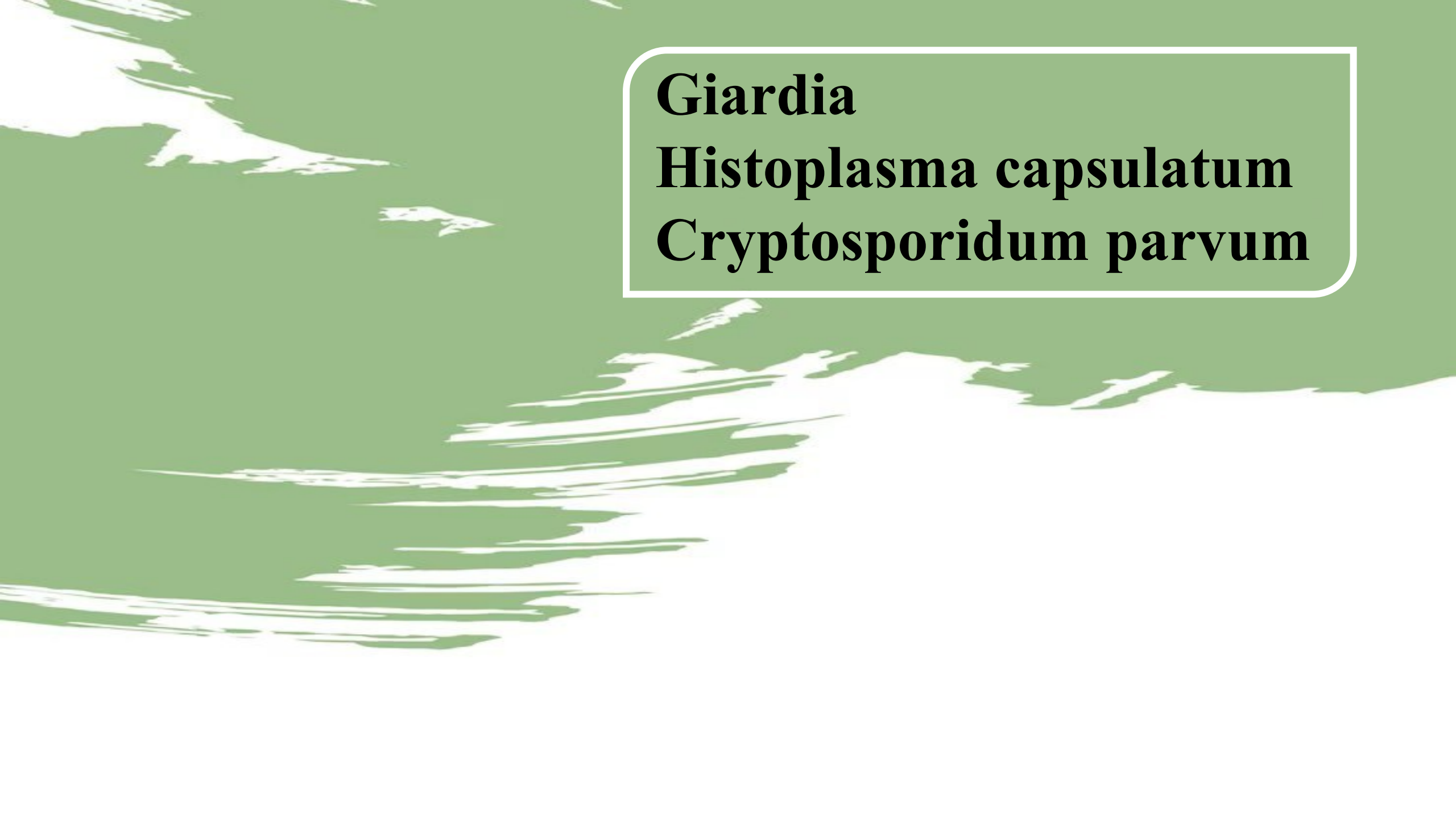
The GI tract represents the largest immune organ in the body, is particularly vulnerable to immune dysfunction, resulting in a wide spectrum of inflammatory, infectious, and structural manifestations



**The clinical presentation
of gastrointestinal disease
was variable**

Chronic diarrhea

The most common symptom



Giardia

Histoplasma capsulatum

Cryptosporidium parvum

Hyper-immunoglobulin M syndrome (HIGM)

- An immunodeficiency with low IgG, IgA, and IgE but normal/elevated IgM
- Inherited mostly autosomal recessively
- Predisposes patients to...

Histoplasma capsulatum
Cryptosporidium parvum

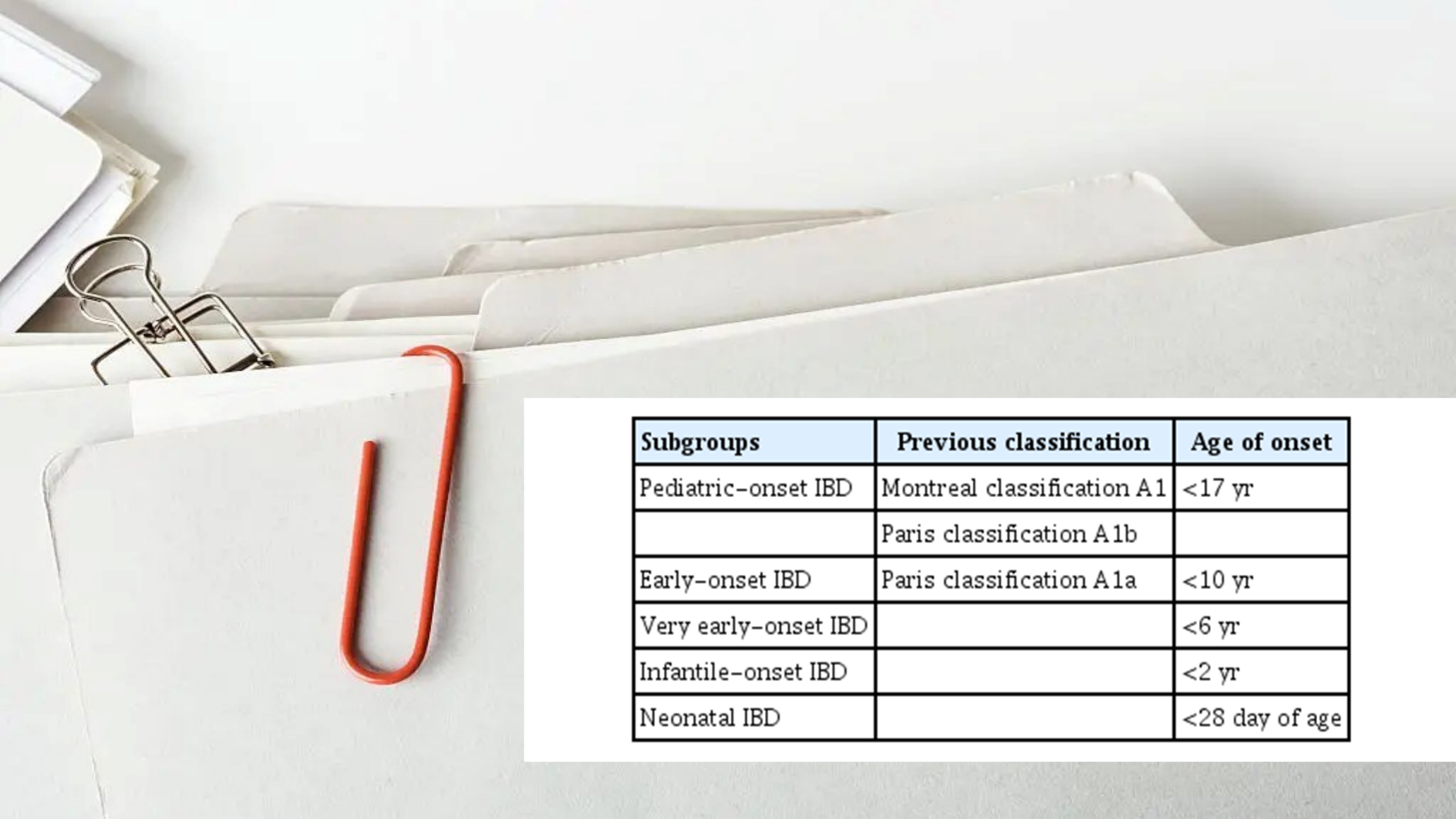
Enteropathy
chronic diarrhea
GI infection

- Sino-pulmonary & opportunistic infections
- Neutropenia
- Autoimmune diseases
- Cancers (liver, pancreas, biliary tract)
- GI symptoms

- Severe cases involve hepatitis, cirrhosis, cholestasis, and potential liver failure requiring transplantation.
- Measuring immunoglobulin levels and testing for genetic mutations in CD40LG, AICDA, CD40 and UNG, are essential for diagnosing HIGM
- Treatment includes Ig replacement, antimicrobials, and sometimes stem cell transplantation

Early Onset & Very Early Onset Inflammatory Bowel Disease



A stack of white folders is shown, with a red paperclip and a silver binder clip attached to the top folder. The folders are slightly offset, showing multiple layers. The background is a plain, light-colored surface.

