Overview of management in Inborn Error of Immunity (Primary Immunodeficiency)

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کریم خطابخش پوزش پذیر

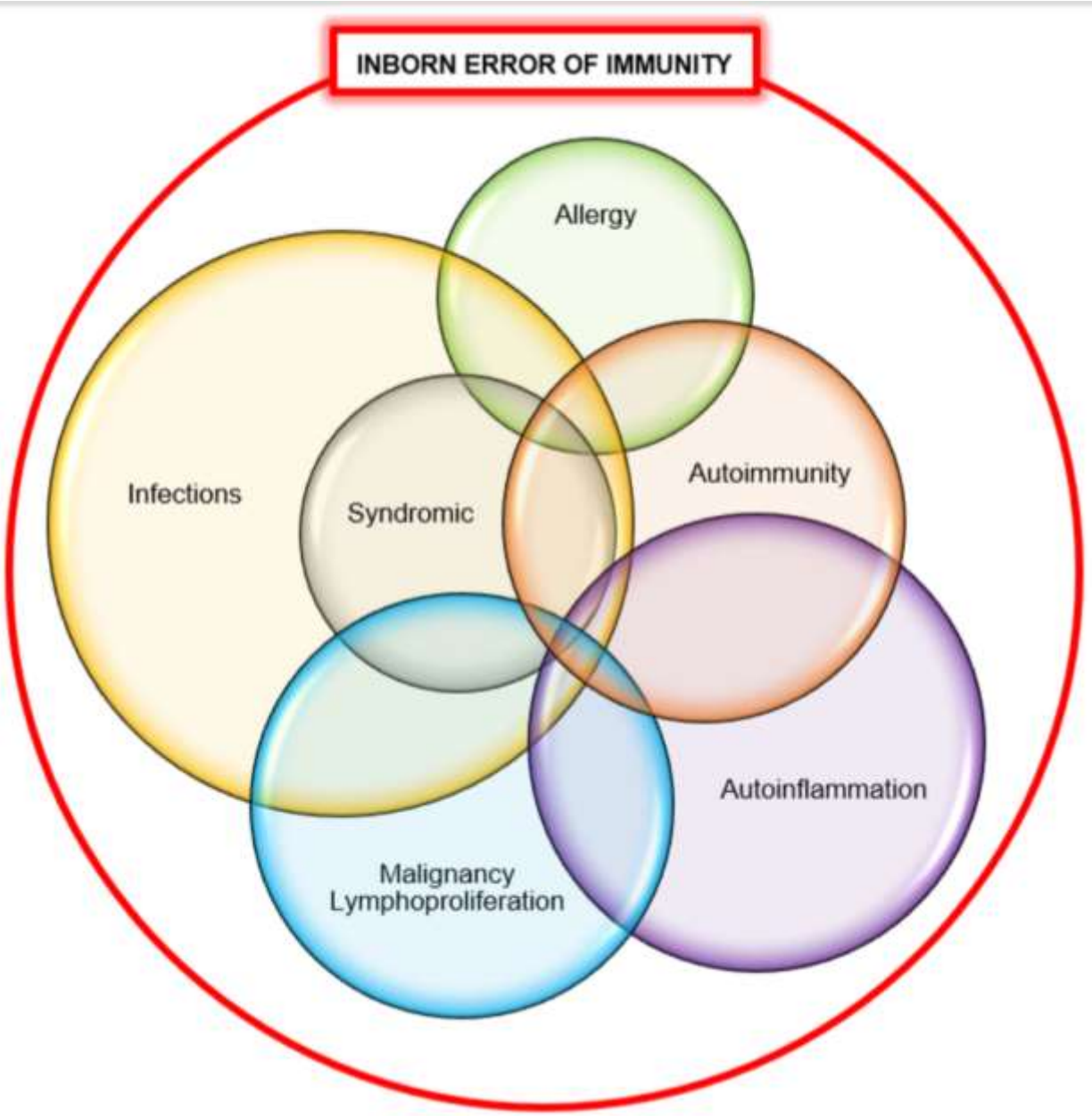
Introduction of Inborn Error Of Immunity

- A total of 555 IEIs, and 17 phenocopies due to mutations in 504 different genes!
- Incidence:
  - For individual IEI are rare , but as a group are not.
  - The incidence of IEIs in the USA was 6 per 10,000 people.
- Genetic variants underlie IEI by altering the encoded gene product, such as:
  - abolition (null) or reduction (hypomorphic) of protein expression
  - titration of the intrinsic function of the protein (gain- or loss-of-function, GOF or LOF)
  - acquiring novel functions (neomorphic)
- Mechanisms of disease in IEIs depend on:
  - Nature of the variant
  - Mode of inheritance

Combined immunodeficiencies (Table I; 3 sub-tables)	**Combined immunodeficiencies with syndromic features (Table II; 9 sub-tables)**	**Predominantly antibody deficiencies (Table III; 3 sub-tables)**	**Congenital defects of phagocytes (Table V; 4 sub-tables)**	**Diseases of immune dysregulation (Table IV; 7 sub-tables)**
Phenocopies of inborn errors of immunity	**Bone Marrow Failure (Table IX)**	**Complement deficiencies (Table VIII)**	**Autoinflammatory diseases (Table VII; 3 sub-tables)**	**Defects in intrinsic and innate immunity (Table VI; 9 sub-tables)**

