When Is a Rash Just a Rash?
Masqueraders of Primary Immunodeficiency

Ricardo U Sorensen, MD
Professor Emeritus
Louisiana State University, New Orleans

Founder and President
Louisiana Primary Immunodeficiency Network, LAPIN

Learning Objectives

- Learn about immunodeficiencies; types and evaluation
- List skin diseases that may be due to an immunodeficiency
- Review main skin diseases and main immunodeficiencies linked to them
- Point out importance of diagnosing an underlying immunodeficiency

Immunodeficiency diseases (IDD)

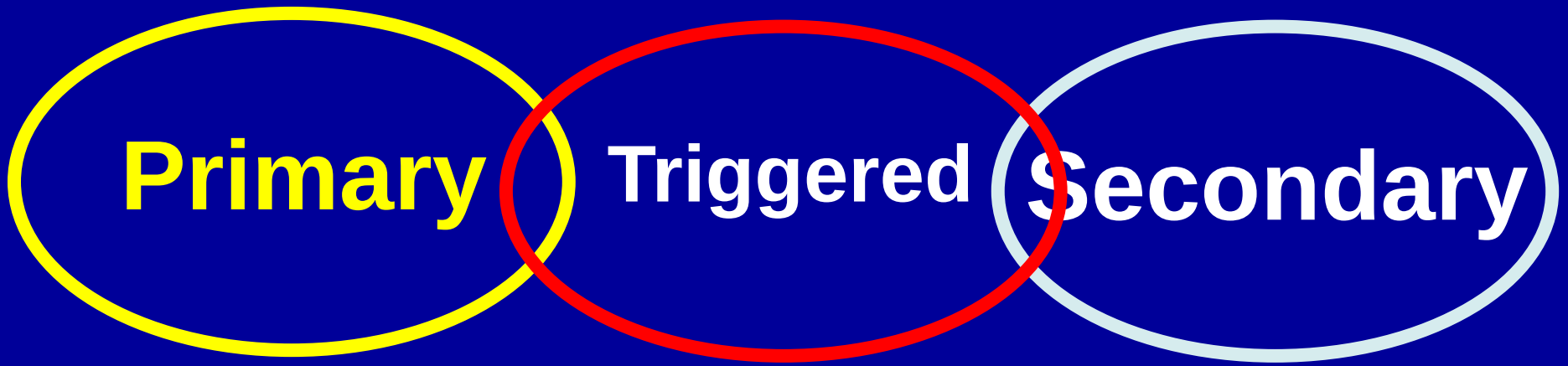
IDD are alterations of a component of the acquired or innate immunity that predisposes to infections, autoimmunity, inflammation, lymphoproliferation, malignancies or hypersensitivity and allergy.

The clinical manifestations of IDD may be expressed in multiple body areas including the skin.