Subgroups	Previous classification	Age of onset
Pediatric-onset IBD	Montreal classification A1	<17 yr
	Paris classification A1b	
Early-onset IBD	Paris classification A1a	<10 yr
Very early-onset IBD		<6 yr
Infantile-onset IBD		<2 yr
Neonatal IBD		<28 day of age

Article

Clinical Phenotypes and Genetic Findings in Very-Early-Onset Inflammatory Bowel Disease: A Vietnamese Pediatric Cohort Study

Manh Cuong Nguyen ^{1,2}, Thi Viet Ha Nguyen ^{2,3,*}, Loi Nguyen ³, Thuy Ha Dang ³, Tam Tran ⁴,
Thi Van Anh Nguyen ⁵, Ngoc Thach Hoang ⁶, Ngoc Quynh Le Nguyen ⁷, Thi Minh Phuong Do ^{2,3},
Van Tinh Nguyen ³, Hai Yen Vu ³, Thi Ngoc Hong Nguyen ³, Thi Thu Trang Nguyen ³, Thi Cam Van Le ³,
Thi Khanh Ngoc Bui ⁸, Thi Thuy Hang Le ¹ and Minh Dien Tran ^{9,*}

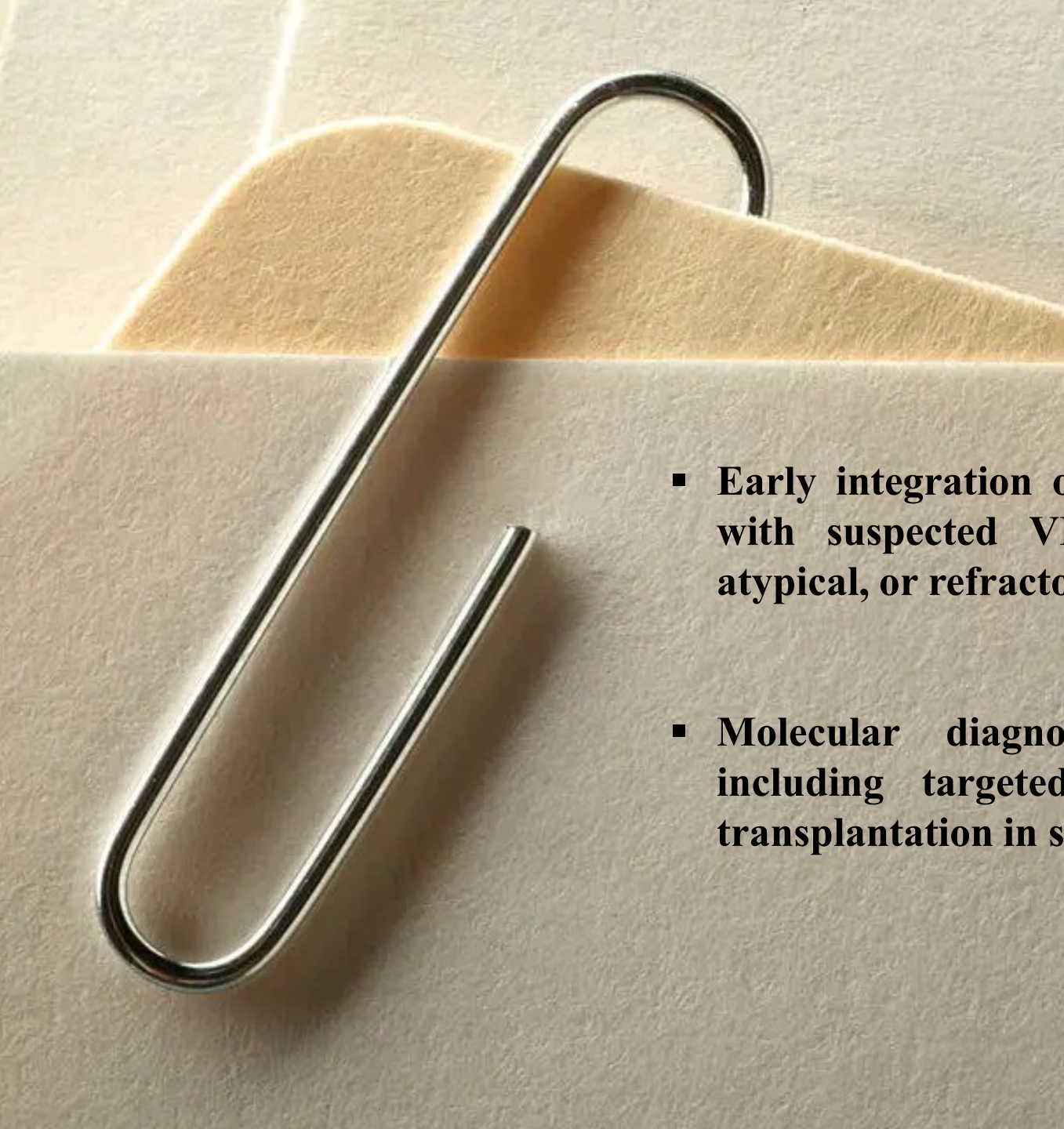
Identified Monogenic etiologies (~30%)

- Immune regulation (IL10RA/IL10RB, FOXP3, XIAP)
- Autoinflammation (TNFAIP3)
- Host defense (CYBB)
- Epithelial function (MYO5B)

- 
- Recurrent infections
 - Eczema/dermatitis
 - Oral ulcers
 - Prolonged fever

These non intestinal clinical features reflect a broader inflammatory or immune dysregulatory phenotype rather than disease confined to the gastrointestinal tract

Non intestinal clinical features were highly prevalent in this cohort



What are the implications of the main findings?

- **Early integration of genomic testing is essential for children with suspected VEO-IBD, particularly those with severe, atypical, or refractory disease.**
- **Molecular diagnosis enables mechanism-based therapy, including targeted biologics or hematopoietic stem cell transplantation in selected patients.**



The Immunologic Profile

The immunologic profile

- Selective T-cell abnormalities, with reduced CD4⁺ and increased CD8⁺ T-cell counts in a subset of patients
- Overall CD3⁺, B cell, and NK cell compartments remained largely preserved

This pattern suggests immune dysregulation rather than overt immunodeficiency



IUIS Classification

Immune Dysregulation with Colitis

Inflammatory Bowel Disease (IBD) recurrent infections

IL-10R deficiency*. **AR**. Folliculitis, arthritis, lymphoma.

IL10RA #613148 Leukocytes unresponsive to IL-10.

IL10RB. # 612567 Leukocytes unresponsive to IL10, IL22, IL26, IL28A, IL28B, IL29

RIPK1 deficiency. **RIPK1**. **AR**. # 618108 Progressive polyarthritis. Low Tc, low or nl Bc.

IL-10 deficiency*. **IL10**. **AR**. *124092 Folliculitis, arthritis. No functional IL-10 secretion.