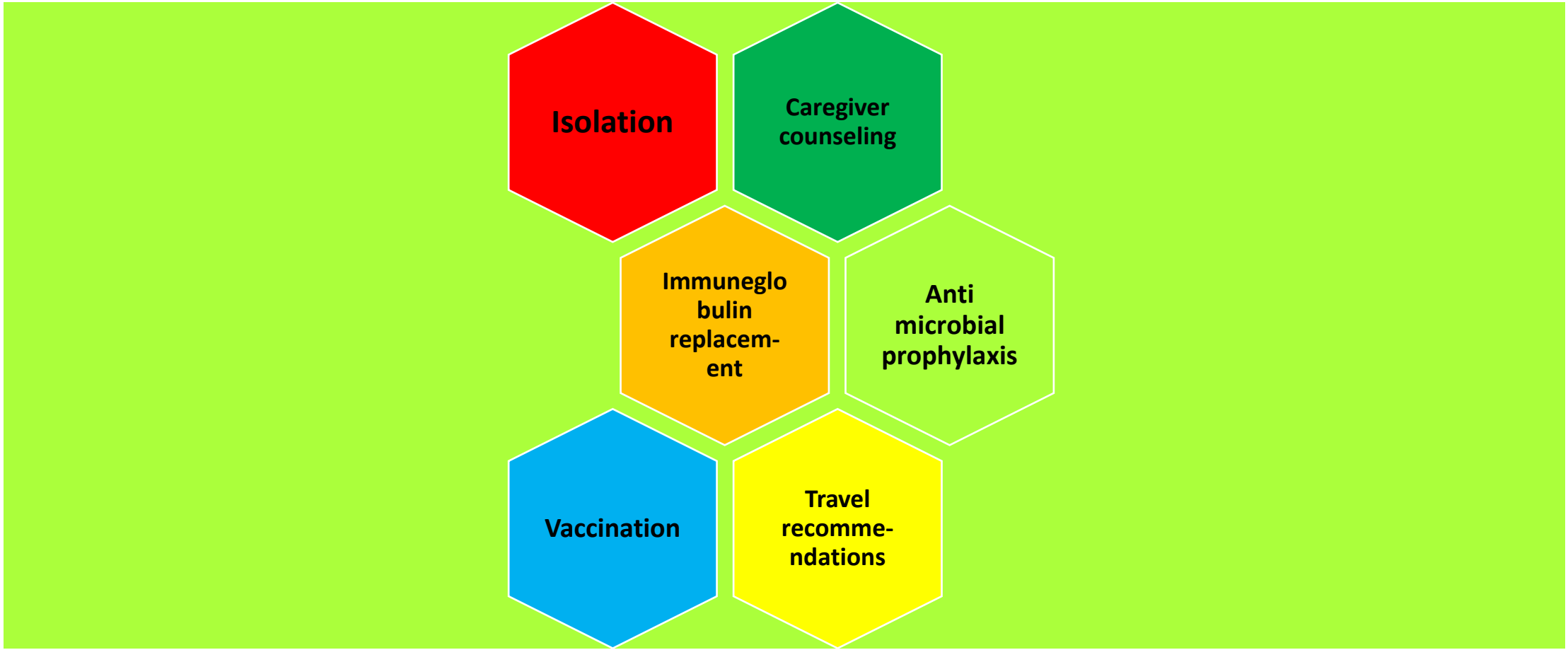
IEIs are currently categorized into 10 Tables, with sub-tables segregating groups of disorders into overlapping phenotypes.

Clinical Presentations:



- Management of IEIs differs across the spectrum of severity and depends largely on the specific defect in question.
- Accurate diagnosis is essential for proper patient management, including tailored screening for known risk factors, targeted pharmacotherapy and biologic use, and consideration of curative therapies such as bone marrow transplantation or gene therapy.

Prevent Initial Infections



Prevent Initial Infections

- Isolation :Once any severe inborn error of immunity (IEI) is suspected or confirmed, isolation measures should be implemented to prevent the patient from acquiring life-threatening infections.
- Managed carefully at home while awaiting HCT or be hospitalized in an isolation room

Prevent Initial Infections

- **Caregiver counseling**
- To minimize transmission of infections
- The degree of precaution depends upon the severity of the disorder.

➢For patients with moderate to severe forms of immunodeficiency, caregivers are encouraged to change their clothing and wash hands prior to interacting with the patient.

➢Good handwashing

➢Minimize the number of guests and visitors

➢up-to-date vaccinations of visitors and caregivers

Prevent Initial Infections

- **Immune globulin replacement**

1. Primary antibody deficiencies
2. SCID and combined immunodeficiencies until B cell function is restored
3. Disorders involving defects in antibody production or function

➢ Obtain baseline immunoglobulin levels and vaccine titers

➢ intravenously (IVIG) or subcutaneously (SCIg)

- dependent on patient preference
- If replacement is needed urgently, the patient should receive IVIG replacement in the hospital

Primary Immune Deficiency: Patients' Preferences for Replacement Immunoglobulin Therapy, Front. Immunol., 04 February 2022

Immunoglobulin replacement therapy

IVIG	SCIG
• Dosing ranges from 400- 800 mg/kg/dose, often every three to four weeks • Patients with bronchiectasis, hypercatabolic states, those with protein losing enteropathy or nephrotic syndrome need higher doses. • Adjust the dose based on trough levels	• FDA, all new IRT recipients should begin therapy with an intravenous loading dose. • The first SCIG dose is given one week after the IV loading dose. • starting dose is often 100 to 200 mg/kg/dose, commonly every seven days • The patients converting from an established IVIG regimen, receive approximately 140% of the monthly IVIG dose.

