Immune Deficiency Foundation

Lunch & Learn: CGD

May 25th, 2022

IDF MISSION

Improving the diagnosis, treatment, and quality of life of people affected by primary immunodeficiency through fostering a community empowered by advocacy, education and research.

Immune Deficiency Foundation

Thank you to our Partners!

CGD ASSOCIATION OF AMERICA

HORIZON

HOUSEKEEPING

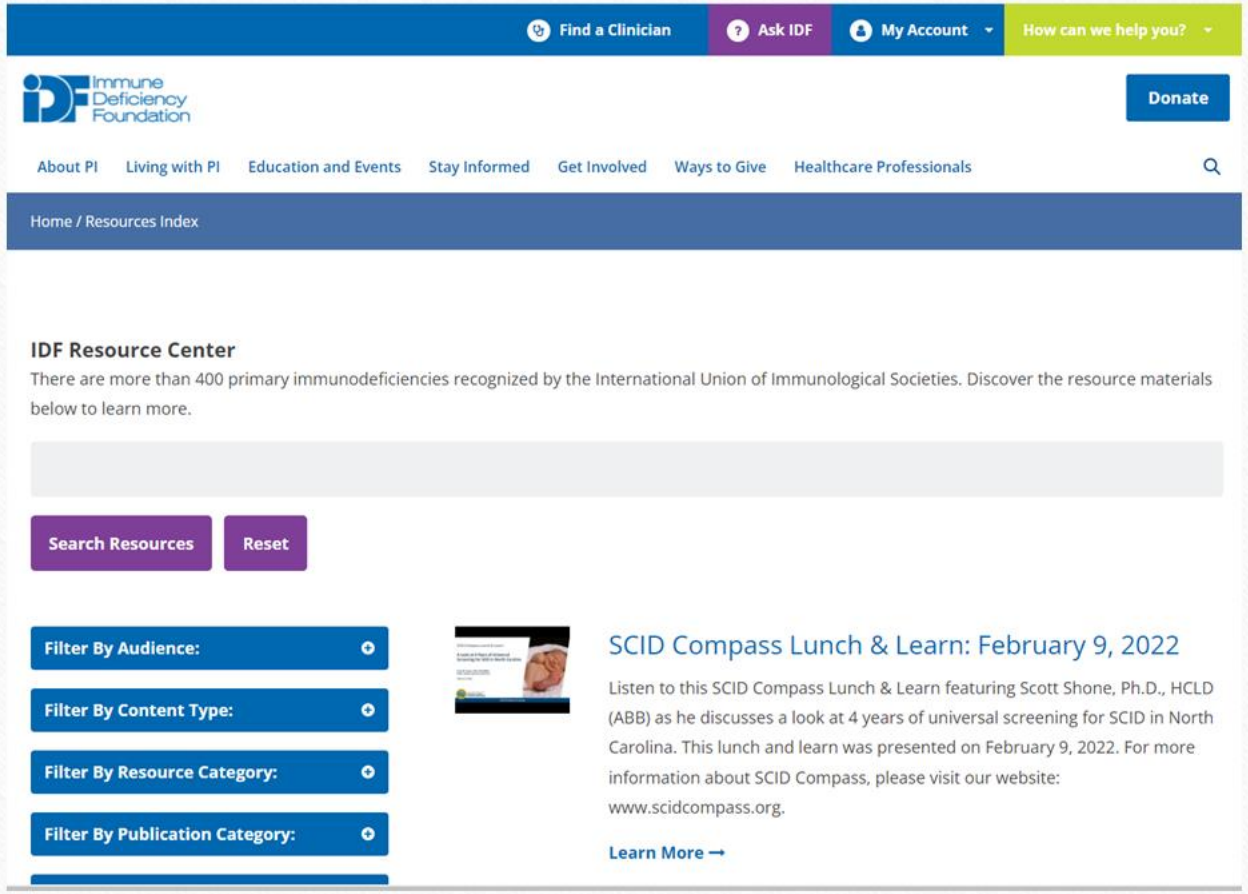
- Attendees will not have access to their microphone or webcam throughout the event.
- To see the full slides, you can adjust the settings on the speaker view panel on the top of the Zoom screen and select "side-by-side" in the dropdown option.
- Please submit all questions for the presenter via the Q&A box

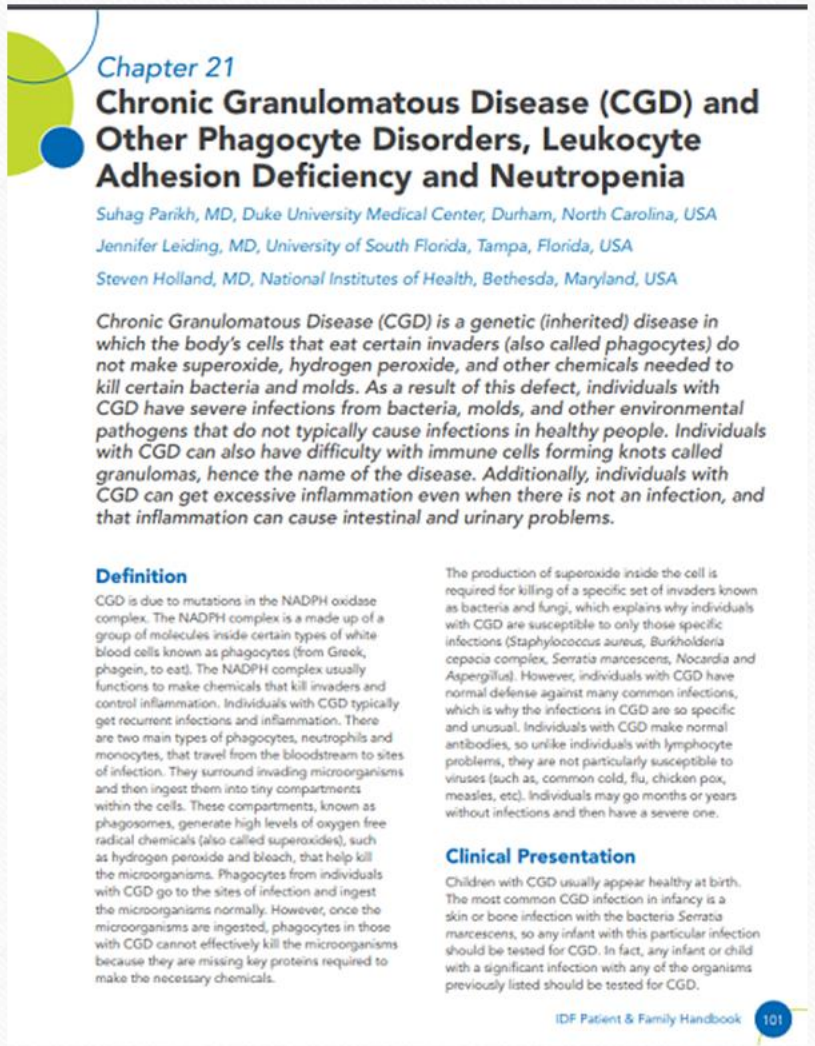
DISCLAIMER

Immune Deficiency (IDF) education events offer a wide array of educational presentations, including presentations developed by healthcare and life management professionals invited to serve as presenters. The views and opinions expressed by guest speakers do not necessarily reflect the views and opinions of IDF.