TGFB1 deficiency*. **TGFB1**. **AR**. # 618213 Microcephaly, encephalopathy. ↓Tc proliferation in response to anti-CD3

ELF4 deficiency*. **ELF4**. **XL**. # 301074 Fevers, ulcers. Responded to IL-1, TNF or IL-12p40 blockade

NFAT5 haploinsufficiency**. **NFAT5**. **AD**. * 604708 Decreased memory Bc and plasmablasts.

IL21 def.** **IL21** **AR**. # 615767 Tc: NL / low function. ↓gG, poor specific antibody responses; ↑ IgE

DOCK11 deficiency. **DOCK11**. **XL**. # 301109 Severe early-onset autoimmunity affecting various organs. Autoimmune cytopenia. Susceptibility to infections with hyperinflammatory response. ↓ switched memory Bc

iRHOM deficiency*. **RHBDF2**. **AR**. * 614404 Pneumatocoles, eczema, HSM, skin abscesses,. Haemorrhagic colitis. ↑ IgE

MD2 deficiency*. **LY96**. **AR**. *605243 Very early onset IBD, recurrent infections, pneumonia, and otitis media

TLR4 deficiency*. **TLR4**. **AR**. *603030

Immune
Dysregulation
with Colitis

Topic review

Red flags to suspect inborn errors of immunity in patients with autoimmune diseases

Natalia Vélez^{1,2}, Juliette De Ávila¹, Jaime Cortés³, Nelson Barrero⁴,
Leosirly Rojas⁵, Juan Manuel Bello^{4,6,7}, Consuelo Romero-Sánchez^{1,4,6,7}

Ten articles were reviewed...

- 4 case reports
 - 1 case series
 - 5 observational studies
-
- 2 articles: monogenic IBD in adults
 - 8 articles: monogenic IBD in pediatric population

Red flags to suspect inborn errors of immunity in patients with autoimmune diseases

Autoimmune disease	Red flags to suspect inborn errors of immunity
Autoimmune cytopenias	1. Chronic, recurrent and refractory cytopenias 2. Recurrent Infections 3. Poly-autoimmunity (autoimmune hemolytic anemia, autoimmune thrombocytopenia, autoimmune neutropenia) along with other findings, such as celiac disease, thyroiditis, and psoriasis. 4. Chronic lymphoproliferation (hepatomegaly, splenomegaly, or lymphadenopathy) 5. Severe infectious complications associated with immunosuppressive treatment
Systemic lupus erythematosus	1. Age of onset before five years 2. Atypical clinical manifestations of the disease 3. Severe organ involvement 4. Chronic lymphoproliferation 5. Refractory immune-mediated cytopenias 6. Recurrent infections 7. Chilblain lesions 8. Resistance to conventional therapies
Inflammatory bowel disease	1. Personal history of recurrent infections 2. Resistance to conventional therapies 3. Atypical symptoms of inflammatory bowel disease 4. Multiorgan involvement associated with manifestations of poly-autoimmunity 5. Abnormal findings in immunological workup 6. Atypical endoscopic or histological findings 7. Young age at presentation 8. Family history of neoplasms and autoimmune manifestations 9. Consanguineous parents 10. Higher rates of severe perianal/fistulating disease* 11. Need for surgical intervention*

* Red flag seen mainly in inflammatory bowel disease pediatric patients

Extraintestinal manifestations: such as arthritis or folliculitis in patients with IL10R deficiency

Symptoms and Signs at the First Visit

Journal of Clinical and Translational Research

ORIGINAL ARTICLE

Diagnostic delay in very early-onset inflammatory bowel disease: A tertiary single-center retrospective study

Juliana Tedesco Dias, Debora Avellaneda Penatti, Jessika Alves de Souza Costa, Gabriela Nascimento Hercos, Carine Dias Ferreira de Jesus, Mary de Assis Carvalho, and Nilton Carlos Machado*

Published online: December 16, 2025

Symptoms/signs	<i>n</i> (%)
Diarrhea	24 (96)
Blood in stool	23 (92)
Abdominal pain	16 (64)
Weight loss	13 (52)
Perineal disease	10 (40)
Plicoma	5 (20)
Fistulas	5 (20)
Genital fistula	3 (12)
Perineal abscess	2 (8)
Perianal fissure	9 (36)
Extraintestinal symptoms	3 (12)

Underlying IEI

- ≥ 4 new ear infections per year
- ≥ 2 months of antibiotic treatment with little effect
- ≥ 2 severe sinus infections in a year
- ≥ 2 pneumonias per year
- Insufficient weight gain or growth delay
- Recurrent deep skin or organ abscesses





Underlying IEI

- Persistent thrush in mouth
- Persistent fungal infection of the skin
- Need for intravenous antibiotics to clear infections
- ≥ 2 deep seated infections
- Positive family history
- History of infection with an unusual microbe (eg, Serratia)



Initial Bloodwork and Stool Studies

	1st Tier Tests	2nd Tier Considerations
Bloodwork	CBC and differential Comprehensive Metabolic Panel (CMP) ESR CRP <i>Consider celiac screen and thyroid function tests depending on presentation</i>	Immunoglobulin classes (IgA, IgG, IgM, IgE) <i>Must use age-specific norms, especially in infants</i> Lymphocyte subsets by flow cytometry Antibody to vaccines—Vaccination <i>history must be obtained to evaluate this</i> Allergen testing for older children DHR testing TREC/TCR repertoire TB testing HIV serology
Stool studies	Occult blood <i>Shigella</i> <i>Salmonella</i> <i>Yersinia</i> <i>Enterohemorrhagic and Enteropathogenic E. coli</i> <i>Campylobacter</i> <i>C. difficile</i> (if >12 months) Calprotectin or quantitative lactoferrin	<i>Giardia</i> <i>Cryptococcus</i>



Clinical spectrum of Inborn Errors of Immunity

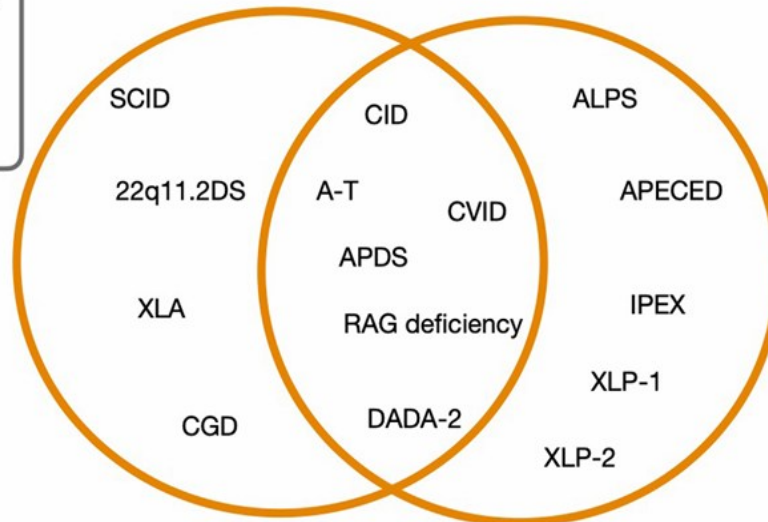
IEI

Infections

Severe infection
Recurrent bacterial or viral infections
Opportunistic infections
Failure to thrive or weight loss
Familiar history of IEI

Immune dysregulation

Lymphoproliferation
Autoimmunity
Enteropathy/IBD
Allergies
Autoinflammatory diseases
Familiar history of IEI



Genetic inborn errors of immunity associated with gastrointestinal inflammation

Gene name	Disease name	Category
ADAM17		Barrier dysfunction
AICDA	Hyper IgM	Humoral
ALPI		Barrier dysfunction
ANKZF1		Immune dysregulation
BACH2		Immune dysregulation
BTK	X-linked agammaglobulinemia	Humoral
CARD8		Immune dysregulation
CD40LG	X-linked hyper IgM	Humoral
CD55		Barrier dysfunction
CTLA4		Humoral
CYBA	CGD	Neutrophil
CYBB	CGD	Neutrophil
DEF6		Immune dysregulation
DKC1	Dyskeratosis congenita	Telomereopathy
DOCK8		Combined immunodeficiency
DUOX2		Neutrophil
FERMT1		Barrier dysfunction
FOXP3	IPEX	Immune dysregulation
HSP4	Hermansky pudlak	Immune dysregulation