Prevent Initial Infections

Hyperimmune globulin:

- IgG isolated from donors with high titer antibody levels to particular antigens
- Indications:

1. pre-exposure prophylaxis (cytomegalovirus in solid organ transplantation)
2. post-exposure prophylaxis (hepatitis B, rabies, vaccinia and varicella)
3. Treatment (anthrax, infant botulism)
4. Treatment of idiopathic thrombocytopenic purpura and prevention of Rh isoimmunization by Anti-Rho (D).
5. Treatment of respiratory syncytial virus, in high-risk groups such as primary immunodeficiency.

Prevent Initial Infections

- **Prophylactic antimicrobials:**
- No standardized approach for prophylactic antimicrobials
- Reduce the frequency and severity of common bacterial sinopulmonary infections
- Antiviral and antifungal treatments may be necessary in particular disorders.
- Screen symptomatic patients for active infections prior to initiation of prophylactic antibiotics .
- Screen for mycobacterial infection prior to azithromycin use.
- Baseline screening based on the adverse effect of drugs, in ex. ECG, audiometry, CBC (diff), …

TABLE 53.1 Suggested prophylaxis, immunomodulation and vaccination considerations for selected primary immunodeficiencies.

Primary immune deficiency	Suggested prophylaxis	Suggested immunomodulation	Vaccination considerations[a]
Chronic granulomatous disease	TMP/SMX Itraconazole	IFNγ	Avoid BCG and live typhoid vaccines Consideration of avoiding live viral vaccination with systemic immunosuppression
X-linked agammaglobulinemia	TMP/SMX or amoxicillin Consider azithromycin if bronchiectasis[b]	IVIG or SCIG	Inactivated influenza vaccination
CD40 ligand deficiency	TMP/SMX	IVIG or SCIG G-CSF with neutropenia	Inactivated influenza vaccination
SCID	TMP/SMX Fluconazole Consider acyclovir	IVIG or SCIG	Avoid live vaccinations including BCG
DiGeorge syndrome	If partial, frequently not necessary		Case by case consideration of live viral vaccines
LOF STAT3	TMP/SMX Consider azithromycin if bronchiectasis present[b] Consider fluconazole for chronic *Candida* or if in Coccidioides endemic region; itraconazole if pneumatoceles present	Consider IVIG or SCIG	Polysaccharide pneumococcal vaccine may result in large local reactions
DOCK8 deficiency	TMP/SMX Consider acyclovir or valacyclovir	IVIG or SCIG	HPV vaccine Avoid live viral vaccines
STAT1 GOF	Fluconazole Consider acyclovir or valacyclovir if recurrent HSV/VZV or if JAK inhibitor therapy	Consider IVIG or SCIG if B cell abnormalities	
IL-12/IFNγR mutations	Azithromycin	Consider IFNγ	Avoid BCG
GATA2 deficiency	Azithromycin	Consider IFNγ with disseminated NTM Consider IFNα with widespread HPV	HPV vaccine Avoid live viral vaccines
NEMO	TMP/SMX Azithromycin	Consider IVIG or SCIG if B cell dysfunction	Avoid BCG and live viral vaccines
Complement defects Asplenia	Penicillin or amoxicillin		Meningococcal and pneumococcal vaccination

- **Mild humoral immune defects:**

➢ Antibiotic prophylaxis alone to patients with mild hypogammaglobulinemia, selective IgA deficiency, specific antibody deficiency, or IgG subclass deficiency, if they have a history of recurrent infection and are not receiving immune globulin replacement.

➢ A randomized trial demonstrated:

- comparable efficacy of prophylactic antibiotics versus antibody replacement therapy for specific antibody deficiency
- few adverse events with antibiotic prophylaxis

➢ Lack of evidence for supporting antibiotic use, when offered, trials are suggested with careful monitoring of side effects and rate of infections.

- **Severe humoral immune defects:**

➢ Patients receiving immune globulin may still have an increased rate of bacterial infections chronically and may also benefit from antibiotic prophylaxis.

➢ A randomized trial in patients with primary antibody deficiency demonstrated that azithromycin prophylaxis significantly reduced the rate of pulmonary exacerbations and hospitalizations, with no drug-related adverse events or increase in macrolide-resistance bacterial species.

- **Antiviral Prophylaxis:**

- Herpes simplex virus prophylaxis is indicated in the natural killer cells or toll-like receptor 3 signaling defects.

- In patients with CID and a history of varicella or CMV infection, long-term suppressive antiviral prophylaxis should be considered.

- Influenza prophylaxis should be considered during influenza season for high-risk immunodeficient patients and for patients in close contact with other persons with influenza.

- **Antifungal Prophylaxis:**
- defects in the interleukin (IL)-12/23/Th17 pathway, or in the presence of anti-cytokine autoantibodies which occur in autoimmune poly endocrinopathy disorder type I.
- **Mycobacterial prophylaxis:**
- in patients with mendelian susceptibility to mycobacterial disease, such as defects of the interferon gamma-IL-12 axis, nuclear factor-kappa-B essential modifier (NEMO) deficiency

Prevent Initial Infections

- **Vaccination:**
- benefits and risks of vaccinations

- Live vaccines are contraindicated in patients with moderate to severe forms of immunodeficiency.

➢ Expert consensus recommends that healthy family members and close contacts receive all vaccines in order to provide secondary protection.

Prevent Initial Infections

- **Travel Recommendation:**
- Drink only bottled water
- To wash or avoid fresh produce
- to avoid eating undercooked food
- Medication prophylaxis may be indicated
- Local experts in IEIs should be identified in case of illness during travel.