Components of Immunity and IDD

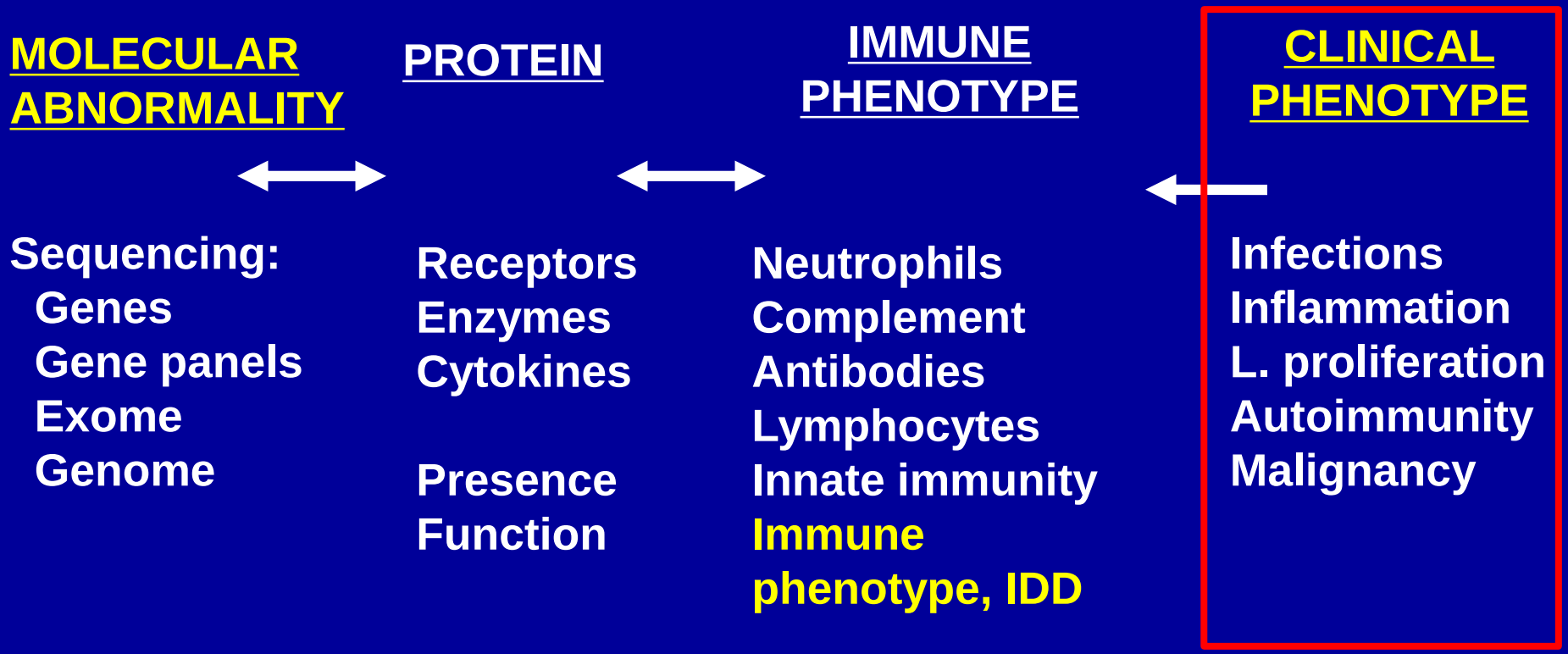
Cell Mediated Immunity	Combined T and B cell ID Combined with syndrome features
Antibody Mediated Immunity	Predominantly Antibody ID
Phagocytosis	Congenital defects of phagocytes
Complement	Complement deficiencies
Innate Immunity	Defects in innate immunity
Regulation of inflammation and fever	Autoinflammatory disorders
Regulation of cell proliferation and self recognition	Dysregulation and autoimmunity

