Best test options for the evaluation of suspected PIDD

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Objectives

- Identify clinical presentations of deficiencies in major immune cell types
- Develop a systematic approach to diagnostic testing in the evaluation of immune mediated disease

Primary Immune disorders can present with a heterogenous phenotype

- Infection
- Autoimmunity
- Autoinflammation
- Allergy
- Lymphoproliferation
- Malignancy

How does the patient present?

- Primary Immunodeficiency
  - Severe infection
  - Sepsis
  - Pathologic Inflammation
- Secondary Immunodeficiency
  - Severe infection
  - Sepsis
  - Pathologic Inflammation
- How do we distinguish between the two???

The Immunologist Thought Process

- Bug
  - Opportunistic infections
  - Recurrent common infections often refractory to treatment
- Frequency of infections and or non-infectious disease flares
- Severity
- Laboratory pattern
- Body Part
  - Autoimmunity
  - Autoinflammation
  - Progression of disease
- Age
- Genetic Testing
- Sex
- Family History
- Medications

The Thought Process for Conner

- Bug
  - Opportunistic infections
  - **Recurrent common infections often refractory to treatment**
- **Frequency of infections** and or non-infectious disease flares
- **Severity**
- **Laboratory pattern**
- **Body Part**
  - Autoimmunity
  - Autoinflammation
  - Progression of disease
- **Age**
- Genetic Testing
- **Sex**
- **Family History**
- **Medications**

Immune Deficiencies: many lessons

El Senior Si, Lilana Bezrodnik, MD

How do we know what cells are important?

- Neutrophils
- Lymphocytes
- Antibody
- Cell trafficking
- Neutrophil killing

- Congenital neutropenia (death 3-4m) 1950
- SCID (death 6-8m) 1950
- Agammaglobulinemia (death 8-25y) 1952
- Leukocyte adhesion deficiency (death 10-20y) 1984
- Chronic granulomatous disease (death 2-20y) 1950

These lessons extended to non-PIDD

- Neutrophils
- Lymphocytes
- Antibody

- Using G-CSF with chemotherapy
- Counts predict outcome in HIV
- Rituximab use for autoimmune disease- vulnerable

Let’s start with infection

Infection category	Mechanism of defense
Conventional bacteria	Antibody, neutrophils, complement
Mycobacteria	Macrophages, T cells
Fungus	Macrophages, neutrophils, T cells
Candida	T cells, mucosal surface
Virus	T cells, NK cells

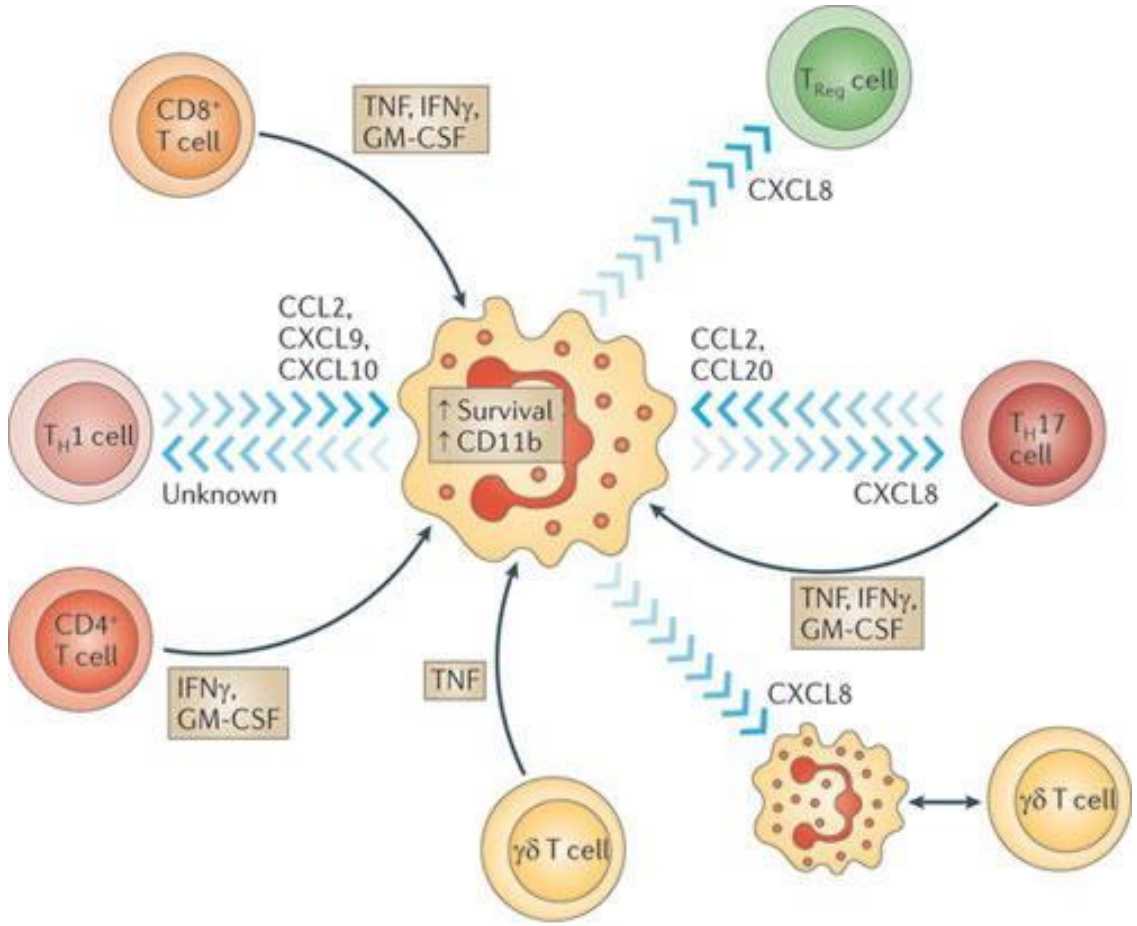
Characteristic infections in immunodeficiencies