- **Caution With Blood Products:**

➢ Patients with suspected or known T cell immunodeficiencies:

  ➢ blood or blood components with no viable lymphocytes

  ➢ Irradiated cell products

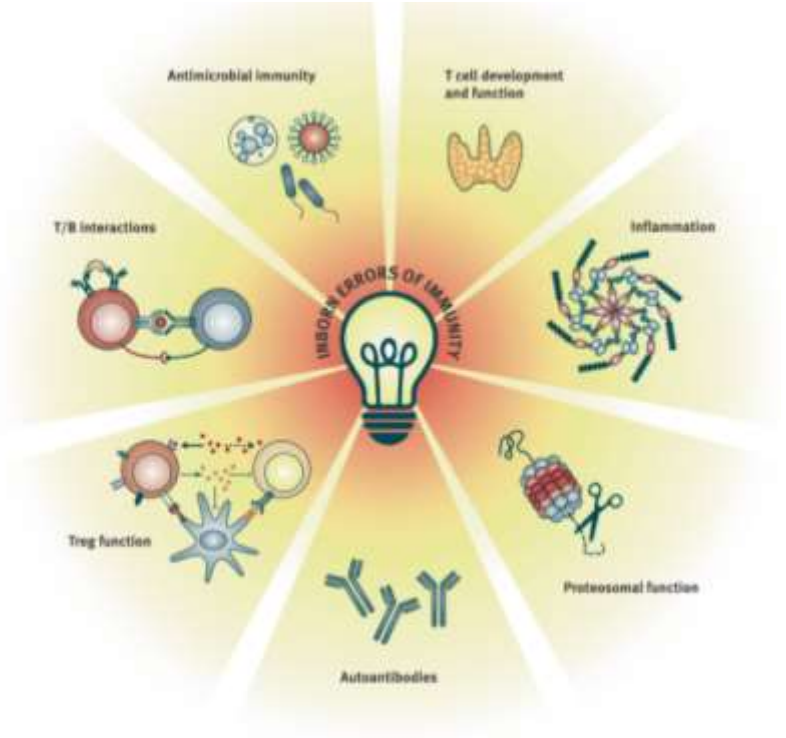
  ➢ Leukocyte reduction

➢ Immunodeficiency with severely compromised T cell function: severe combined immunodeficiencies , Wiskott-Aldrich syndrome, nuclear factor-kappa-B essential modifier [NEMO] deficiency, and complete DiGeorge syndrome

➢ Severe selective IgA deficiency have a potential risk of anaphylaxis to IgA-containing blood products.

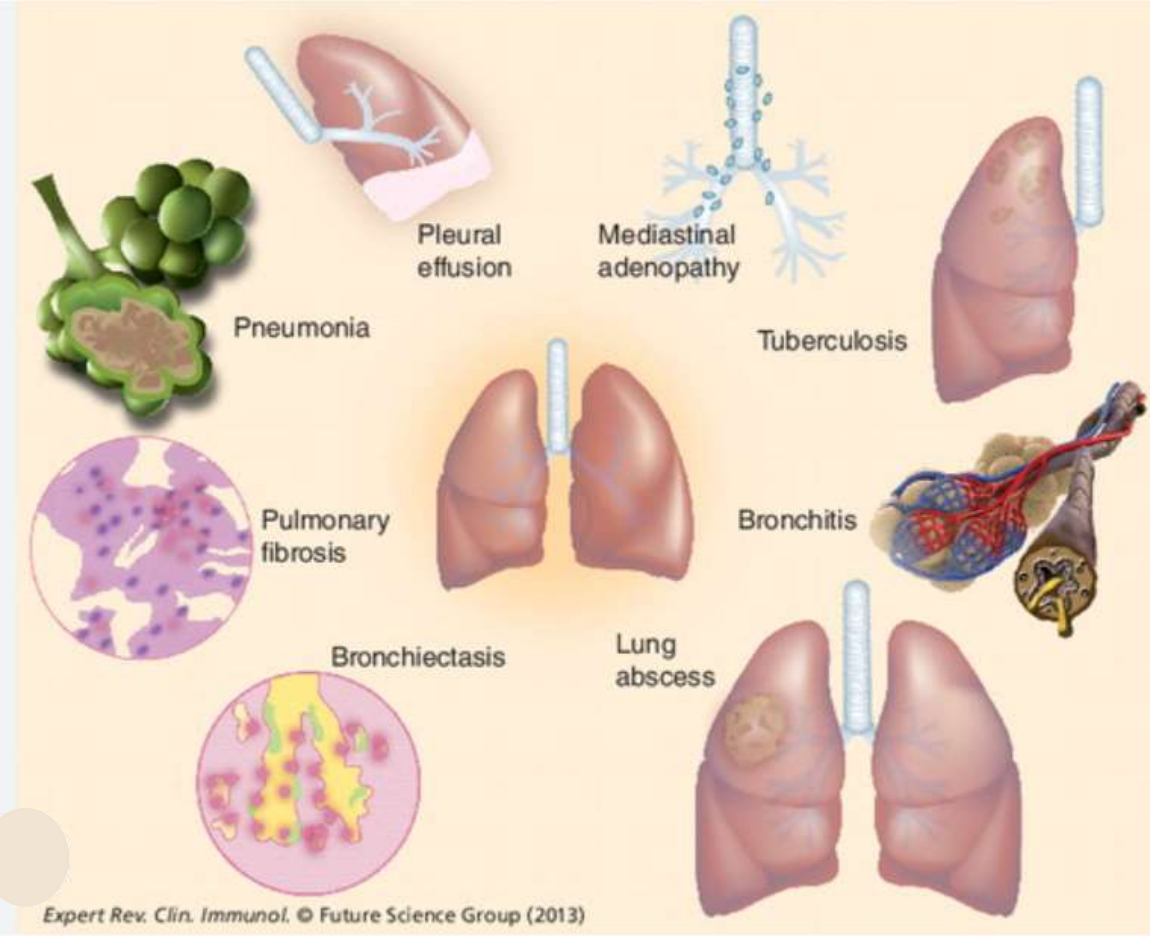
Management Of Complications

- **Infectious disease**
- The most common complication
- culture and identify the pathogen
- Initiate antibiotics as rapidly as possible
  - Optimal duration of antimicrobial treatment may be two to three times longer than standard
  - Specific IEIs increase risk for specific types of infection