Genetic inborn errors of immunity associated with gastrointestinal inflammation

Gene name	Disease name	Category
ICOS		Immune dysregulation
IKBKG	NEMO	Combined immunodeficiency
IL10		Immune dysregulation
IL10RA		Immune dysregulation
IL10RB		Immune dysregulation
IL21		Humoral
IL2RA		Combined immunodeficiency
IL2RB		Combined immunodeficiency
ITCH		Immune dysregulation
ITGB2	LAD1	Neutrophil
LIG4		Combined immunodeficiency
LRBA		Immune dysregulation
MEFV	Familial Mediterranean fever	Immune dysregulation
MVK	Hyper IgD syndrome	Immune dysregulation
NCF2	CGD	Neutrophil
NCF4	CGD	Neutrophil
NFAT5		Immune dysregulation
NLRC4		Immune dysregulation
PIK3CD		Immune dysregulation
PIK3R1		Immune dysregulation

Genetic inborn errors of immunity associated with gastrointestinal inflammation

Gene name	Disease name	Category
PLGC2		Immune dysregulation
RBCK1 (HOIL-1)		Immune dysregulation
RIPK1		Immune dysregulation
RNF31		Immune dysregulation
RTEL1	Dyskeratosis congenita	Telomereopathy
SKIV2L	THE syndrome	Combined immunodeficiency
SLC7A4	Lysinuric protein intolerance	Immune dysregulation
STAT1 GOF		Immune dysregulation
STAT3 GOF		Immune dysregulation
STIM1		Combined immunodeficiency
STXBP2	HLH	Immune dysregulation
STXBP3	HLH	Immune dysregulation
TGFB1		Immune dysregulation
TRIM22		Immune dysregulation
TTC7A	Multiple intestinal atresia SCID	Combined immunodeficiency
TTC37	The syndrome	Combined immunodeficiency
WAS	Wiskott Aldrich syndrome	Combined immunodeficiency
XIAP	XLP2	Immune dysregulation

Monogenic defects involved in early-onset IBD with or without accompanying susceptibility to infections

IL-10 signalling	IL10 IL10RB IL10RA STAT3	TCR signalling	IL2RG STIM1 ORAI1	inflammasome activation	NLRC4 MEFV MVK
Treg function	FOXP3 IL2RA CTLA4 LRBA	DNA repair	DKC1 RTEL1 ZBTB24	RNA processing	TRNT1 TTC37
cytoskeleton remodelling	WASP	VDJ recombination	LIG4 DCRE1C RAG2 RAG1	epithelial anti-complement defence	CD55 MASP2
protein degradation	ITCH	nucleic acid metabolism	ADA POLA1 SKIV2L	bacterial clearance	FCN3
		signalling and co-stimulation	ICOS PTEN PIK3CD AICDA CD40LG PIK3R1 BTK	Adhesion and migration	ITGB2
		signalling defects	PLCG2 TNFAIP3	NADPH oxidase activity and ROS production	NCF2 NCF4 NOX1 DUOX2 G6PC3 CYBA CYBB NCF1
				intrinsic defects in epithelia	GUCY2C SLC9A3 SLC02A1 PLA2G4A STXBP2
				epithelial organization	TTC7A FERMT1



Autoimmunity and inborn errors of immunity: a complex coexistence

Ahamada Elamine^{1*}, Ibtihal Benhsaien^{1,2}, Fatima Ailal^{1,2},
Mohammed Hbibi¹, Mohammed Fahi^{1,3}, Ahmed Aziz Bousfiha^{1,2}
and Jalila EL Bakkouri^{1,3,4*}

¹Laboratory of Clinical Immunology, Infection and Autoimmunity (LICIA), Faculty of Medicine and Pharmacy, Hassan II University, Casablanca, Morocco, ²Department of Pediatric Infectious Diseases and Clinical Immunology, Mother-Child Hospital Abderrahim El Harouchi, Ibn Rochd University Hospital Center, Casablanca, Morocco, ³Immuno-serology Laboratory, Ibn Rochd University Hospital Center, Casablanca, Morocco, ⁴Immunopathology-Immunotherapy-Immunomonitoring Laboratory, Faculty of Medicine, Mohammed VI University of Health Sciences (UM6SS), Casablanca, Morocco



Case Presentation

- A 15-year-old girl with chronic diarrhea since she was 4 y/o
- Recurrent respiratory infection
- Autoimmune thrombocytopenia in the past 1 year
- Splenomegaly
- FTT (25kg)

WBC	61290
Neut	3440
Lymph	54850
Hb	10.1
MCV	73
Plt	14000

IgG	31	CD3	98%
IgM	36	CD4	10%
IgA	8	CD8	87%
		CD19	0.5%
		CD20	0.5%
		CD16	2%
		CD56	2%

Bone marrow aspiration and biopsy

Hypercellular marrow (lymphoid series)

WES

MALT1 gene

Prevalence

- **A national cohort by
Alain Fischer et al**

Prevalence of autoimmunity
of 26.2% among 2,183
patients with IEI

- **A study in Slovenia**

Autoimmune manifestations
in 22% of cases



Autoimmune Enteropathies

Autoimmunity and IEI

Prevalence of Autoimmunity Across Different IEI Registries



frontiers
in Immunology

TYPE Mini Review
PUBLISHED 11 March 2026
DOI 10.3389/fimmu.2026.1787739

Country, publication date'	Number of IEI cases	Frequency of autoimmunity
Morocco, 2025	769	14%
France, 2017	2183	26,2%
Slovenia, 2016	235	22%
Kuwaït, 2020	286	19,9%
Iran, 2021	461	20%
Turkey, 2020	822	10,1%
Mexico, 2021	40	7,5%
Tunisia, 2014	710	4,2%



Organ-Specific Autoimmune Diseases

- IPEX | Immune dysregulation
Polyendocrinopathy
Enteropathy
X-linked syndrome
- Up to 10% of patients with
CVID



Autoimmune Enteropathies

Autoimmunity and IEI

Organ-Specific Autoimmune Diseases

- LRBA
Deficiency | Lipopolysaccharide-
Responsive
Beige-like
Anchor protein

- CTLA4
Deficiency | Cytotoxic
T-Lymphocyte
Antigen-4

Autoimmune Enteropathies

Autoimmunity and IEI

Up to 80%
of patients

Organ-Specific Autoimmune Diseases

- PIK3CD
GOF | Phospho
Inositide-3
kinase
Catalytic subunit
Delta
- WAS | Wiskott-
Aldrich
Syndrome
- Omenn Syndrome



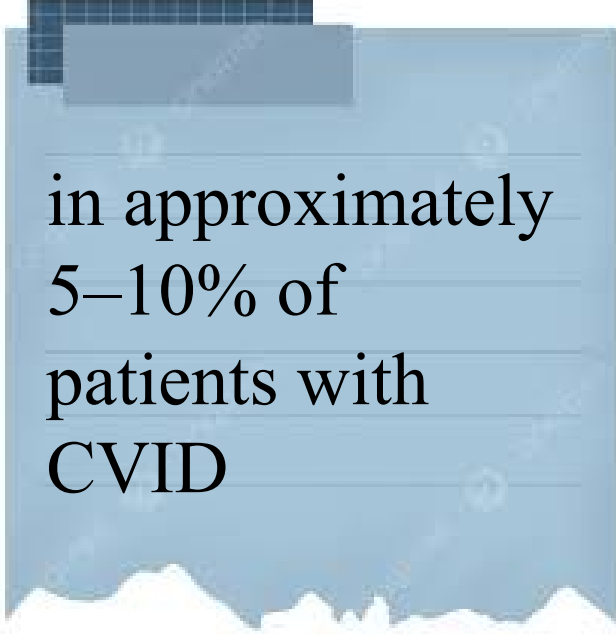
Autoimmune Enteropathies

Autoimmunity and IEI

A medical clipboard with a silver stethoscope and a white pen resting on it. The clipboard has a form titled "Medical Examination Report" with fields for Name, Sex, Age, and Occupation.