The information presented during this event is not medical advice, nor is it intended to be a substitute for medical advice, diagnosis or treatment. Always seek the advice of a physician or other qualified health provider with questions concerning a medical condition. Never disregard professional medical advice, or delay seeking it based on information presented during the event.

IDF Website: www.primaryimmune.org





Chapter 21

Chronic Granulomatous Disease (CGD) and Other Phagocyte Disorders, Leukocyte Adhesion Deficiency and Neutropenia

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Jennifer Leiding, MD, University of South Florida, Tampa, Florida, USA

Steven Holland, MD, National Institutes of Health, Bethesda, Maryland, USA

Chronic Granulomatous Disease (CGD) is a genetic (inherited) disease in which the body's cells that eat certain invaders (also called phagocytes) do not make superoxide, hydrogen peroxide, and other chemicals needed to kill certain bacteria and molds. As a result of this defect, individuals with CGD have severe infections from bacteria, molds, and other environmental pathogens that do not typically cause infections in healthy people. Individuals with CGD can also have difficulty with immune cells forming knots called granulomas, hence the name of the disease. Additionally, individuals with CGD can get excessive inflammation even when there is not an infection, and that inflammation can cause intestinal and urinary problems.

Definition

CGD is due to mutations in the NADPH oxidase complex. The NADPH complex is a made up of a group of molecules inside certain types of white blood cells known as phagocytes (from Greek, phagein, to eat). The NADPH complex usually functions to make chemicals that kill invaders and control inflammation. Individuals with CGD typically get recurrent infections and inflammation. There are two main types of phagocytes, neutrophils and monocytes, that travel from the bloodstream to sites of infection. They surround invading microorganisms and then ingest them into tiny compartments within the cells. These compartments, known as phagosomes, generate high levels of oxygen free radical chemicals (also called superoxides), such as hydrogen peroxide and bleach, that help kill the microorganisms. Phagocytes from individuals with CGD go to the sites of infection and ingest the microorganisms normally. However, once the microorganisms are ingested, phagocytes in those with CGD cannot effectively kill the microorganisms because they are missing key proteins required to make the necessary chemicals.

The production of superoxide inside the cell is required for killing of a specific set of invaders known as bacteria and fungi, which explains why individuals with CGD are susceptible to only those specific infections (*Staphylococcus aureus, Burkholderia cepacia* complex, *Serratia marcescens, Nocardia* and *Aspergillus*). However, individuals with CGD have normal defense against many common infections, which is why the infections in CGD are so specific and unusual. Individuals with CGD make normal antibodies, so unlike individuals with lymphocyte problems, they are not particularly susceptible to viruses (such as, common cold, flu, chicken pox, measles, etc). Individuals may go months or years without infections and then have a severe one.

Clinical Presentation

Children with CGD usually appear healthy at birth. The most common CGD infection in infancy is a skin or bone infection with the bacteria *Serratia marcescens*, so any infant with this particular infection should be tested for CGD. In fact, any infant or child with a significant infection with any of the organisms previously listed should be tested for CGD.

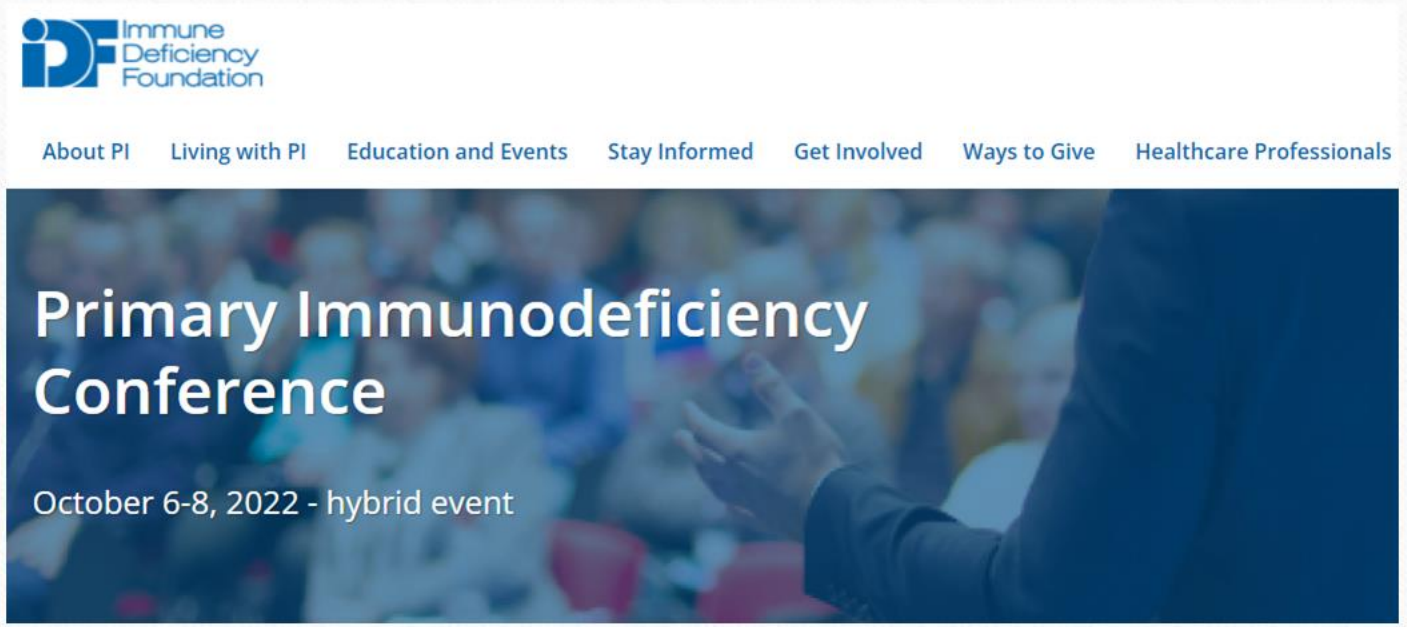
Living with CGD
Chronic Granulomatous Disease

- https://primaryimmune.org/living-with-cgd

PROGRAM OFFERINGS

- Monthly Lunch & Learns- medical experts present on various diagnosis-specific topics
- Get Connected Groups: share experiences, receive information, and gain support
- IDF Forums
- Ask IDF
- Annual PI Conference

To view a list of all upcoming IDF events, visit: https://community.primaryimmune.org/s/events?language=en_US



2022 Primary Immunodeficiency Conference
October 6-8, 2022

For questions regarding the PI Conference, email us at conference@primaryimmune.org