Pulmonary disease:

- A leading cause of morbidity and mortality in patients with IEIs.
- In addition to pulmonary infections, other manifestations include bronchiectasis, granuloma formation, interstitial lung disease, bronchiolitis obliterans, and mediastinal adenopathy
- Regular follow up with pulmonary function test and imaging

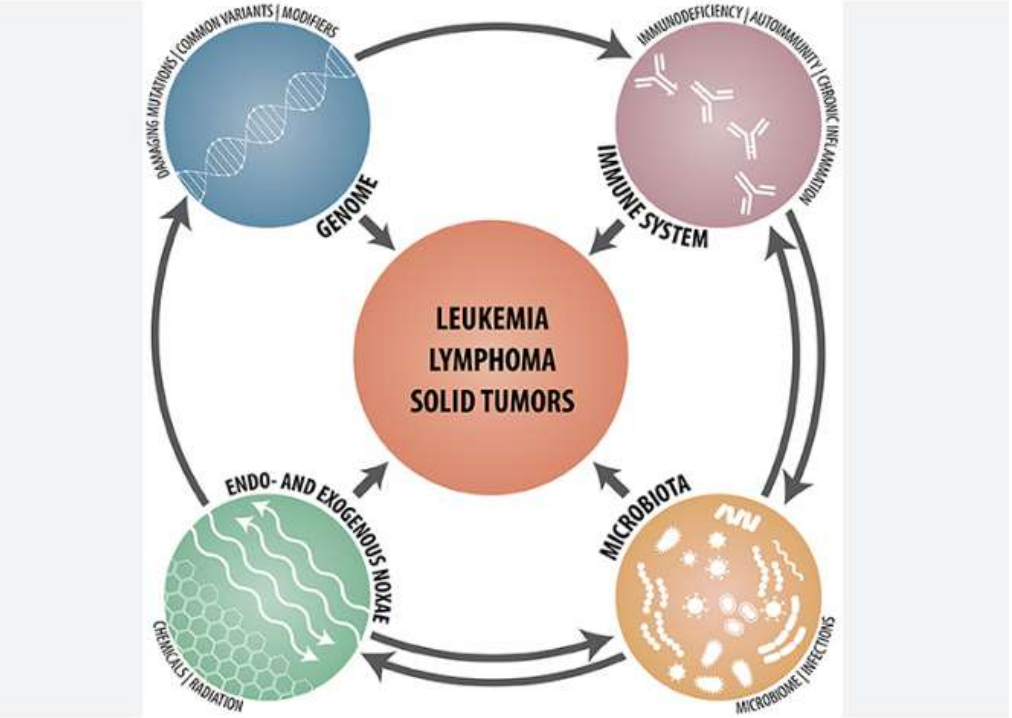


Pulmonary manifestations of chronic granulomatous disease
Pages 153-160 | Published online: 10 Jan 2014

- **Gastrointestinal disorders**
- Are common
- Manifestations include infection, autoimmune inflammation, malabsorption, granuloma formation, and lymphoproliferative disorders
- Primary treatment efforts should focus on the type of IEI and underlying gastrointestinal disorder such as aggressive, extended antibiotic and/or immune modulating therapy

Lymphoproliferative and malignant disease

- Many forms of IEIs increase risk for malignancies.
- It occurs at younger age.
- Causes of malignancies: including immune dysregulation, genetic predisposition, and impaired viral clearance.



Primary Immunodeficiency and Cancer Predisposition Revisited, Front. Immunol., 12 February 2019

- Screening for EBV and HPV In IEIs with impaired antiviral response.
- In radiation sensitivity disorders, strict avoidance of radiation exposure
- Modification of standard cancer therapy and transplantation protocols often require in IEI patients.

Atopy and autoimmune diseases

- **IgE and Non-IgE mediated allergy:**
- sensitivity to foods, medications, and/or environmental allergens
- Severe eczema in Job syndrome, Wiskott-Aldrich syndrome, IPEX syndrome, and Omenn syndrome

- **Autoimmune diseases:**
- Increased in defects of innate, humoral, and cellular immunity
- Autoimmunity can impact multiple organ systems such as endocrinopathy, hepatitis, vitiligo, autoimmune enteropathy, systemic lupus erythematosus (SLE), and cytopenias.

- Management of autoimmunity:
- Similar to the populations of patients with similar autoimmune disorders
- First-line therapies may need to be altered depending on specific infectious.
- Genetic diagnosis may also aid in guiding therapy.

> - New-onset autoimmune disorders should be suspicious of an IEI, if the presentation is atypical in **age of onset**, **severity**, or if the patient has **multiple autoimmune** manifestations.
> - Patients who carry an IEI diagnosis should be aware of autoimmune sequelae related to their disorder, and regular screening is recommended.