- T cell
  - Opportunistic, prolonged viral infections (autoimmune)
- Phagocytic
  - Staphylococcal, Pseudomonas, fungal, mycobacteria
- Antibody
  - Usual organisms: recurrent respiratory/GI infections (autoimmune)
- Complement
  - Encapsulated organisms, Neisserial disease (SLE, aHUS)
- NK cells
  - Herpes family viruses, Human Papilloma Virus, ?influenza ?(autoimmune)

Neutrophils

Neutropenia

Compromised function



Referral Patterns

- Recurrent Bacterial infections
- Abscess formation
- Staph Susceptibility
- Fever
- Mucositis
- Recurrent ulcers
- Neutropenia or Neutrophilia on CBC

Clinical and Laboratory Features

- Level – on CBC w diff
- Function – DHR testing for CGD
- Physical Exam
  - Isolated
  - Anatomic abnormalities
  - Syndromic features

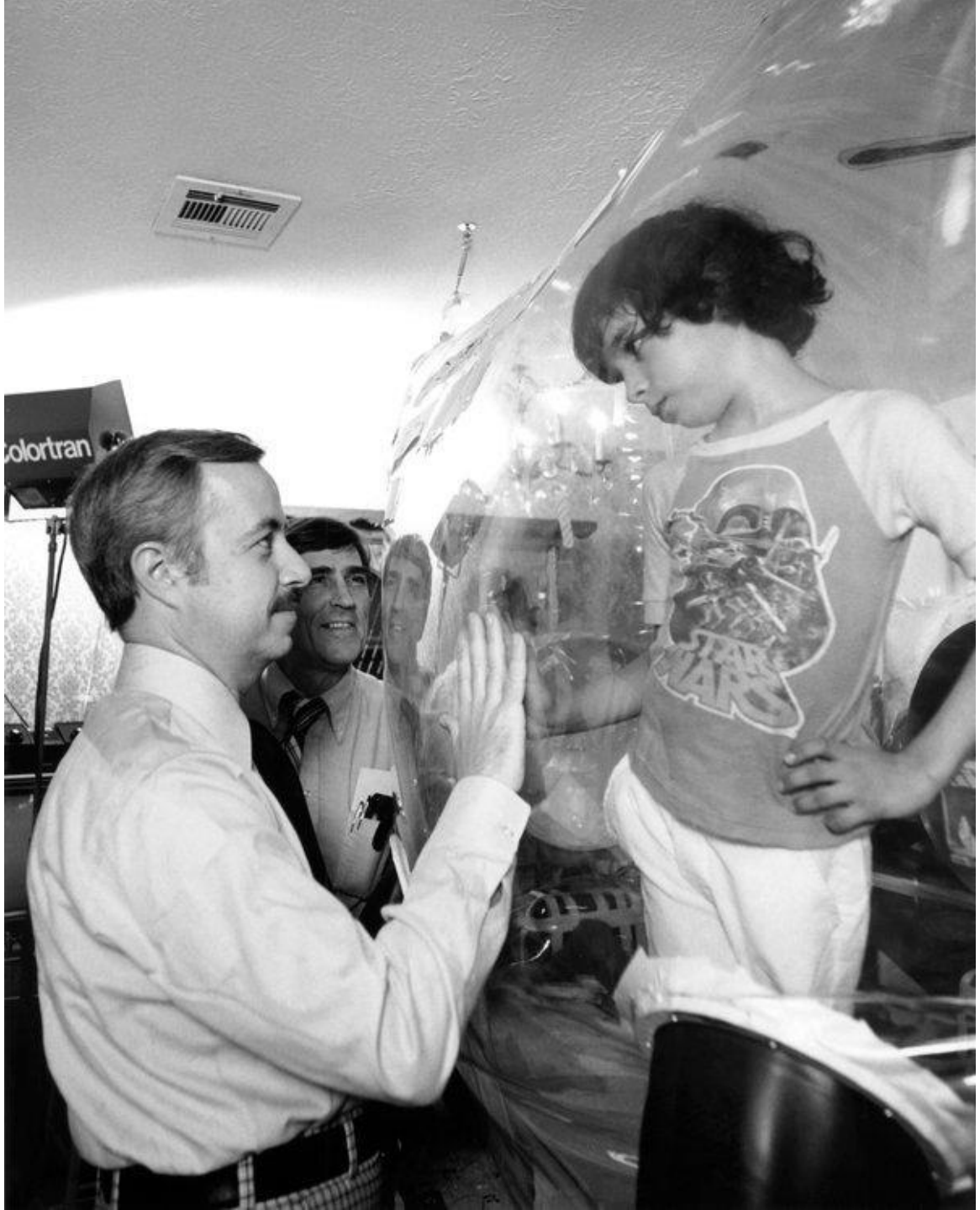
Neutrophil defects

- Defense against surfaces
  - Skin abscesses
  - Lung infections
    - Bacterial
    - Fungal
  - Sepsis
    - Gram negative organisms


Early onset
Bacteria and fungi
Fatal without therapy

T cell defects

- Not enough T cells
- Poor function



Reference intervals for lymphocyte subsets in preterm and term neonates without immune defects

George S. Amatuni, BS,[a,b] Stanley Sciortino, PhD, MPH,[c] Robert J. Currier, PhD,[a] Stanley J. Naides, MD,[d] Joseph A. Church, MD,[e,f] and Jennifer M. Puck, MD[a,g,h,i] *San Francisco, Richmond, San Juan Capistrano, and Los Angeles, Calif, and Bronx, NY*

- Effective gestational age of 22 to 52 weeks and birth weight were assessed.
- 338 infants studied by EGA and 301 by BW
- Reference intervals in preterm and term neonates
  - T cell counts
    - naive and memory markers
  - B Cell counts
  - NK cell counts

JACI 2019

Severe combined immunodeficiency/T cell Deficiency

- Absent or very low T cells (<50 cells/µl)
- Poor antibody production (secondary to lack of T cells and/or B cells)
- Previously presented with severe infections
  - Pneumocystis
  - Respiratory viruses
  - Candida
- Today- identified by newborn screening
- Treatment is bone marrow transplant/gene therapy
- Many genetic causes

Dvorak et al JACI 2023

T cell functional defects

- This is the most complex category
- Infections
- Autoimmunity
- Usually have low T cells (but not always)
- Function is compromised but lab tests are limited for this finding
- Genetic testing is the best approach