FELICIA MORTON,
CGD ASSOCIATION OF AMERICA

Self-Reported Symptom Burden of Female X-linked Chronic Granulomatous Disease Carriers

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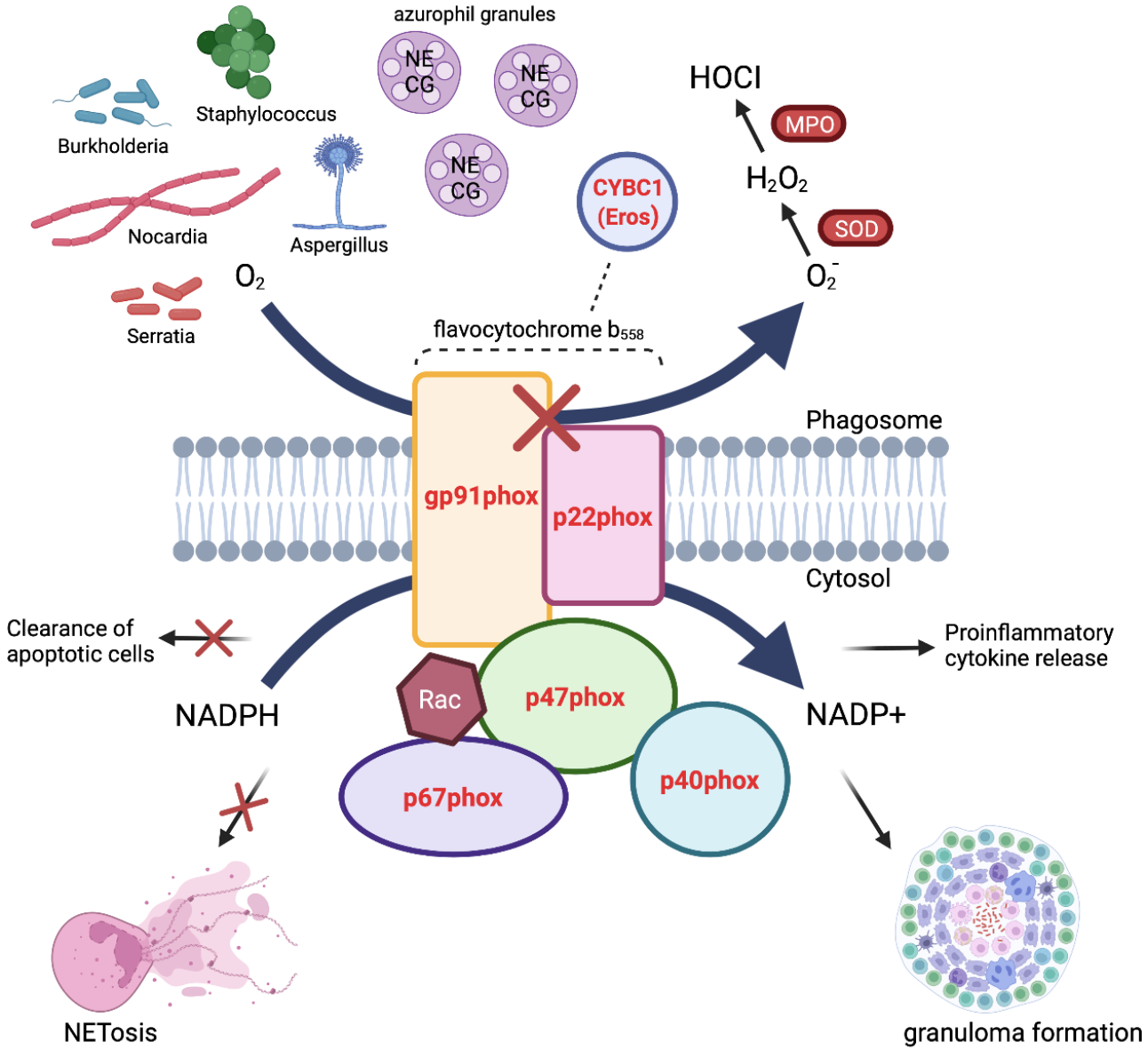
Disclosures

- Employee and shareholder of bluebird bio.
- Speaker and Consultant for: Sobi, Horizon Therapeutics, Pharming.

Chronic Granulomatous Disease



- Due to defects in any of the components of the NADPH oxidase complex or *CYBC1*/Eros → impaired production of reactive oxygen species
- Recurrent &/or severe infections with a subset of oxidase-positive bacteria and fungi
- Granuloma formation
- High rates of inflammatory and autoimmune disease, especially of the gut (CGD colitis), lungs and liver

Primary Immune Deficiency Treatment Consortium

Diagnosis of CGD

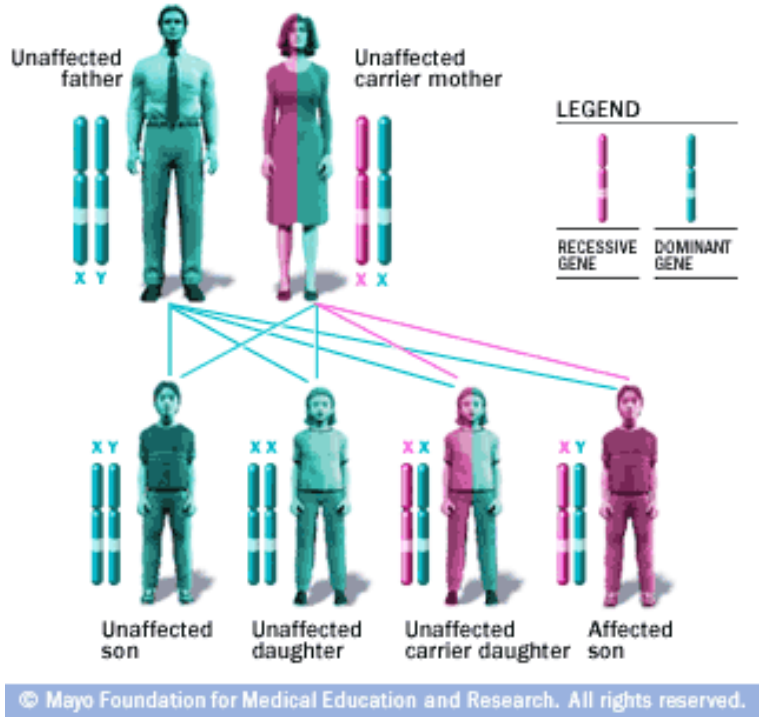
- Frequency 1/100,000 – 1/200,000
- Presentation usually in childhood but more adult cases now recognized