Immunologic reconstitution

- Hematopoietic stem cell transplantation
- Thymic transplantation
- Enzyme replace
- Gene therapy

Hematopoietic cell transplantation

- General considerations include:

➢ Available donor options

➢ Patient health prior to transplant, with particular focus on infections, nutritional status, and general organ function

➢ Whether a disorder is limited to the hematopoietic compartment or not.

➢ A genetic diagnosis is helpful but not required for HCT.

➢ Genetic diagnosis is important for:

1. Radiosensitive disorder; long-term toxicities from alkylating agents
2. Immune dysregulatory disorders; transplant risks including graft rejection and inflammatory complications such as hemophagocytic lymphohistiocytosis.

HCT has been used as the treatment of SCID since 1968.

2nd HSCT has been used for Wiskott Aldrich syndrome in 1968 successfully.

There after more IEIs have been cured by HSCT.

Hematopoietic stem cell transplant (HSCT) is now the standard of care for the treatment of several IEIs.
In many of these otherwise lethal genetic diseases, BMT can completely reverse the immunological abnormality and patients may be permanently cured.

Hematopoietic Stem Cell Transplantation in Primary Immunodeficiency Diseases: Current Status and Future Perspectives

TABLE 2 | Indications for HSCT in PID.

HSCT curative	HSCT partially curative	HSCT controversial
SCID	Cartilage Hair Hypoplasia	CVID
CID^	PGM3 deficiency	Agammaglobulinemia
CGD	STAT1-GOF	Complement deficiencies (other than C1q deficiency)
DOCK8 deficiency	STAT3- GOF	DGS
DOCK2 deficiency	Severe congenital neutropenia	IKBA deficiency
IPEX	ADA2 deficiency	NEMO deficiency
WAS	CIQ deficiency	
WIP deficiency	CD25 deficiency	
ARPC1B deficiency	IL-10 deficiency	
CD40 ligand deficiency	IL-10 Receptor deficiency	
CD40 deficiency	DNA double-strand break repair disorders	
XLP1, XLP2		
APDS		
MHC Class II deficiency		
AD Hyper IgE syndrome		
CTLA4 haploinsufficiency		
LRBA deficiency		
Familial HLH types 1–5		
GATA2 deficiency		
RAB27A deficiency		
LAD I		
Reticular Dysgenesis		

Indications for hematopoietic cell transplantation (HCT) for inborn errors of immunity

Type of inborn error of immunity	Indications
SCID	Required in all patients for survival.
Leaky SCID	Required in almost all patients for survival.
Combined immunodeficiencies	Potentially indicated, depending upon the severity of the phenotype and availability of suitable donor. Examples: ▪ CD40L deficiency ▪ DOCK8 deficiency ▪ MHC class II deficiency ▪ Purine nucleoside phosphorylase deficiency
Combined immunodeficiencies with associated or syndromic features	Potentially indicated based upon predicted lifetime risks and patient-specific manifestations. Examples: ▪ Cartilage-hair hypoplasia ▪ NEMO deficiency ▪ Wiskott-Aldrich syndrome
Combined immunodeficiencies due to athymia	**Not** indicated because allogeneic HCT will not replace thymic tissue. Patients with congenital athymia are best treated with cultured thymus tissue implantation (CTTI).
Predominantly antibody deficiencies	Generally **not** indicated for patients for whom IgG infusions confer protection from infection. Exceptions may be patients with common variable immunodeficiency who experience severe manifestations, including immune dysregulation.
Diseases of immune dysregulation	Indicated for many patients because disease may be life threatening. Examples: ▪ Familial hemophagocytic lymphohistiocytosis ▪ X-linked lymphoproliferative disease due to *SH2D1A* mutations ▪ Some patients with X-linked lymphoproliferative disease due to *XIAP/BIRC4* mutations ▪ Immune dysregulation, polyendocrinopathy, enteropathy, X-linked
Phagocytic cell defects	Indicated for most patients. Examples: ▪ Chronic granulomatous disease ▪ Leukocyte-adhesion deficiency ▪ Severe congenital neutropenia
Defects of innate immunity	Potentially indicated for some diseases, although experience is

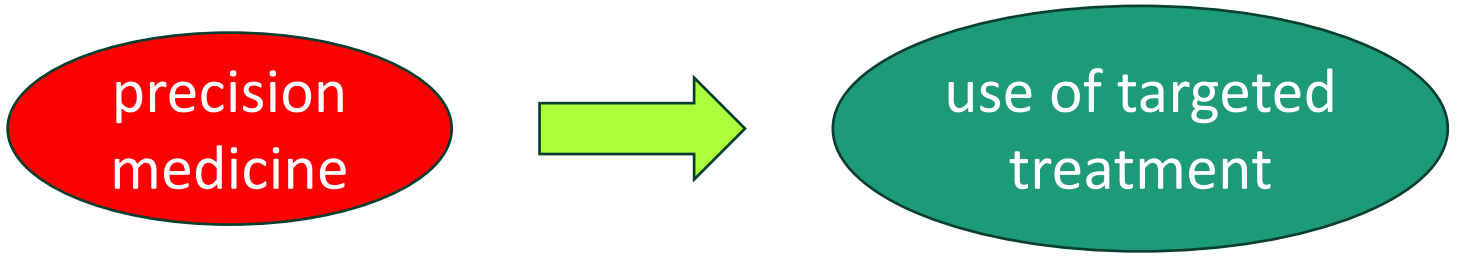
Indications for hematopoietic cell transplantation (HCT) for inborn errors of immunity

Type of inborn error of immunity	Indications
	limited. Examples: ▪ Interferon gamma receptor 1 deficiency ▪ STAT1 loss of function
Autoinflammatory disorders	Generally **not** indicated for patients in this category, but there is limited experience for some disorders.
Complement deficiencies	**Not** indicated for most complement defects, because most complement factors are produced by the liver. Allogeneic HCT is a potential option for C1q deficiency as hematopoietic cells produce C1q.