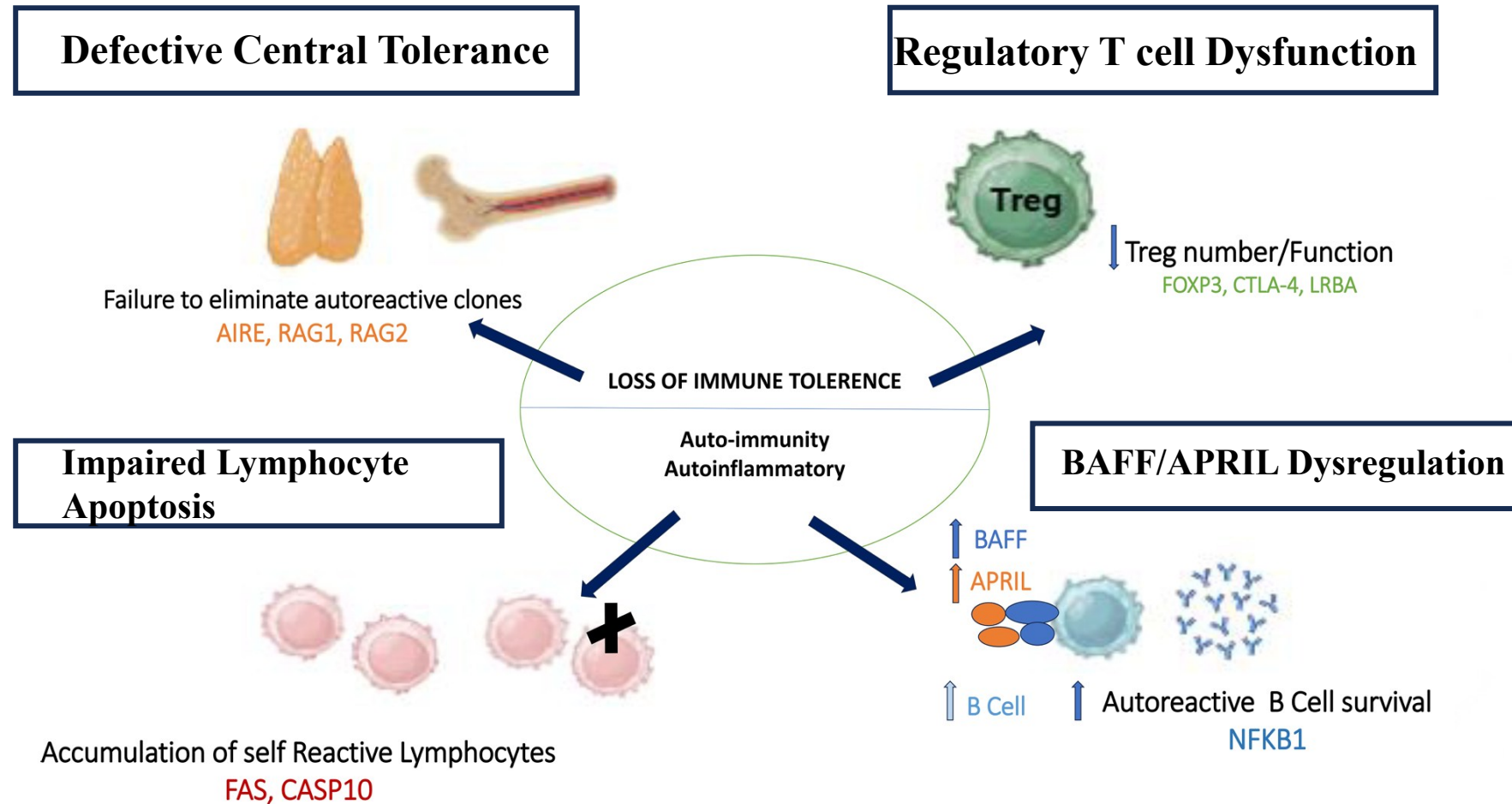
Celiac-like disease without autoantibodies

- A celiac disease-like enteropathy lacking classical autoantibodies

A blue sticky note with a torn bottom edge, featuring faint circular patterns.

in approximately
5–10% of
patients with
CVID

Shared mechanisms of immune tolerance breakdown in inborn errors of immunity



Schematic overview of the shared immunopathological mechanisms involved in autoimmunity associated with IE

A medical clipboard with a silver stethoscope and a white pen resting on it. The clipboard has a 'Medical Examination Report' form with fields for Name, Sex, Age, and various medical history sections.

IPEX

Immune dysregulation
Polyendocrinopathy
Enteropathy
X-linked syndrome

FoxP3
gene

An essential gene for the development, transcriptional regulation, and function of Tregs and regulation of IgA and IgE production by B lymphocytes



The clinical presentation is highly variable

Classical triad

Poly endocrinopathy
Enteropathy
Eczematous dermatitis

- Gastrointestinal symptoms are the most common and typically manifest around six months of age.
- IPEX usually presents early in life and evolves over time with the emergence of new clinical signs.

When and how should IEI be diagnosed in patients with autoimmune manifestations?

- The onset of autoimmunity at a young age
- The presence of poly autoimmunity
- Autoimmunity occurring after infections
- A family history of autoimmune diseases



When and how should IEI be diagnosed in patients with autoimmune manifestations?

- Failure to thrive
- Recurrent or severe infections
- The need for hospitalization due to infections
- Prolonged or repeated antibiotic use
- Infections caused by unusual or opportunistic pathogens



Baseline Immunological Evaluation

- **Serum Ig levels**
- **Analysis of lymphocyte subsets**
- **Further investigations**
 - **Should be guided by the specific autoimmune phenotype**



Transient Hypogammaglobulinaemia of Infancy

- A temporary drop in IgG levels in infants aged 5 to 24 months
- Typically returning to normal by 2–6 years
- Diagnosis is made when IgG levels are more than two standard deviations below the mean for their age



Transient Hypogammaglobulinaemia of Infancy

Note	
No.	Date
- Gastroenteritis	
- Chronic diarrhea	
- Lactose intolerance	

- Treatment involves antibiotics, with IVIG recommended for severe infections



Common Variable ImmunoDeficiency



Enteroviruses
Salmonella
C. jejuni
Giardia lamblia

- Recurrent infections (mainly in the respiratory and GI tracts)
- Non-infectious enteropathy (IBD, celiac disease) affects 20–60% of patients

Treatment

Immunoglobulin Replacement Therapy

IVIG is ineffective for enteropathy

Steroids help reduce inflammation and restore mucosal structure



X-linked agammaglobulinaemia (XLA)

- Mutation in Bruton's tyrosine kinase
- B cell development arrest
- Pneumonia, Chronic diarrhea, and meningitis
- Treatment involves lifelong Ig replacement

Diarrhea is commonly caused by pathogens like *Giardia lamblia* and *Salmonella* spp

Selective immunoglobulin A deficiency (SIgAD)

- The most common primary antibody deficiency
- Prevalence of 1 : 223 to 1 : 1000
- Most children and adults with IgA deficiency remain healthy and show no apparent symptoms
- IgA helps protect mucosal surfaces
- Prone to lung infections, allergies, autoimmune diseases, and **gastrointestinal issues**

- **GI infections**

- **Celiac disease**

- **IBD**

Immune dysregulation with colitis

Interleukin 10 (IL-10) deficiency

Interleukin 10 receptor (IL-10R) deficiency

IL-10, produced by
regulatory T-cells
and macrophages

- IL10 regulates inflammation and tissue repair
- IL10/IL10R defects cause a hyper-inflammatory state, mainly in the intestines, leading to early-onset IBD