Types of CGD

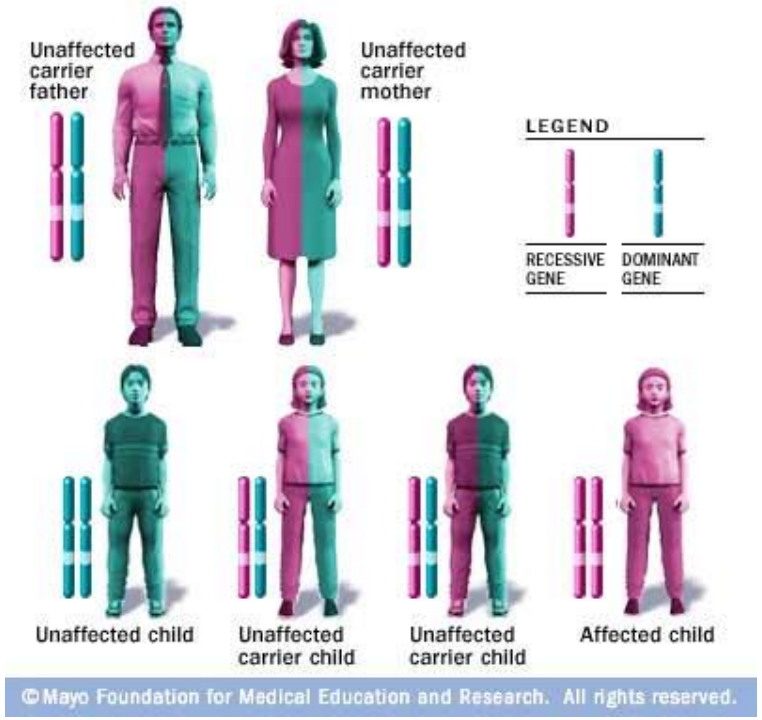
XL – *CYBB*, gp91^{phox}	66%
Female carriers	
AR – *NCF1*, p47^{phox}	20%
NCF2, p67^{phox}	7%
CYBA, p22^{phox}	7%
NCF4, p40^{phox}	<1%
CYBC1, EROS	Few Persons

Inheritance Patterns

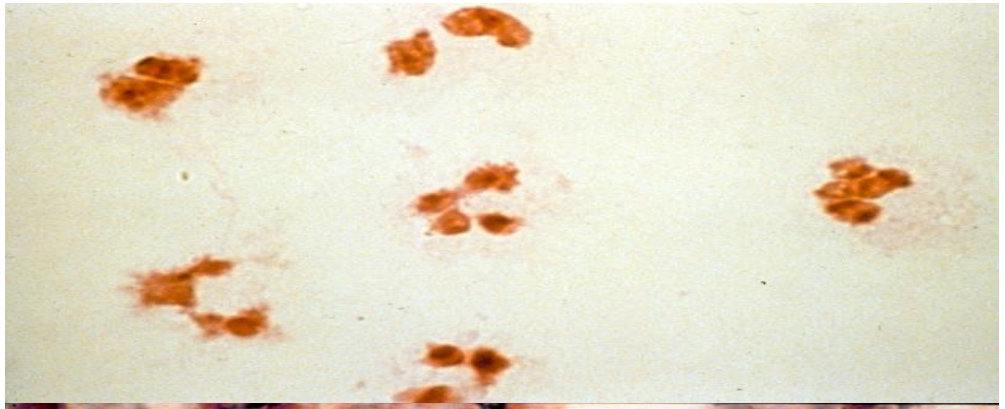
X – linked inheritance



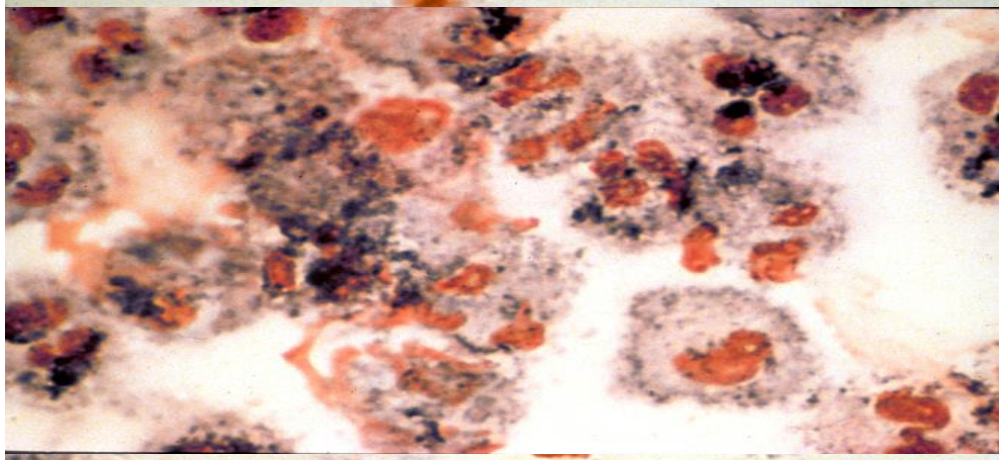
Autosomal recessive inheritance



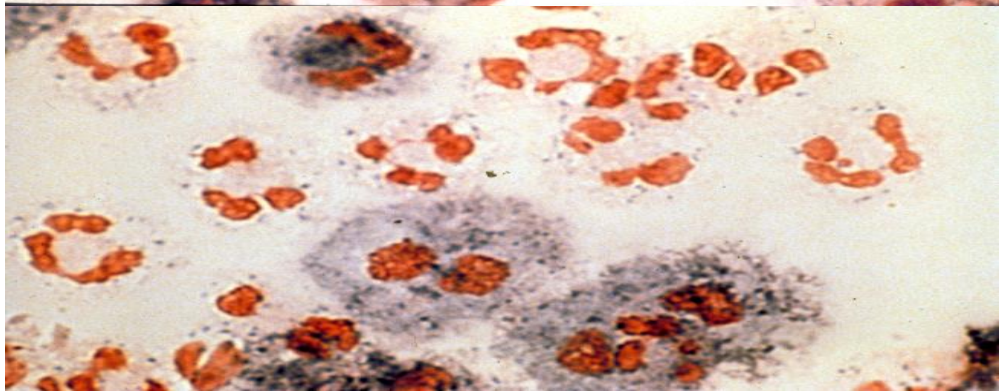
The Nitroblue Tetraszolium Test (NBT)