Enzyme replacement and metabolic therapy

- Despite major advances in HSCT for IEIs, several challenges still remain, such as, donor selection and the potential risk of post-HSCT complications (e.g., graft versus host disease).

- Pinto and Neves, report the application of precision medicine in the treatment of IEIs.



Enzyme replacement and metabolic therapy

- Several IEIs stem from defects in cell metabolism that impair development or survival of lymphocytes.

Adenosine deaminase (ADA) deficiency can be treated via enzyme replacement with polyethylene glycol (PEG-ADA), which partially reconstitute immune function by detoxification of immunotoxic metabolites, is recommended primarily as a bridge to other definitive therapies.

Signal transducer and activator of transcription (STAT) 3 gain-of-function (GOF) syndrome is successfully treated with targeted therapy using Janus kinase (JAK) inhibitors and/or anti–IL-6R blockade.

- The JAK/STAT signaling pathway plays a crucial role in immune functions, and several IEIs have been described owing to a defect in this pathway directly or indirectly.
- JAK inhibitors a new class of small molecules targets the JAK-STAT pathway.

- Ruxolitinib (JAK inhibitor) was used in a child with a gain-of-function (GOF) mutation in the STAT1 gene (c.854A>G, p.Q285R), to control the hyperinflammation and hemolysis for bridging the HSCT.
- Also, Ruxolitinib were successfully used in the management of familial hemophagocytic lymphohistiocytosis (fHLH) type 3 patients that managed patient's cytokine storm and allowing them for successful HSCT.

Cytotoxic T lymphocyte antigen 4 (CTLA-4) haploinsufficiency leading to an immune dysregulation syndrome with CID.
The CTLA-4 fusion proteins Abatacept and Belatacept have shown promising results in these cases.

Sirolimus inhibits the CD28 signaling pathway which decreases T cell hyperactivity, and enhances T regulatory cells and has been shown to be effective in CTLA4 haploinsufficiency and LRBA.

Thymic transplantation

- For combined immunodeficiency due to athymia such as complete DiGeorge syndrome, and Forkhead box N1 (FOXN1) deficiency.