Opportunistic infections
Early onset
Autoimmunity

Antibody deficiencies

Lack of antibody

Poor function

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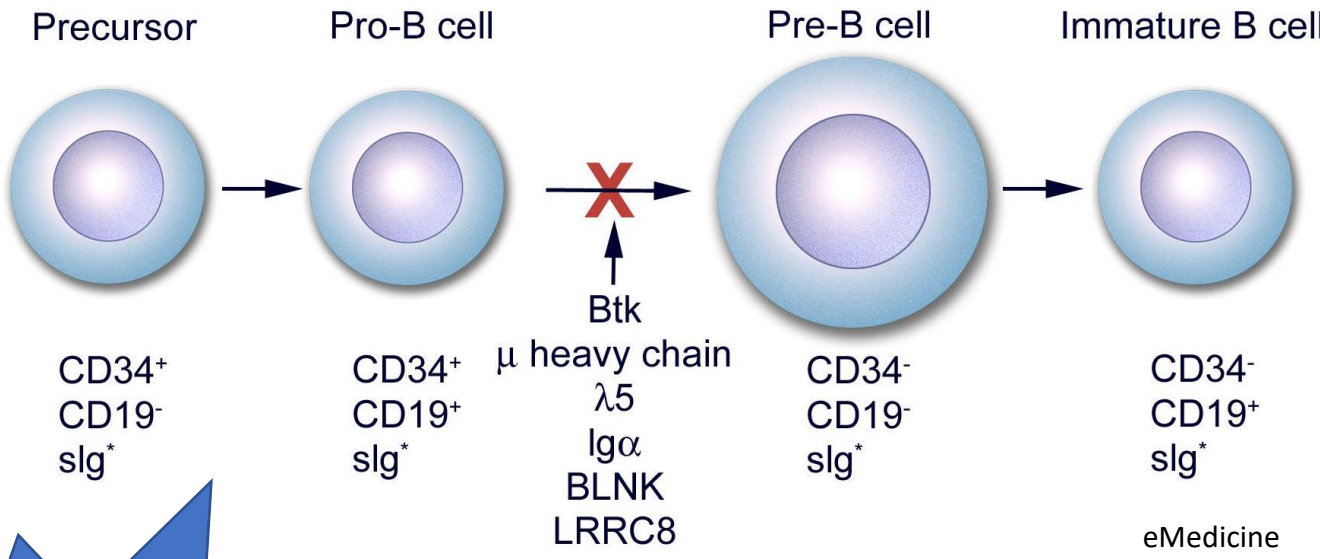
Antibody deficiencies

- Common types of infections
- Too many of them
- Both monogenic and polygenic

- Autoimmunity variable

X-linked agammaglobulinemia

- Block in B cell development
- No B cells
- BTK mutations
- No antibody
- Infections begin after maternal antibody wanes
  - Sinusitis
  - Bronchitis
  - Pneumonia



Typical infections

Common variable immunodeficiency

- Polygenic disorder
- Arises at any age
- Gradual loss of antibody production
- Recurrent infections
  - Sinusitis
  - Pneumonia
  - Bronchitis
  - Bronchiectasis
- Variable autoimmunity: autoimmune cytopenias, arthritis, granulomas, inflammatory bowel disease

Specific Antibody Deficiency

	SAD	
	ESID Criteria [3]	US Practice Parameters [6]
Clinical presentation	Recurrent or severe bacterial infections	Recurrent respiratory tract infections
Antibody levels	Normal IgG, IgA, and IgM and IgG subclasses	
Response to vaccines	Profound alteration of the antibody responses to polysaccharide vaccine	Impaired response to pneumococcal capsular polysaccharide
B cells	Not considered	Normal B-cell levels
T cells	Exclusion of T-cell defect	Not considered
Other diagnostic criteria	None	Patients older than 2 y

Perez and Ballow Immunology and Allergy Clinics of North America, 2020

Specific Antibody Deficiency

Phenotype [a]	Age >6 y	Age <6 y	Notes
Severe	<2 protective titers	<2 protective titers	Protective titers present are low
Moderate	<70% of serotypes protective	<50% of serotypes protective	Protective titers to >3 serotypes
Mild	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 70% of serotypes	Failure to generate protective titers to multiple serotypes or failure of a 2-fold increase in 50% of serotypes	2-fold increases assume a prevaccination titer of <4.4–10.3 μg/mL, depending on the pneumococcal serotype
Memory	Loss of response within 6 mo	Loss of response within 6 mo	Adequate initial response to >50% of serotypes in children <6 y of age and >70% in those >6 y of age