CGD PATIENT

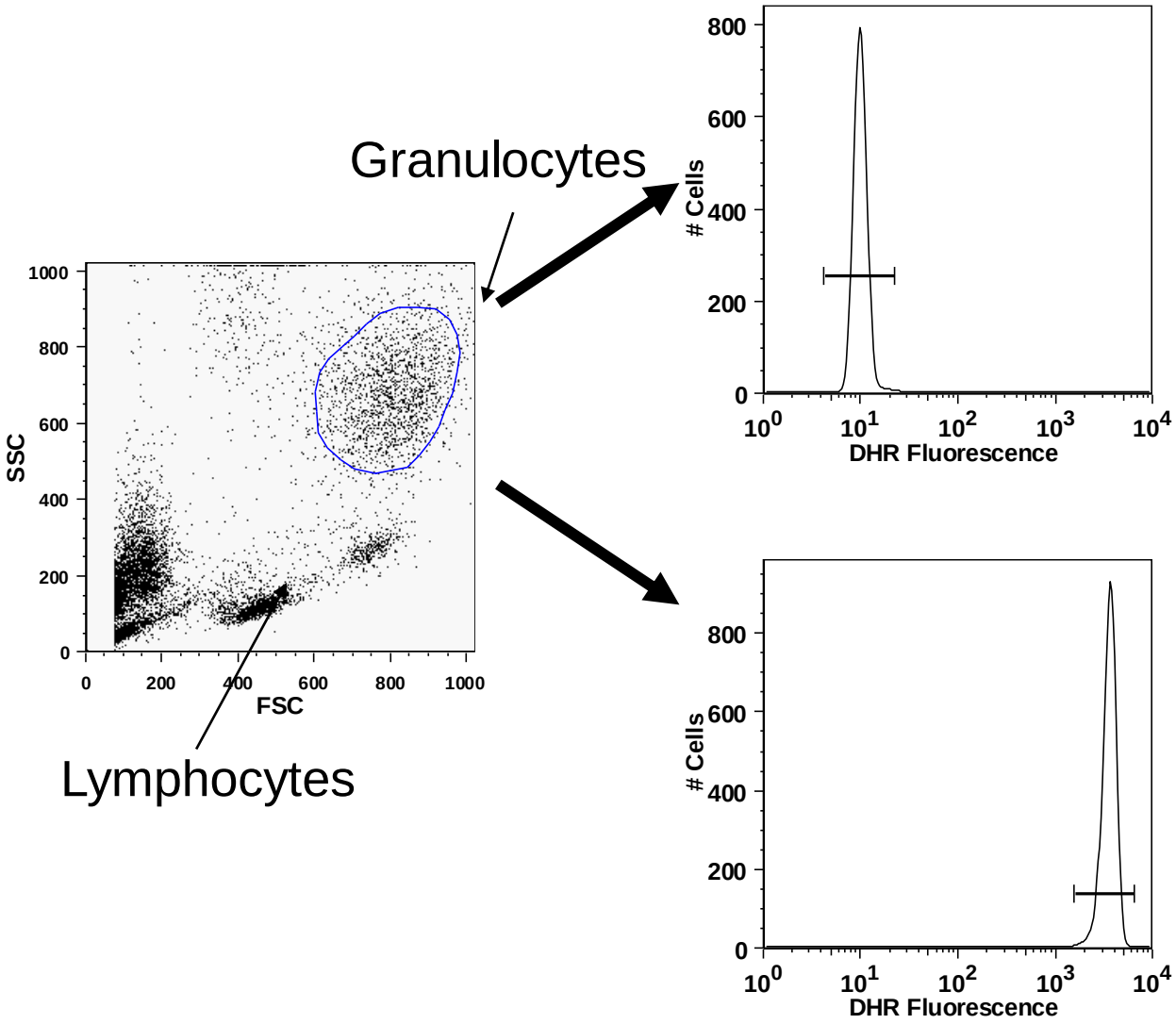


NORMAL



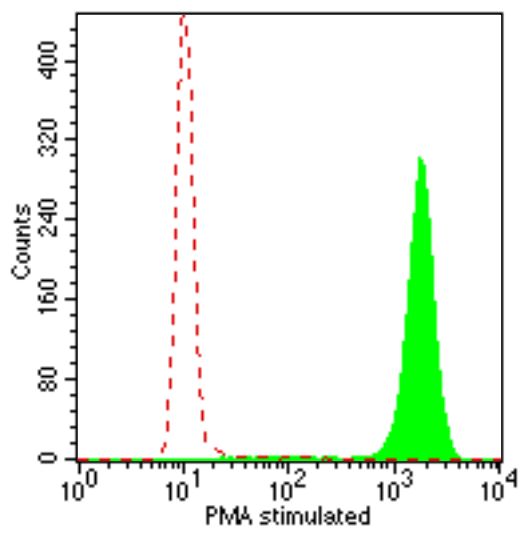
X-CGD CARRIER
(Lyonization)

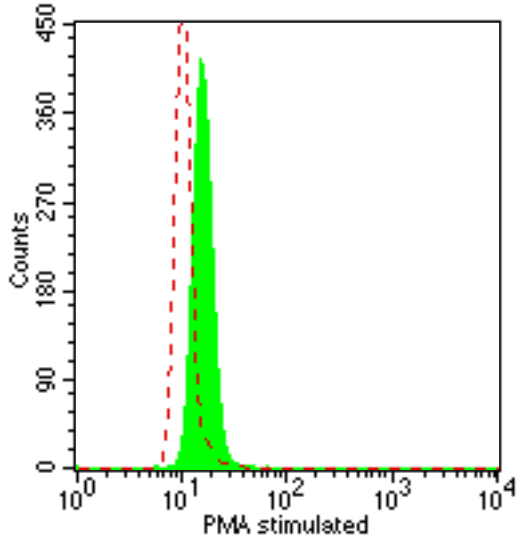
Flow Cytometry Analysis of Granulocyte Respiratory Burst Using Dihydrorhodamine



DHR Assay to Diagnose CGD

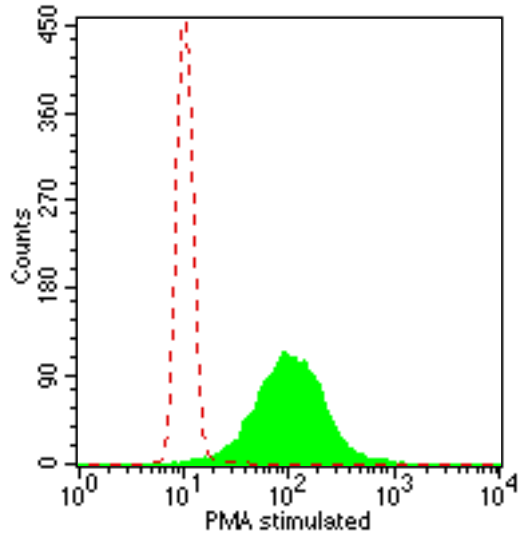
Normal

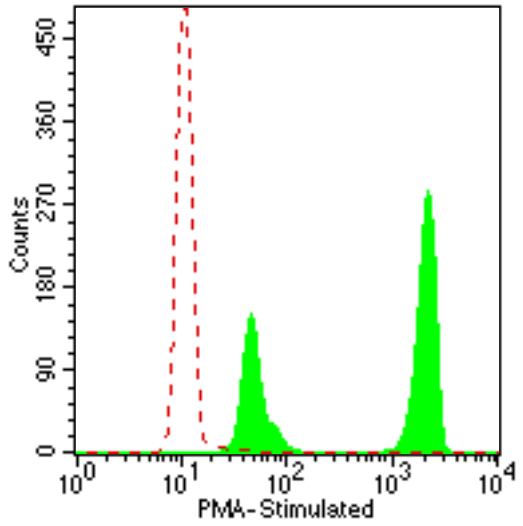




Phox^{91} deficient CGD (X-linked)