Causes of Immunodeficiency

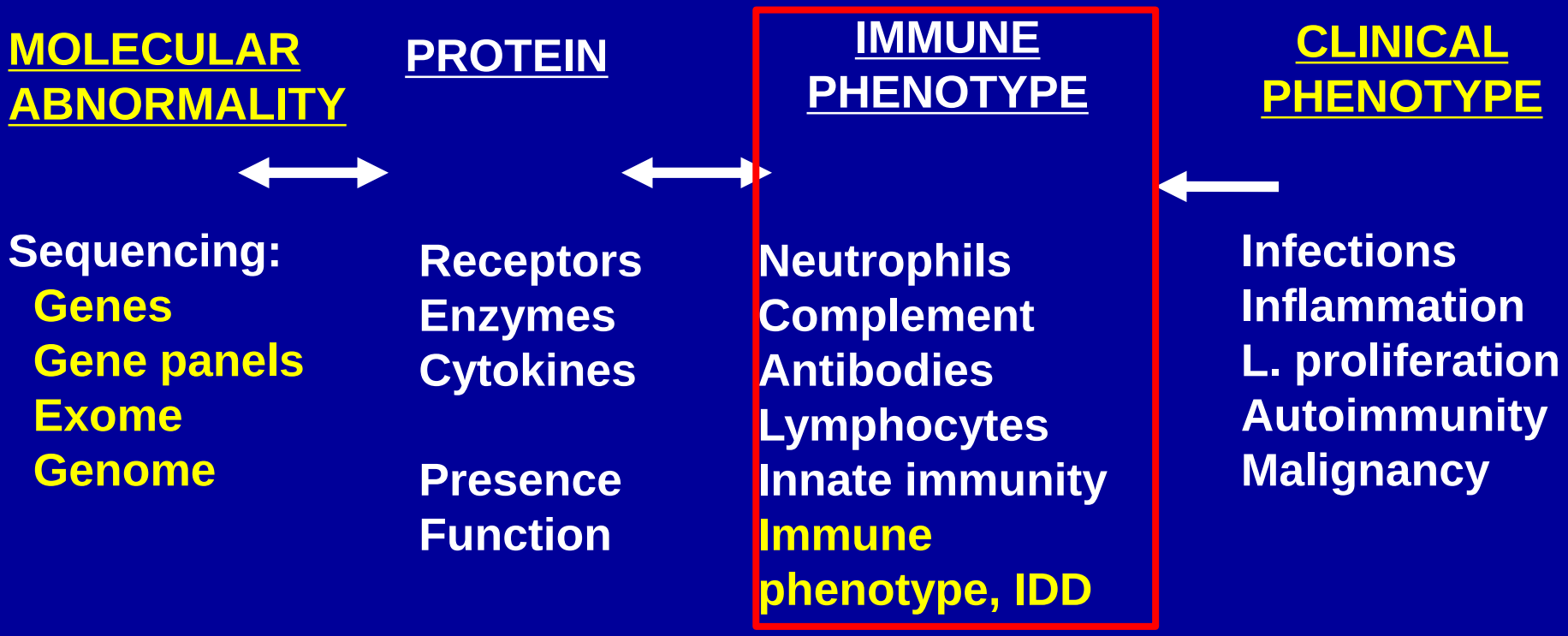


Early **Variable Onset**

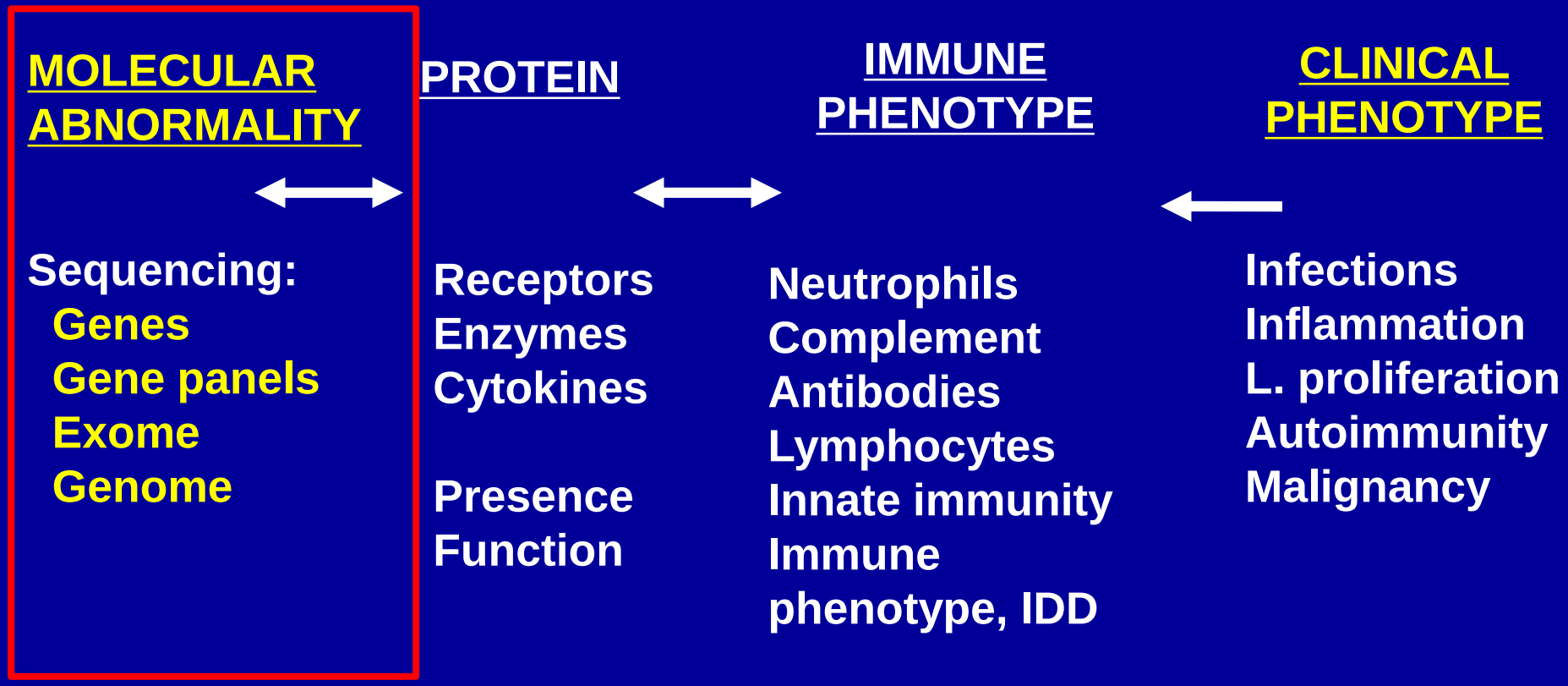
Phenotype / Molecular / Genotype Diagnosis of Primary Immunodeficiencies