Perez and Ballow Immunology and Allergy Clinics of North America, 2020

Specific antibody testing

- Immunoglobulin levels and antibody responses pre and post PPSV23 to assess humoral responses
- What are we going to do about PCV 20?
  - >65 years old
  - >19 with diabetes, asthma, COPD, chronic heart disease, or chronic kidney failure, non functional spleen, HIV

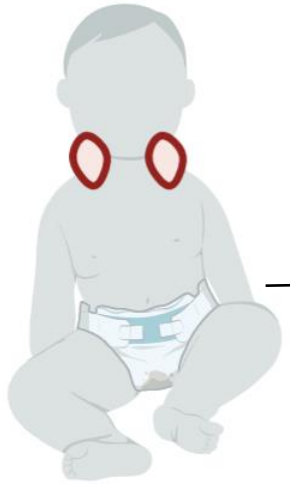
PCV20	PPSV23
1	1
	2
3	3
4	4
5	5
6A	
6B	6B
7F	7F
8	8
	9N
9V	9V
10A	10A
11A	11A
12F	12F
14	14

PCV20	PPSV23
15B	15B
	17F
18C	18C
19A	19A
19F	19F
	20
22F	22F
23F	23F
33F	33F

Neoantigen:
Salmonella Typhi Vaccine

Manufacturer prescribing information

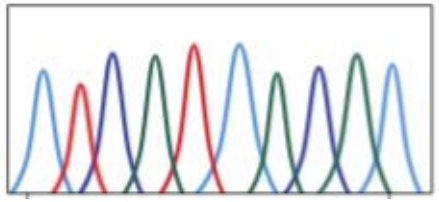
Evaluation of a patient with Primary Immunodeficiency or Primary Immune Regulation Disorder



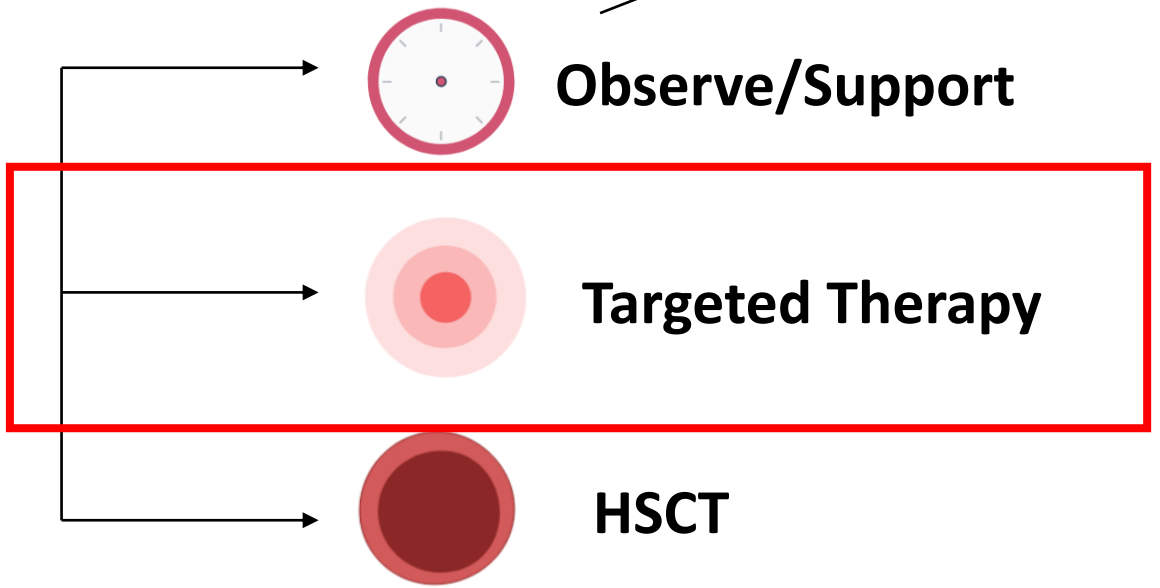
Recurrent infections
Autoimmune symptoms

Specific testing:
1. Infection work-up
2. Immune levels and function
3. Imaging
4. Tissue biopsy if necessary

GENETIC EVALUATIONS



Informed therapy



biorender

Suspected Immune Disorder

Recurrent Typical Infections:

- CBC and diff: Check the ALC and ANC
- IgG, IgA, IgM, IgE
- Diphtheria, tetanus, pneumococcal titers
- Lymphocyte phenotyping
- DHR
- Infectious studies/Imaging

Opportunistic/severe viral infections:

- Lymphocyte phenotyping
  - T, B and NK cell subsets
- Lymphocyte function studies
- Humoral immunity testing
- DHR
- HIV testing
- Infectious studies/Imaging

Autoimmunity/Autoinflammation

- Antibody testing
- Protein expression levels
- Cytokine testing/inflammatory markers
- Refer to specialist for specific organ system involved

Genetic Testing

Diagnosis/Targeted therapy

Adapted from:
Heimall et al JACI in practice 2019
Agarwal Ann All Asthma 2019
Stray-Peterson et al JACI 2017

Autoimmune/Autoinflammatory/Lymphoproliferative features with recurrent infections

- Engage your colleagues in other specialties – this is a team sport!

- Systemic Lupus features – ANA panel, complement testing
- Interstitial Lung Disease – pulmonary referral, lymphocyte subsets, antibody testing, genetic testing
- Inflammatory Bowel Disease – DHR, antibody testing, Treg testing, lymphocyte subsets
- Lymphoproliferation – lymph node biopsy, Transitional B cells, immunoglobulins, EBV
- Endocrinopathy – Type 1 DM panel, thyroid, adrenal testing
- JIA/other arthritis – serology, joint exam, systemic features?
- Psoriasis, severe eczema, neutrophilic dermatosis – biopsy

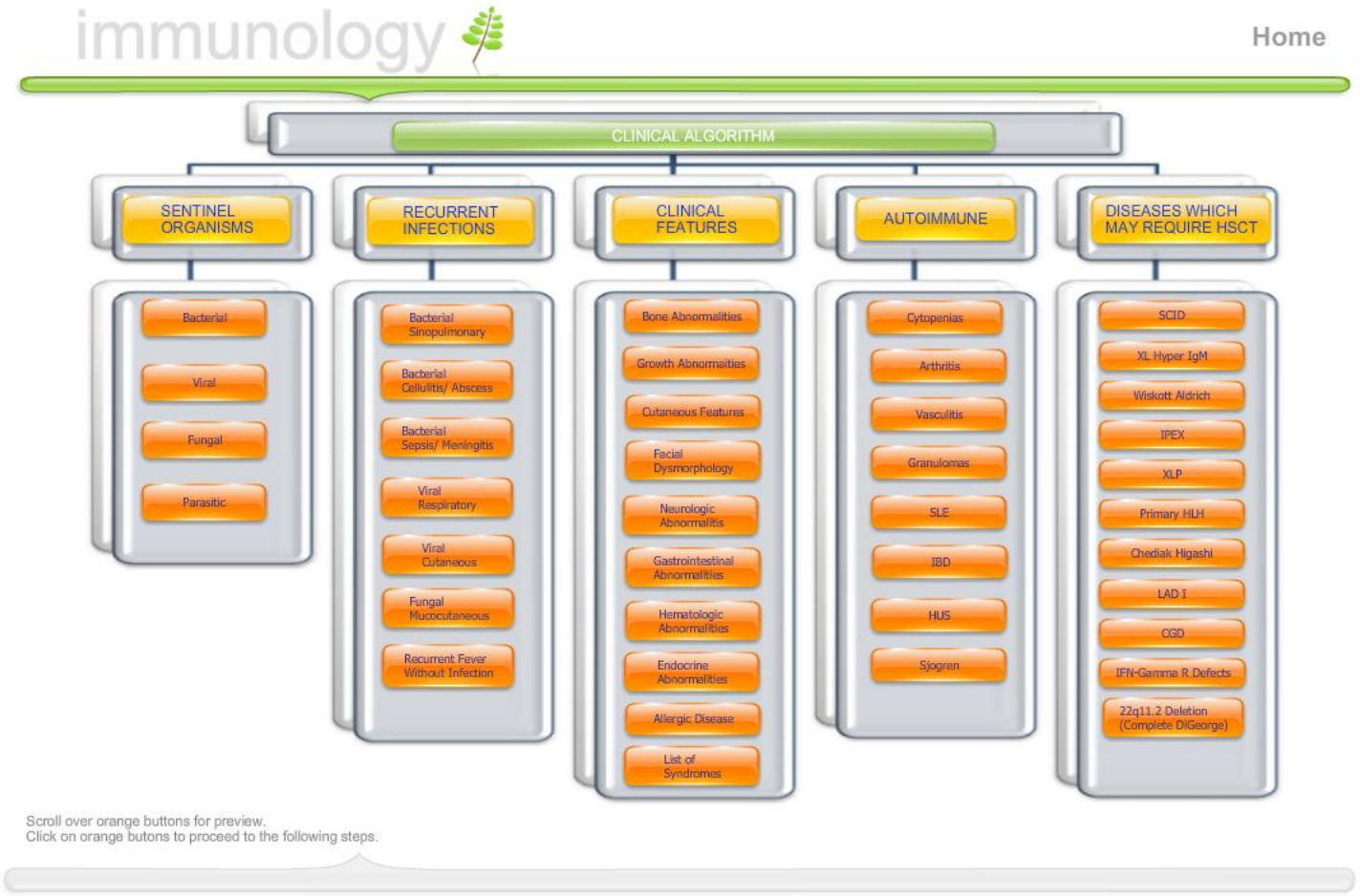
The Immunologist Thought Process – for Conner