AR deficient CGD





X-linked CGD carrier

CGD Infections

Primarily:

Bacteria

Fungus

No major problems with viruses

Staphylococcal aureus
liver, lymph nodes, skin, bone

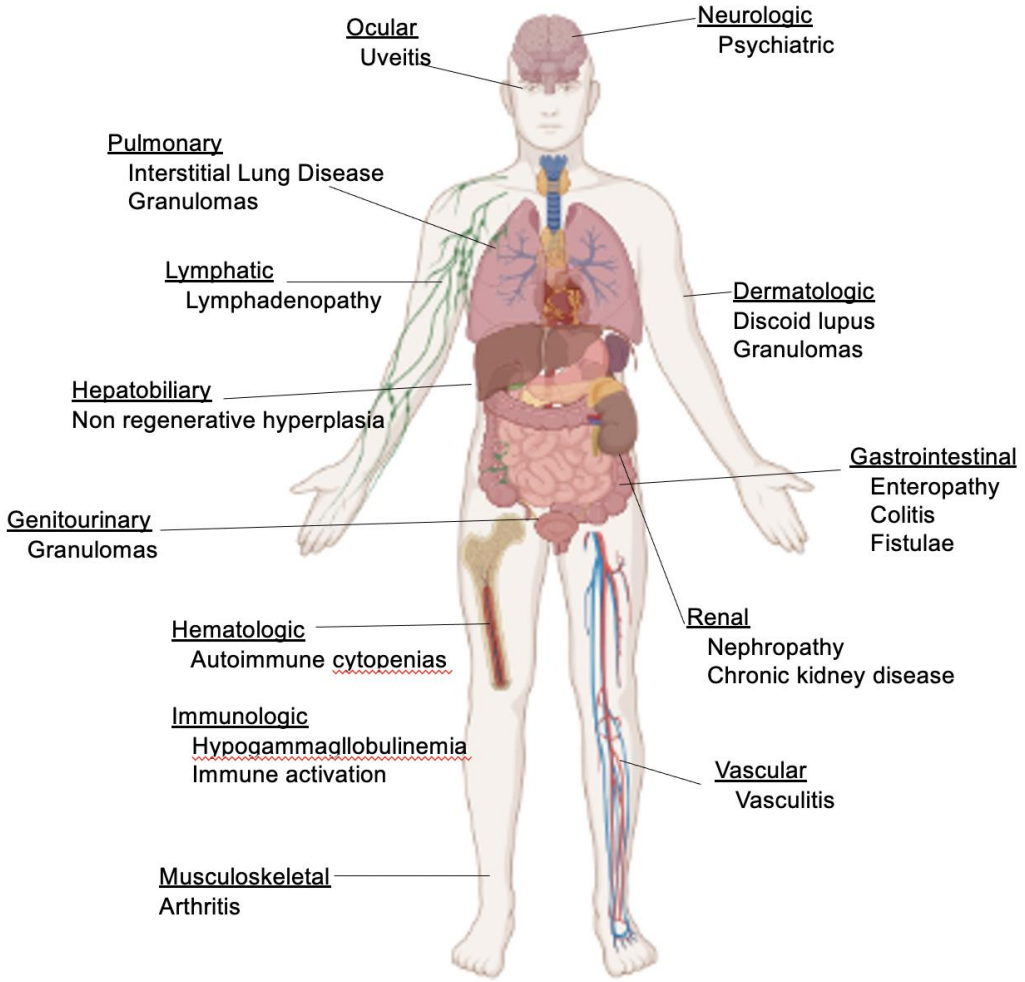
Serratia marsescens
bone, skin, lung, lymph

Burkholderia
lung, blood

Nocardia
lung, brain, liver

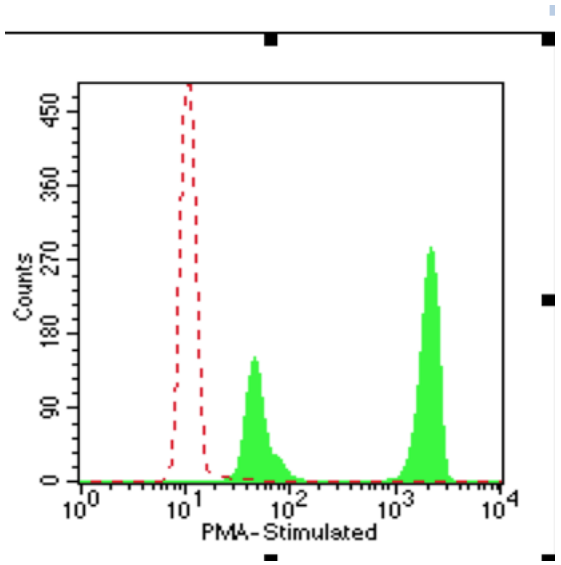
Aspergillus
lung

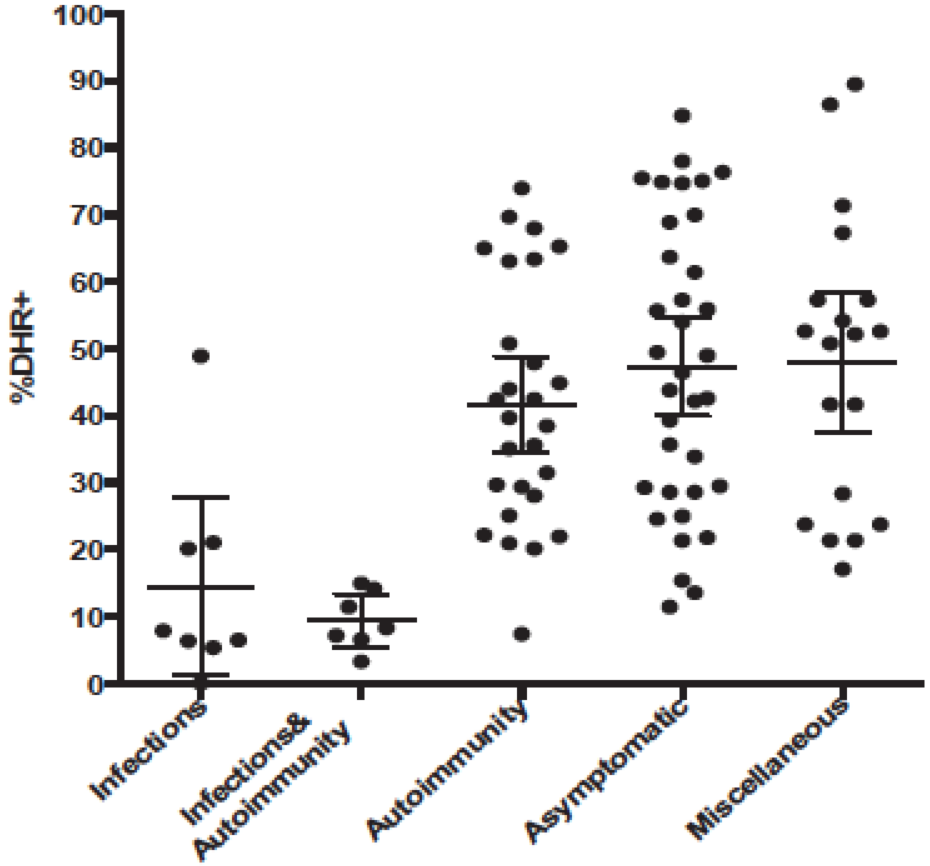
CGD Inflammatory Disease



Carriers of X-linked CGD

- Discoid lupus
- Mouth ulcers
- Joint pain





Marciano et al. *JACI*. 2018.