Phenotype / Molecular / Genotype Diagnosis of Primary Immunodeficiencies



Phenotype / Molecular / Genotype Diagnosis of Primary Immunodeficiencies



Types of Genetic Testing

- Sanger Single Gene – gDNA, cDNA
- Next-Gen – Disease Panels
- Next-Gen – Whole Exome Seq.
- Next-Gen – Whole Genome Seq.

Table I Screening laboratory tests for the non-immunology specialist in order to detect patients with possible PIDD

Possible PIDD	Screening Tests
Antibody mediated immunity (AMI)	• CBC and differential • Serum IgG, IgA, IgM • Antibody titers to protein and polysaccharide vaccines
Cellular mediated immunity (CMI)	• CBC and differential • Lymphocytes: CD3, CD4, and CD8; CD19; CD16/56 • Chest x-ray

J Clin Immunol (2014) 34:10-22

Table I Screening laboratory tests for the non-immunology specialist in order to detect patients with possible PIDD

Possible PIDD	Screening Tests
Complement (C)	• C4 (if angioedema without urticaria)CBC • CH50
Phagocytosis (P) Neutropenia Neutrophil function	• Neutrophil counts • Oxidative burst by DHR test
Autoimmunity	• ANA, RCP
Innate immunity (II)	• Specialized tests (consult an immunologist

J Clin Immunol (2014) 34:10-22

Skin Disorders

- Dermatitis-like lesions
- Erythematous skin lesions
  - Erythema
  - Erythroderma
- Rash
- Urticaria
- Psoriasis-like disorders
- Hair abnormalities
- Nail disorders

Skin Disorders, cont'd.

- **Skin infections**
  - **Fungal skin infection**
  - **Viral skin infections**
  - **Bacterial skin infections**
  - ***Mycobacterial* infections**

Skin Disorders, cont'd.

- Acne-like disorders
- Ulcers
- Vascular disorders
- Pigmentation disorders
- Neoplastic disorders

- Discoid lupus

What Makes a Skin Disease a Likely Manifestation of PID?

- Chronicity
- Severity
- Non-infectious and infections
- Multiple skin disorders
- Systemic manifestations
- Wrong age

Warning signs of IDD. Dermatology

Eczema	IDD	Laboratory
+Petechiae	Wiscott-Aldrich syndrome (WAS)	CBC including platelet number and size (small sized platelets); CMI, AMI
+Abnormal facies +Skin abscesses	Hyper IgE syndrome (HIES)	Serum IgE, eosinophils
+Polyendocrinopathy +Enteropathy	Immunodysregulation, X-linked (IPEX)	CMI, ANA, CRP TSH
+Neonatal diabetes mellitus		
+Hypothyroidism		
+Hemolytic anemia thrombocytopenia.		
+Dermatitis (eczema)		

Warning signs of IDD. Dermatology

Erythema	IDD	Laboratory
+Edema +Erythematous plaques +Food allergies +Sandpaper-like skin rash	Zn deficiency	CMI, IgE, Zn levels

Warning signs of IDD. Dermatology

Erythroderma	IDD	Laboratory
+Infections, +Failure to thrive +opportunistic infections ,	Severe combined immuno-deficiency (SCID)	CMI, AMI
+Skin rash	SCID with maternal engraftment and GVHD	
+Severe erythroderma early onset +Lymphadenopathy +Hepatosplenomegaly +Eosinophilia	Omenn syndrome	

Warning signs of IDD. Dermatology

Hair abnormalities	IDD	Laboratory
Partial oculo-cutaneous albinisima +albinisima +gray hair **+**Recurrent pyogenic infections	Chediak-Higashi syndrome	Enlarged cytoplasm granules in blood smear
Fragile hair, conic teeth no sweat infections, Gram +/-	Ectodermal dysplasia	IID
Hypopigmented hair	Griscelly syndrome	CMI, AMI