- Bug
  - ~~Opportunistic infections~~
  - Recurrent common infections often refractory to treatment
- Frequency of infections ~~and or non-infectious disease flares~~
- Severity - moderate
- Laboratory pattern - meets criteria for Common Variable Immunodeficiency with autoimmunity

- Body Part – sinopulmonary infections
  - Autoimmunity - IBD
  - ~~Autoinflammation~~
  - Progression of disease – as he gets older
- Age – started in childhood
- Genetic Testing – yes send!
- Sex – male
- Family History – unremarkable
- Medications – frequent antibiotics

Online algorithm for diagnosis

- http://www.immunodeficiencysearch.com/



Soma Jyonouchi- CHOP

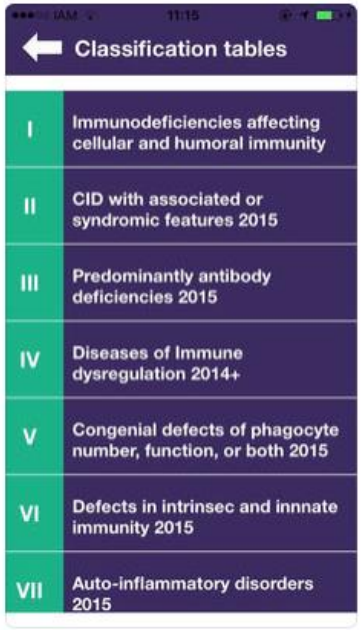
Cell phone app

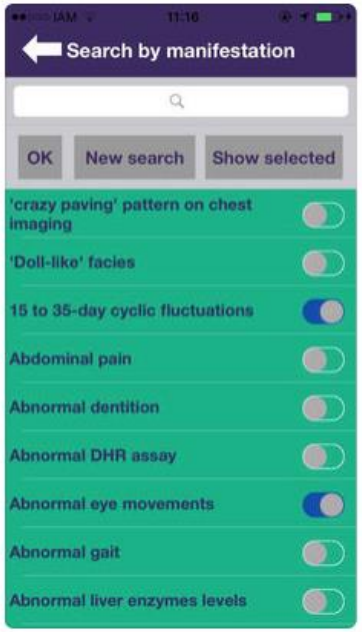
PID Phenotypical Diagnosis 17+

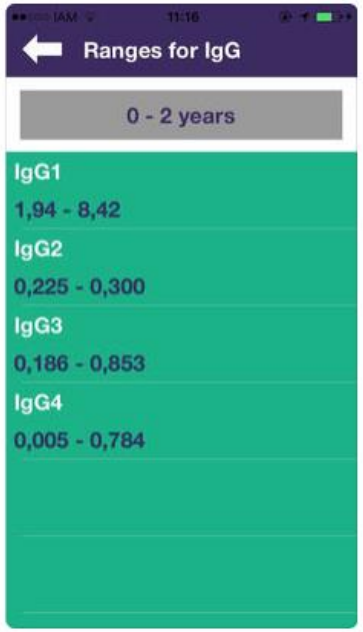
Amine Ahmmouch

Free

iPhone Screenshots







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