Carriers of X-linked CGD

- Susceptible to CGD-related infections
- Immune dysregulation and autoimmunity
  - Systemic lupus, discoid lupus
  - Aphthous stomatitis
  - Colitis
  - Arthritis
- Immune Abnormalities
  - Hypogammaglobulinemia
  - Increased CD19+ B cells, CD56bright-NK cell percentage, and reduced INFγ-production by CD4+ and CD8+ T cells.
- Lower quality of life scores
  - Increased rates of anxiety, higher rates of depression, lower self esteem.

Marciano et al. *JACI*. 2018.
Chiriaco et al. *Antioxidants.* 2021
Battersby et al. *JOCI*. 2019.

PAG-PIDTC Interaction

Self-Reported Symptom Burden of Female X-linked Chronic Granulomatous Disease Carriers – a PIDTC Report

IRB approved 57 question survey administered through the CGD Association of America was completed by female XL-CGD carriers.

Data gathered included demographics, method of diagnosis, medical history, utilization of medical care and treatments.

171 Responders

Figure 1A: Relation of XL-CGD Female Carriers to Patients with CGD (n=151)

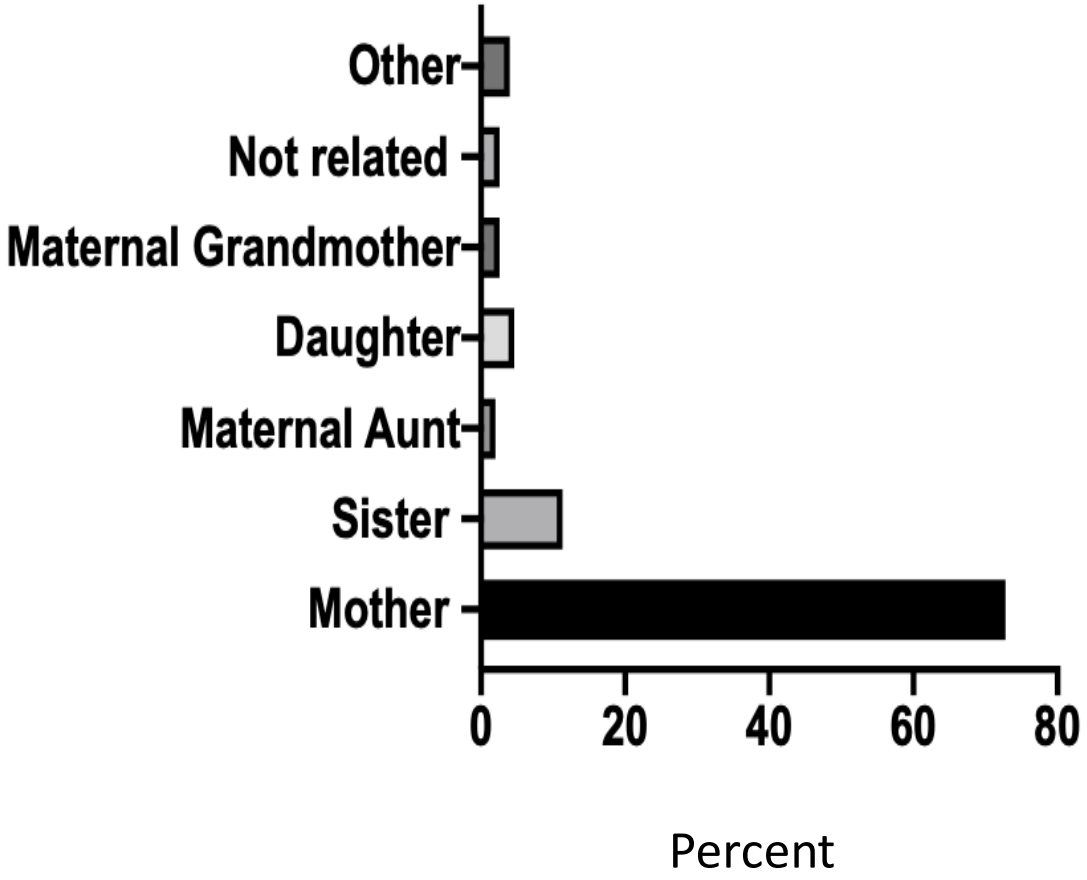


Figure 1B: Mode of Diagnosis of XL-CGD Female Carriers (n=153)