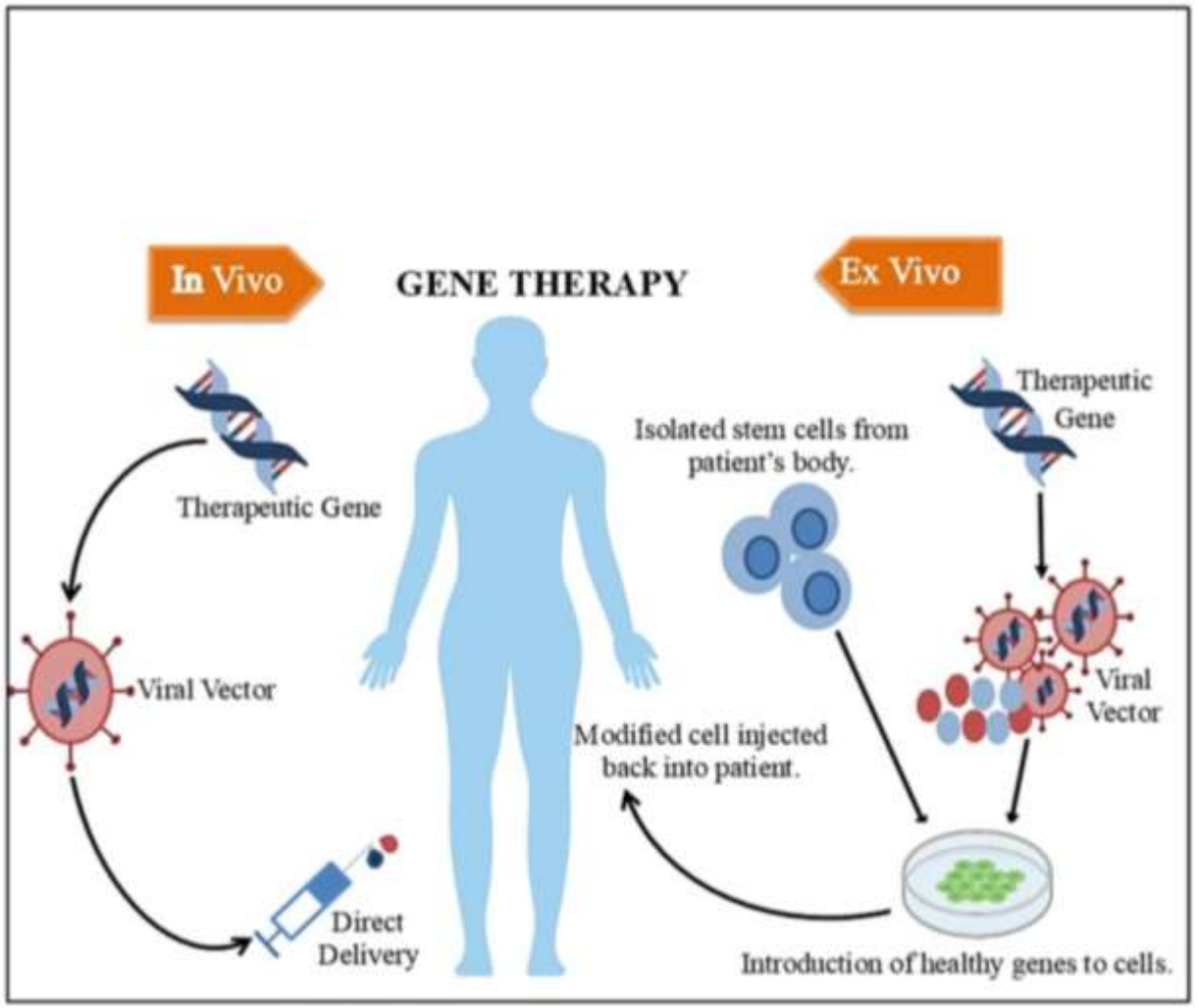
Gene therapy

Gene therapy was first pioneered for adenosine deaminase-deficient (ADA) SCID in the 1990s.

Thereafter gene therapy was pioneered for x-SCID in 1990s.

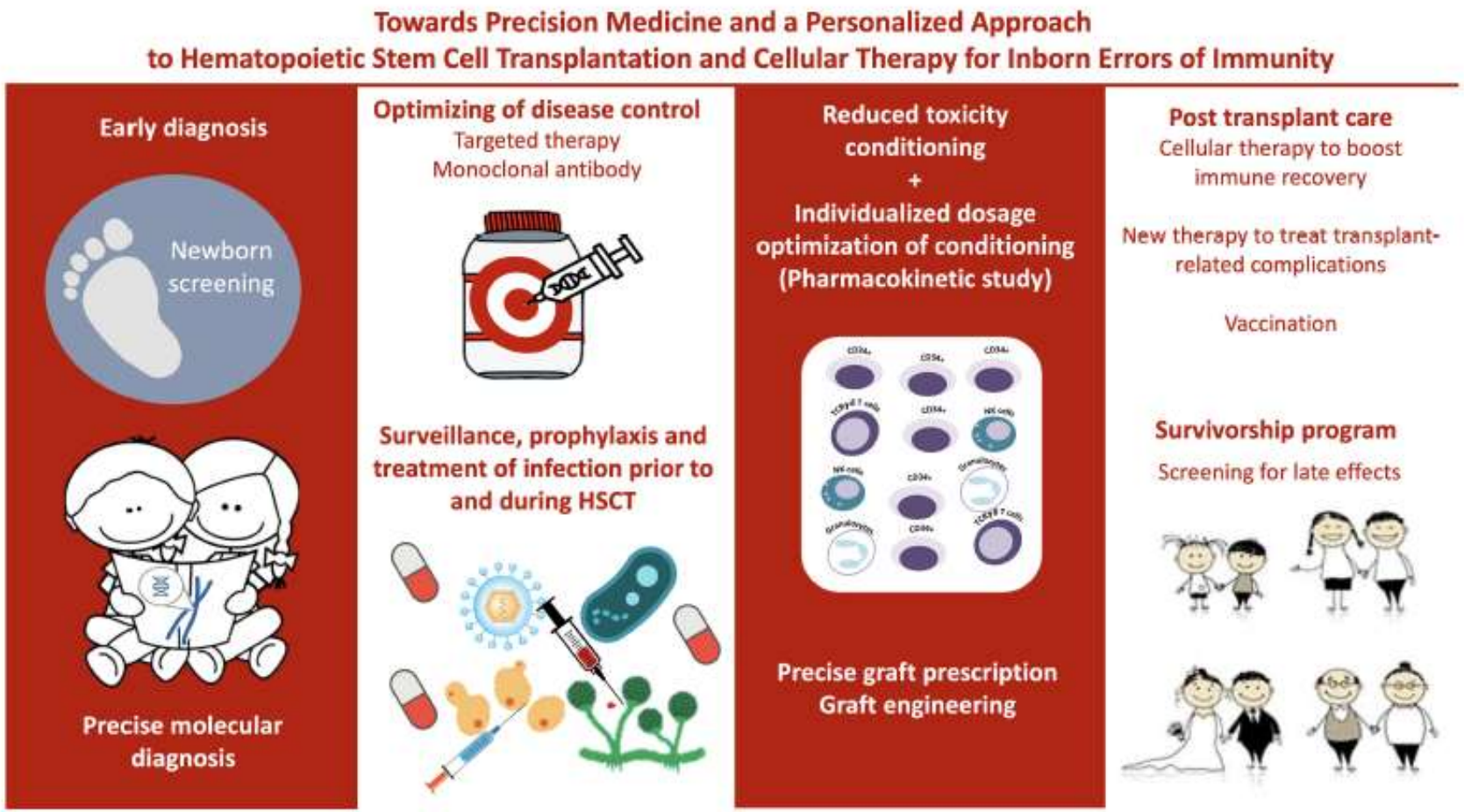
Soon after SCID gene therapy were pioneered for CGD and WAS. Now, has been successful for patients with other IEIs.

- **Gene therapy:**
- Feasible and effective in severe immunodeficiency disorders that are limited to hematopoietic cell lineages.
- Transduction of autologous hematopoietic stem cells with a vector containing the corrected gene product, which is then administered to the patient.
- Advances in vector engineering have minimized this risk
    - Self-inactivating lentiviral vectors



Genetic testing and counseling

- Helpful in situations where there is ambiguity or uncertainty in the approach
- Beneficial for the patient and family
- Parental genetic sequencing



GRAPHICAL ABSTRACT

Personalized hematopoietic stem cell transplantation for inborn errors of immunity,
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Thank you for your attention