Treatment

Allogeneic stem cell transplantation

Monoclonal antibodies like anakinra and adalimumab



Immune dysregulation with colitis

TGFB1 (transforming growth factor beta 1)
deficiency

**Essential for
intestinal immune
homeostasis and
CNS function**

- **The TGF- β 1 gene encodes a key regulator of embryogenesis, tissue homeostasis, and immune balance**
- **Overactivity can lead to cancer, fibrosis, or diaphyseal dysplasia**
- **Reduced activity is linked to early tumorigenesis, vascular dysplasia, developmental defects, severe IBD, and atherosclerosis**



ELF4 deficiency

(E74-like ETS transcription factor 4)

- A newly identified X-linked IEI
- Classified as a disease of immune dysregulation
- Hemizygous loss-of-function mutations in the ELF 4 gene on the X chromosome (Xq26.1)

Treatment includes the use of glucocorticosteroids and biologics

- Recurrent and prolonged ulcerations in the GI tract
- Chronic diarrhea
- IBD-like symptoms
- Fever of unknown origin



WAS

Wiscott
Aldrich
Syndrome

Combined
immunodeficiencies
with associated or
syndromic features

In 5 – 10 % of patients

Severe early-onset IBD

- Chronic diarrhea
- Rectal masses
- Rectal ulcers
- Malabsorption

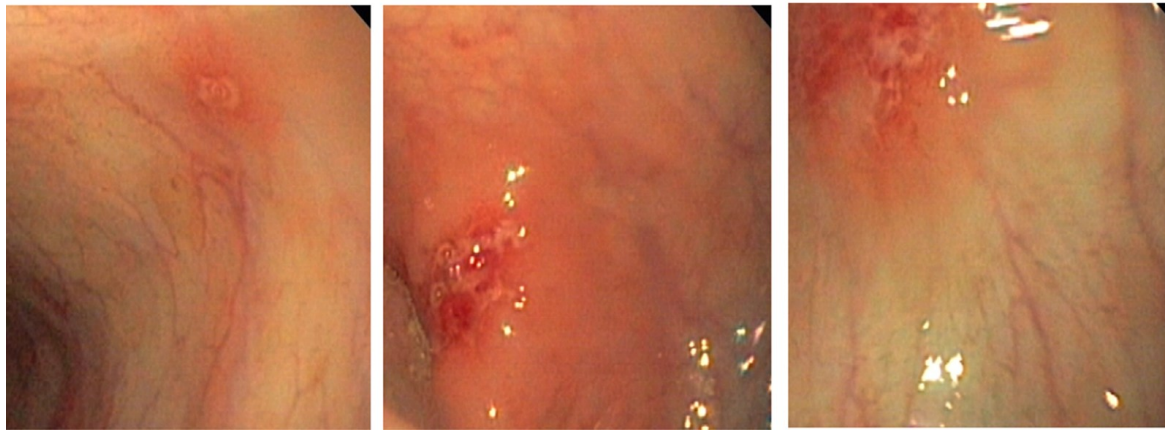
- X-linked immunodeficiency
- Microthrombocytopaeni and bleeding diathesis
- Eczema
- Recurrent infections,
- Autoimmunity
- Malignancies

IEIs with HLH

A 22-month-old male was admitted to Department of Gastroenterology because of a more than one-year history of recurrent fever, chronic diarrhea, abdominal distension with anaemia.

Case presentation

- Perianal abscess resection at the ages of 6 months and 8 months
- His parents and sister were healthy
- Weight: 10 kg (z score: -1.55)
- Height: 80 cm (z score: -2.05)
- Spleen extended 4 cm below the rib cage
- Multiple mesenteric lymph nodes
- Endoscopy: mucous hyperemia in the membrane with ulcers and erosions from the ileocecum to the rectum



The pathology of colonoscopy

Chronic active enteritis

Immunological test
(normal value)

IgG 10.6 g/L (5.09–10.09 g/L)
IgM 0.677 g/L (0.98–1.78 g/L)
IgA 0.861 g/L (0.31–0.67 g/L)

Anti-nuclear antibody IgG: weakly positive;
IBD antibody anti-intestinal goblet cell
antibody weakly positive;
Anti-neutrophil cytoplasmic antibody
perinuclear type: weakly positive

EBV-IgG: positive; EB-DNA: < 5.0E+ 2 copies/ml (< 5.0E+ 2
copies/ml)
CMV-DNA: < 5.0E+ 2 copies/ml (< 5.0E+ 2 copies/ml)
Parasite set: negative
Blood bacterial culture: negative

Different degrees of eosinophils infiltration (about 80/HPF)
in transverse colon, sigmoid colon and rectum

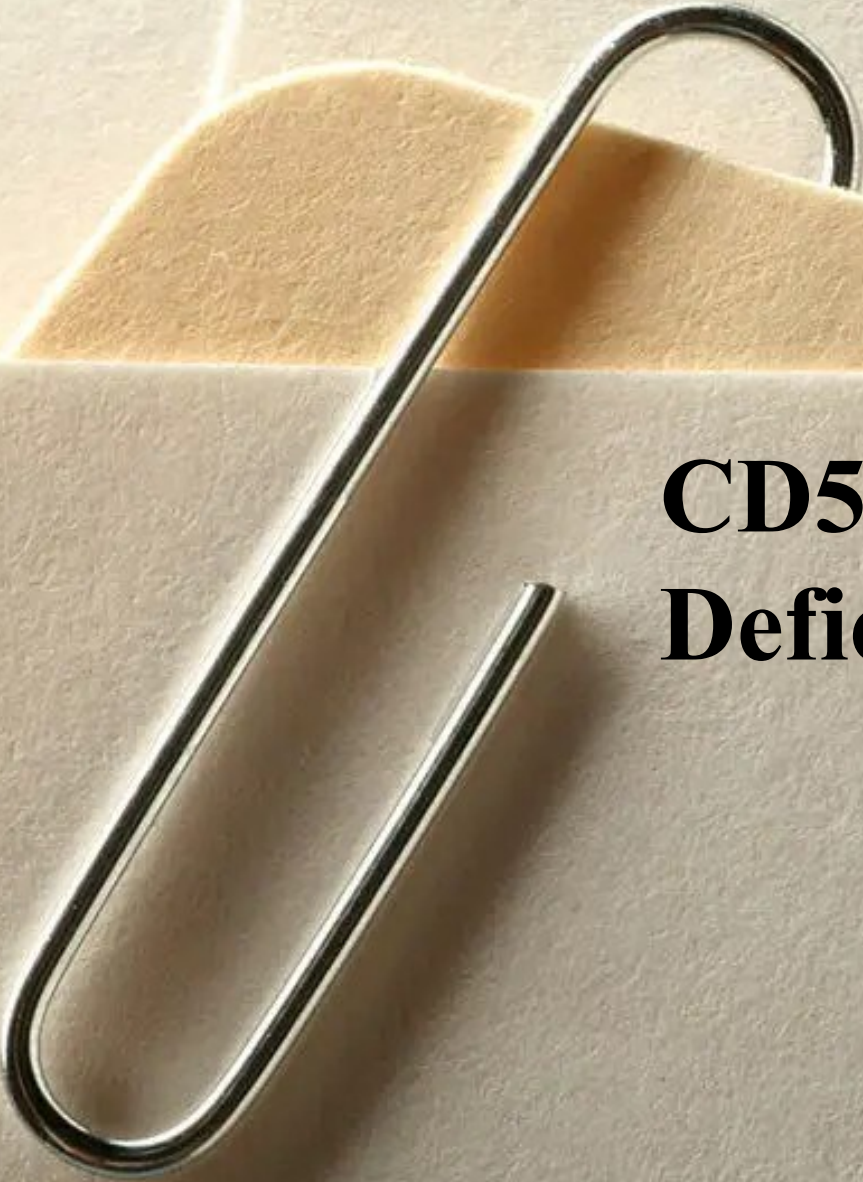


**A novel frameshift
mutation in exon 3
of the XIAP gene**

**c.888-892delTAAAG
(p. Asp296Aspfs*12)**

**The most common characterization of XIAP deficiency
is a key triad of clinical manifestations**

- High susceptibility to developing HLH frequently triggered by EBV infection
- Recurrent splenomegaly
- IBD with the features of Crohn's disease



CD55 Deficiency

CHAPLE syndrome

CD55 deficiency

Hyper-activation of complement

Angiopathic thrombosis, and severe

Protein-Losing Enteropathy

-
- Usually manifests in childhood
 - Can be life-threatening
 - Eculizumab
 - A humanized anti-C5 monoclonal antibody and complement inhibitor



The immune system study when a specific diagnosis is suspected...