Warning signs of IDD. Dermatology

Viral Skin Infections	IDD	Laboratory
Warts, disseminated		
+hypogamma-globulinemia +Infections +Myelokathexis	(WHIM) syndrome	AMI, CMI
+Chronic, recurrent warts	Idiopathic CD-4T cell lymphopenia	CMI
	Multiple molecular defects	DNA Sequencing

Recurrent warts. Multiple molecular defects:

- CXCR4 (MIM:162643): WHIM : Warts , Hypogammaglobulinemia ,Infection and Myelokathexis syndrome (CXCR4)
- CARMIL2/RLTPR (MIM:610859)Respiratory infections ,MC, hyperkeratosis, IBD, COPD,asthma , nasal congestion
- DOCK8 (MIM:611432) Hyper-IgE recurrent infection, autosomal recessive
- GATA2 (MIM:137295) WILD, Emberger, MonoMAC, DCML, Nkdeficiency , LES like
- MCM4(MIM:602638) Natural killer def, glucocorticoid deficiency DNA repair defect
- STK4 (MIM:604965) MST1 T-cell immunodeficiency, recurrent infections, autoimmunity, and cardiac malformations, hipergamma
- RHOH (MIM:602037) Rho GTPase
- TMC6 (MIM:605828) EVER1 Epidermodysplasia verruciformis
- TMC8 (MIM:605829) EVER2 Epidermodysplasia verruciformis
- MAGT1 (MIM:300715) Immunodeficiency, X-linked, with magnesium defect, Epstein-Barr virus infection and neoplasia

Warning signs of IDD. Dermatology

Viral Skin Infections	IDD	Laboratory
Cutaneous herpes infections	Dedicator of Cytokinesis8, DOCK8 deficiency	CMI, AMI

Warning signs of IDD. Dermatology

Bacterial Skin infections	IDD	Laboratory
Abscesses due to catalase + organisms *Staph aureus, Serratia, E. coli, Aspergillus Chromobacterium, Mycobacteria*	Chronic granulomatous disease, CGD	P
Delayed separation of umbilical cord Early onset of S. aureus, Pseudomonas infections Elevated neutrophils	Leukocyte adherence deficiency	CBC, neutrophil count
Salmonella skin infections	IL-12/ **IFN**γ mutation	Referral

Warning signs of IDD. Dermatology

Fungal Skin Infections	IDD	Laboratory
Mucocutaneous Candidiasis +Autoimmune endocrinopathies	Dedicator of Cytokinesis8, DOCK8 deficiency	CMI, AMI
	Human Dectin-1 deficiency	
	Card-9 mutations	
+Eczema	DOCK 8	

Warning signs of IDD. Dermatology

***Mycobacterial* infections**	**PIDD**	**Laboratory**
Atypical Mycobacteria BCGosis	Combined immunodeficiencies	CMI
	Hyper-IgM syndromes	AMI
	Mendelian susceptibility to mycobacterial diseases	II
	Chronic granulomatous diseases (CGD)	P
BCGitis	Multiple CMI deficiencies CGD	CMI P

Warning signs of IDD. Dermatology

Vascular disorders	PIDD	Laboratory test
Telangiectasias +Sinopulmonary infections, +lymphoreticular malignancies	Ataxia-telangiectasia	AMI; serum alfa-feto protein
Angioedema +Sudden painless edema +Recurrent abdominal pain +Upper airway edema	C1esterase inhibitor deficiency	C

Warning signs of IDD. Dermatology

Discoid lupus	PIDD	Laboratory test
+ Family history	X-linked CGD	P

Management of Immunodeficiency Diseases

- Prevention of infection exposure. Allow normal, unrestricted life
- Immunization of patient and family members
- Avoid live vaccines
- Preventive antibiotics
- Intensified antibiotic treatments
- immune serum globulin treatment

IDD Management, continued

- Treatment of infections, inflammation, lymphoproliferation, autoimmunity
- Prevention of infections
  - Avoidance of exposure
  - Preventive antibiotics
  - Gammaglobulin, monoclonal antibodies
- Mechanism-based precision therapy
- Cytokine and enzyme therapy

IDD Management, continued

- Stem cell transplantation
- Gene therapy, gene editing
- Thymus transplant
- Genetic counseling and pre-symptomatic diagnosis and treatment of family members

For access to a list of skin diseases and immune deficiencies please visit our Website
www.lapininc.org

Louisiana Primary Immunodeficiency Network

(LAPIN)

Email: lapin @ lapininc.org