- Quantitative and qualitative evaluation of T and B cell subpopulations or the innate system
- It is crucial to exclude secondary causes such as protein loss, hematologic malignancies, and certain medications, to diagnose primary antibody immunodeficiencies or humoral defects in patients with hypogammaglobulinemia

A medical clipboard with a silver stethoscope and a white pen resting on it. The clipboard has a form titled "Medical Examination Report" with fields for Patient Name, Gender, Birth Date, and Occupation.

The immune system study when a specific diagnosis is suspected...

The functional study of the humoral response

➤ Antibody assessment

- **T-dependent response:**

IgG to vaccines such as tetanus, diphtheria, rubella, and mumps

- **T-independent response:**

IgG to the 23-valent pneumococcal vaccine

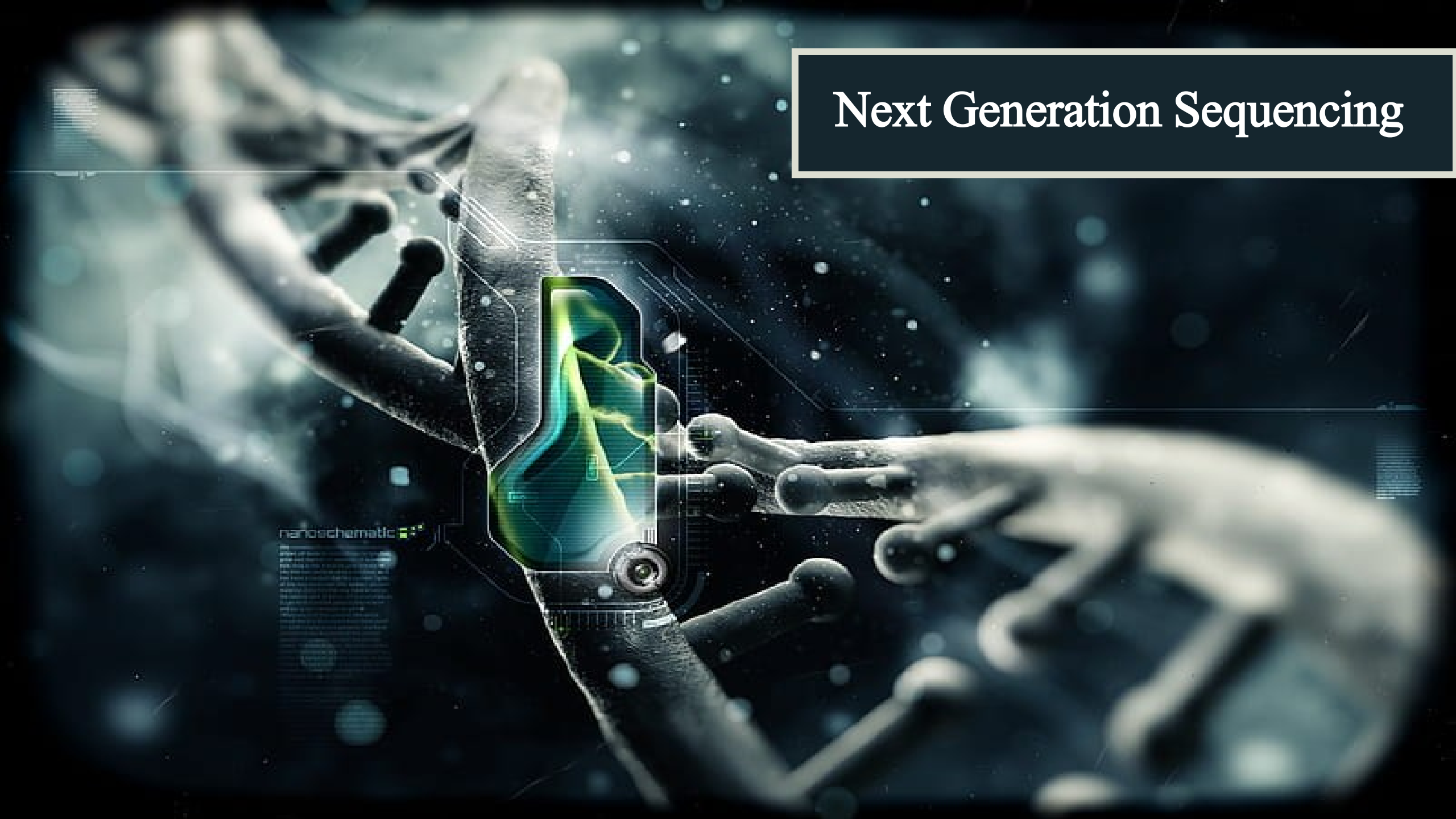
A medical examination report form is shown on the left side of the slide. It features a stethoscope and a pen resting on it. The form has fields for 'Name', 'Age', 'Sex', 'Occupation', 'Referral', 'History', 'Examination', 'Investigations', and 'Diagnosis'. The title 'Medical Examination Report' is printed at the top of the form.

The immune system study when a specific diagnosis is suspected...

- The initial cellular quantitative evaluation includes measuring T lymphocytes (CD3+, CD4+, CD8+), B lymphocytes (CD19+, CD20+), and natural killer cells (CD16+, CD56+), and the functional assessment should include lymphoproliferation studies.

CD45	CD11a
CD55	CD11b
	CD11c

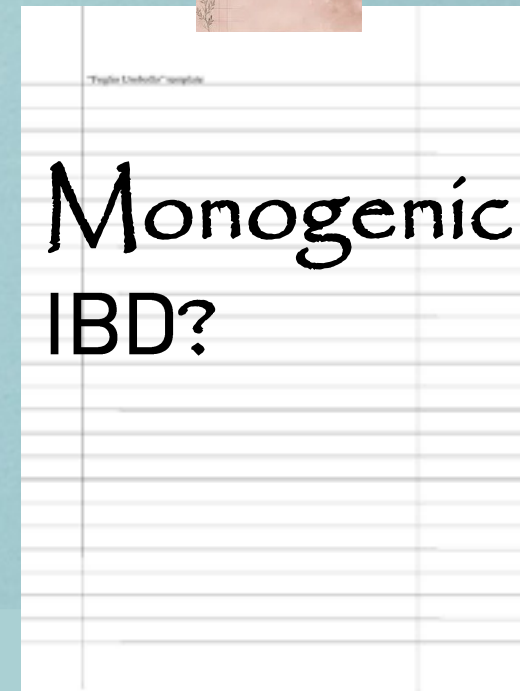
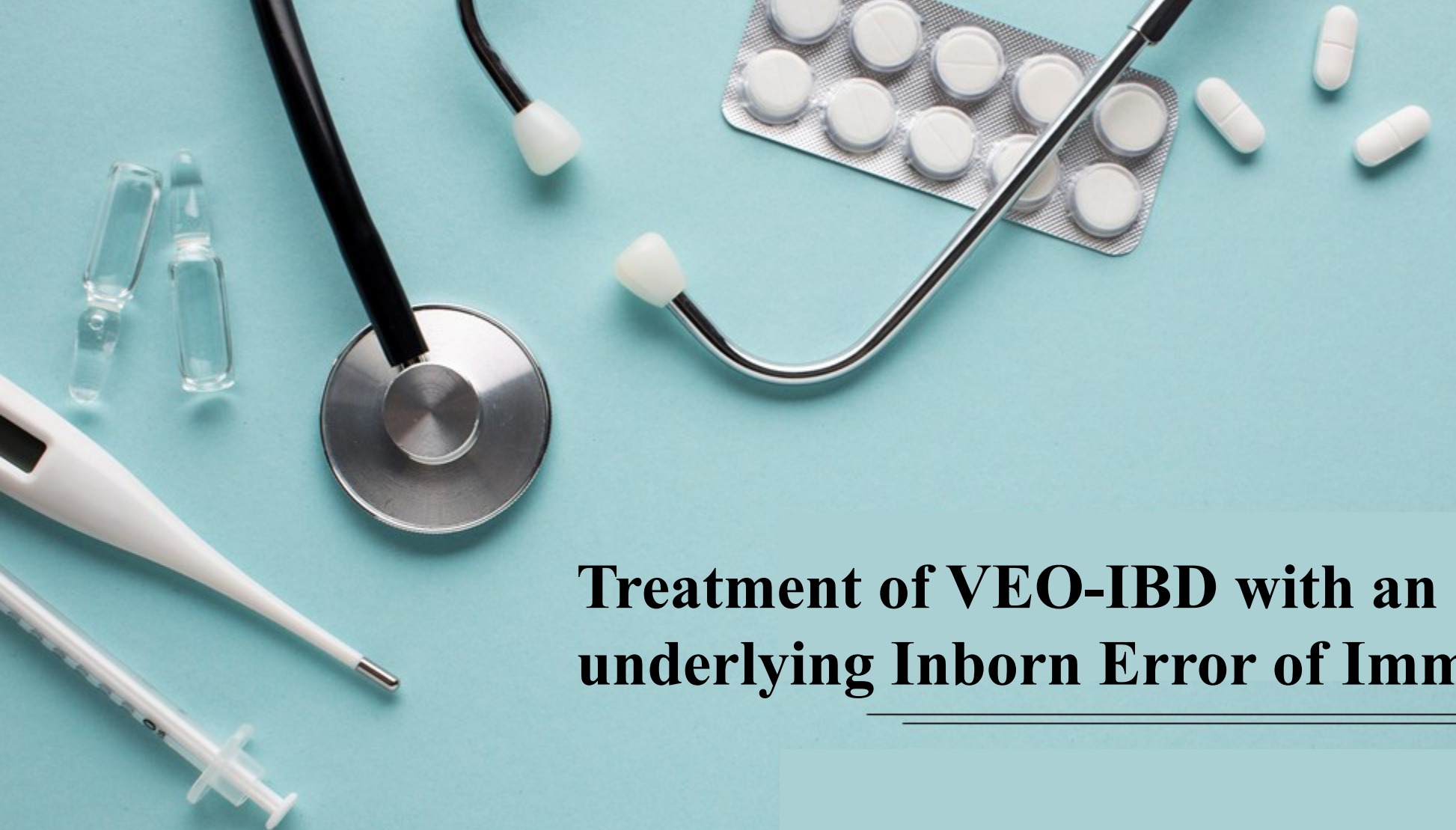
Next Generation Sequencing



Benefits of Genetic Diagnosis

- Potential complications
 - Target therapy
 - Prognosis
- Counseling patients and their families, as most will adjust their reproductive plans according to the information received





Treatment of VEO-IBD with an underlying Inborn Error of Immunity

Specific Treatments

The treatment of non-infectious manifestations of IEI is, at least initially, similar to that performed for these same manifestations when they occur outside the context of IEI.

- The use of immunosuppressive medications requires extra care, as there is a risk of increasing the chance of infections
- Hematopoietic stem-cell transplantation
- Gene therapy



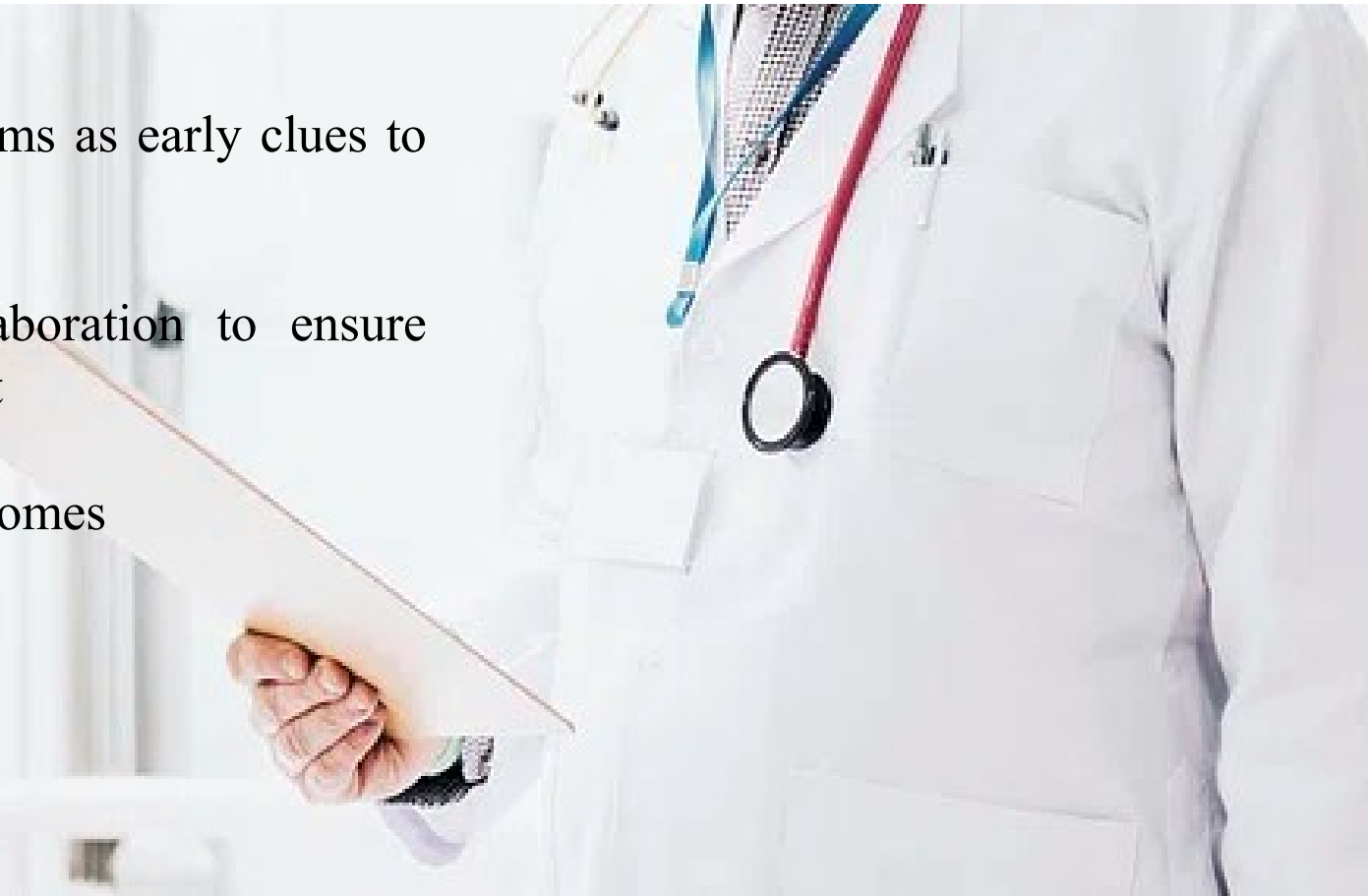
Efficacy of Healing Intestinal Disease With Stem Cell Transplantation in Some Cases of VEO-IBD

Condition	HSCT May Be Efficacious for Intestinal Disease	HSCT Not Efficacious for Intestinal Disease
	IL-10RA, IL-10RB, IL-10 deficiency IPEX WAS Many forms of SCID CD40L XIAP CGD LRBA CTLA4 DOCK8	TTC7A STXBP2 IKBKG (NEMO)



Take home message

- The importance of recognizing GI symptoms as early clues to underlying IEIs
- The necessity for multidisciplinary collaboration to ensure effective patient diagnosis and management
- Targeted therapies to improved patient outcomes
- Refer selected patients for HSCT
- Family planning





The best is yet to come