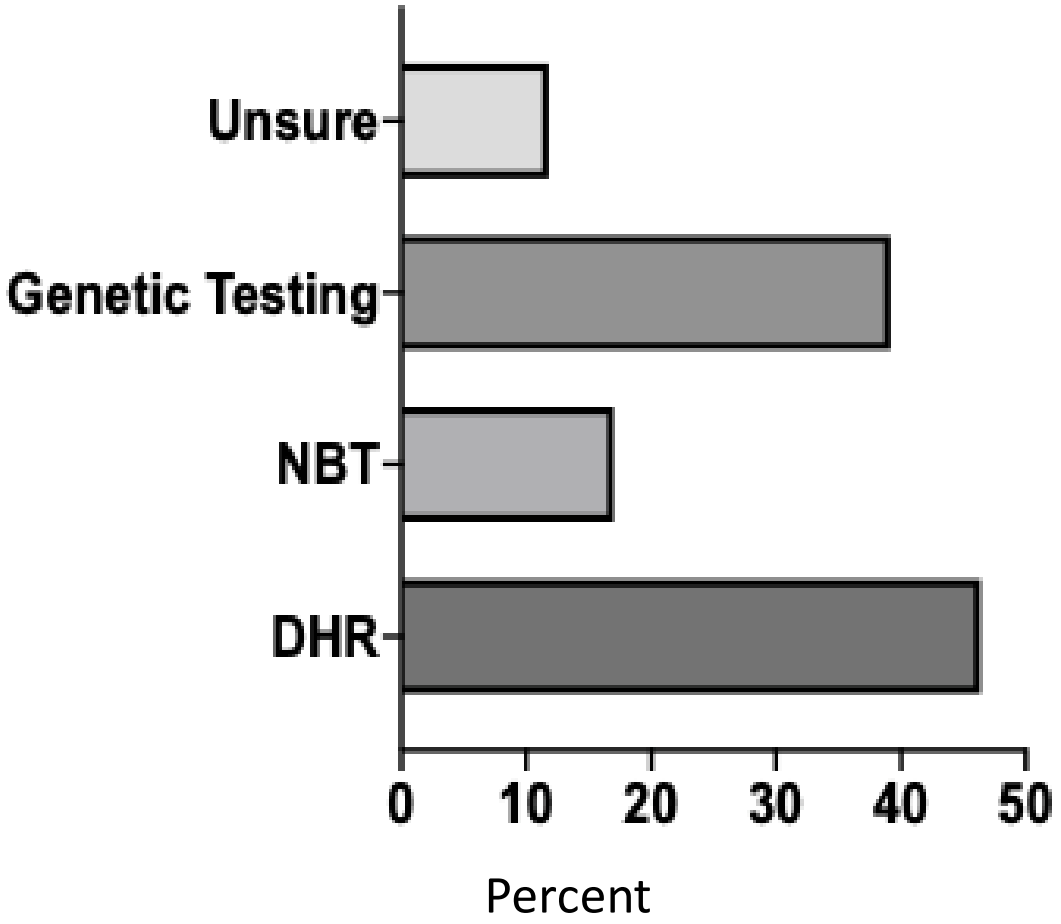


Figure 2A: Education Level of XL-CGD Female Carriers (n=150)

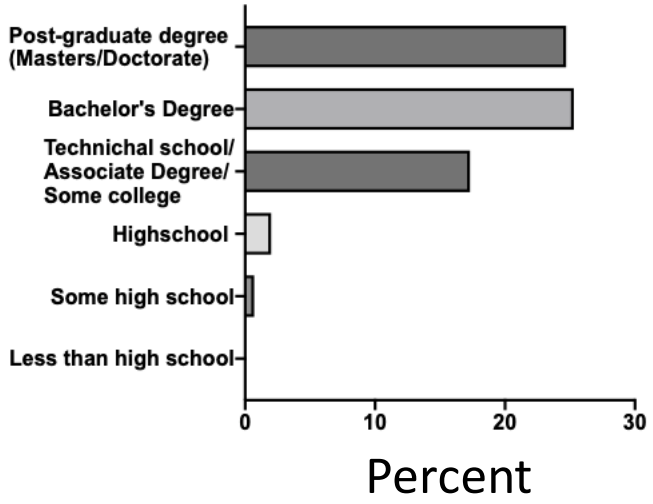


Figure 2B: Employment Status of XL-CGD Female Carriers (n=150)

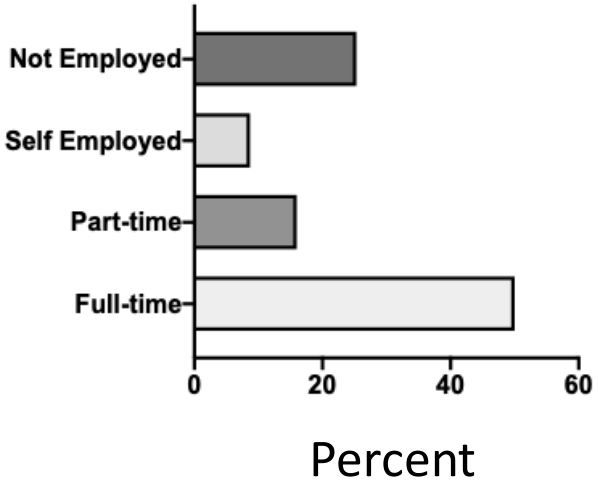


Figure 2C: Overall Health as Assessed by XL-CGD Female Carriers (n=148)

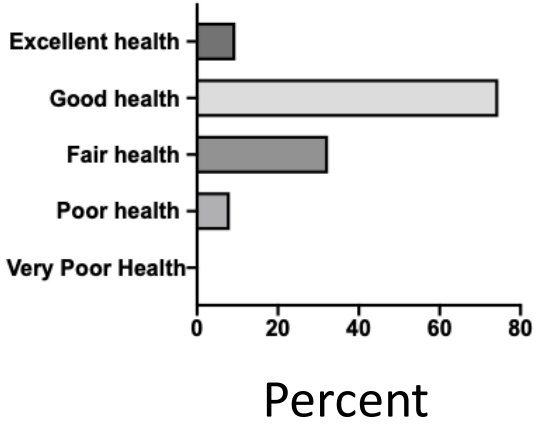


Figure 2D: Reasons for Impairment in Daily Activities in XL-CGD Female Carriers (n=34)

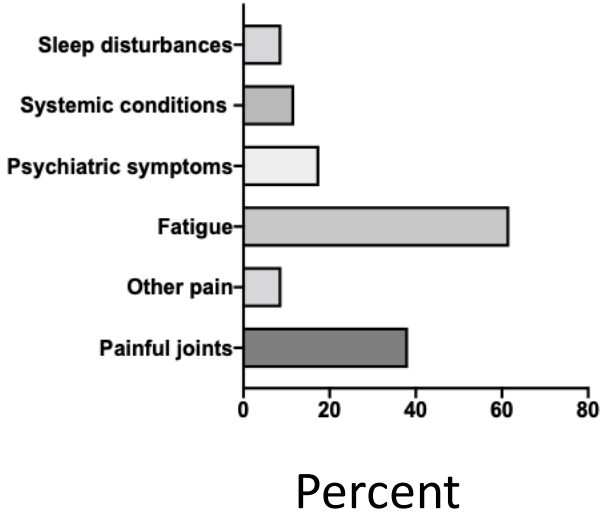
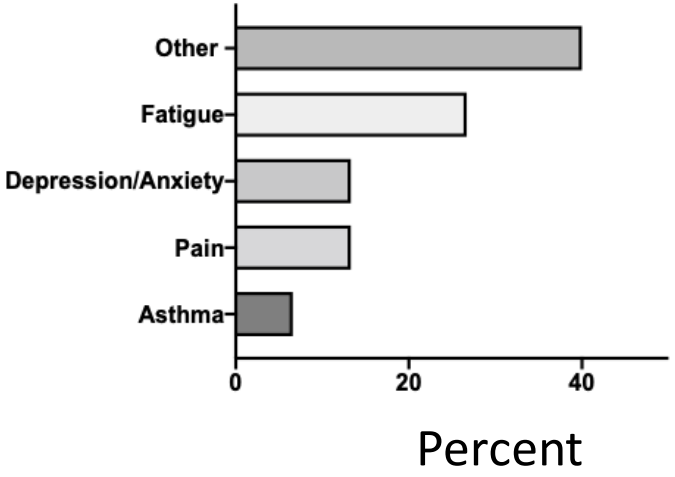
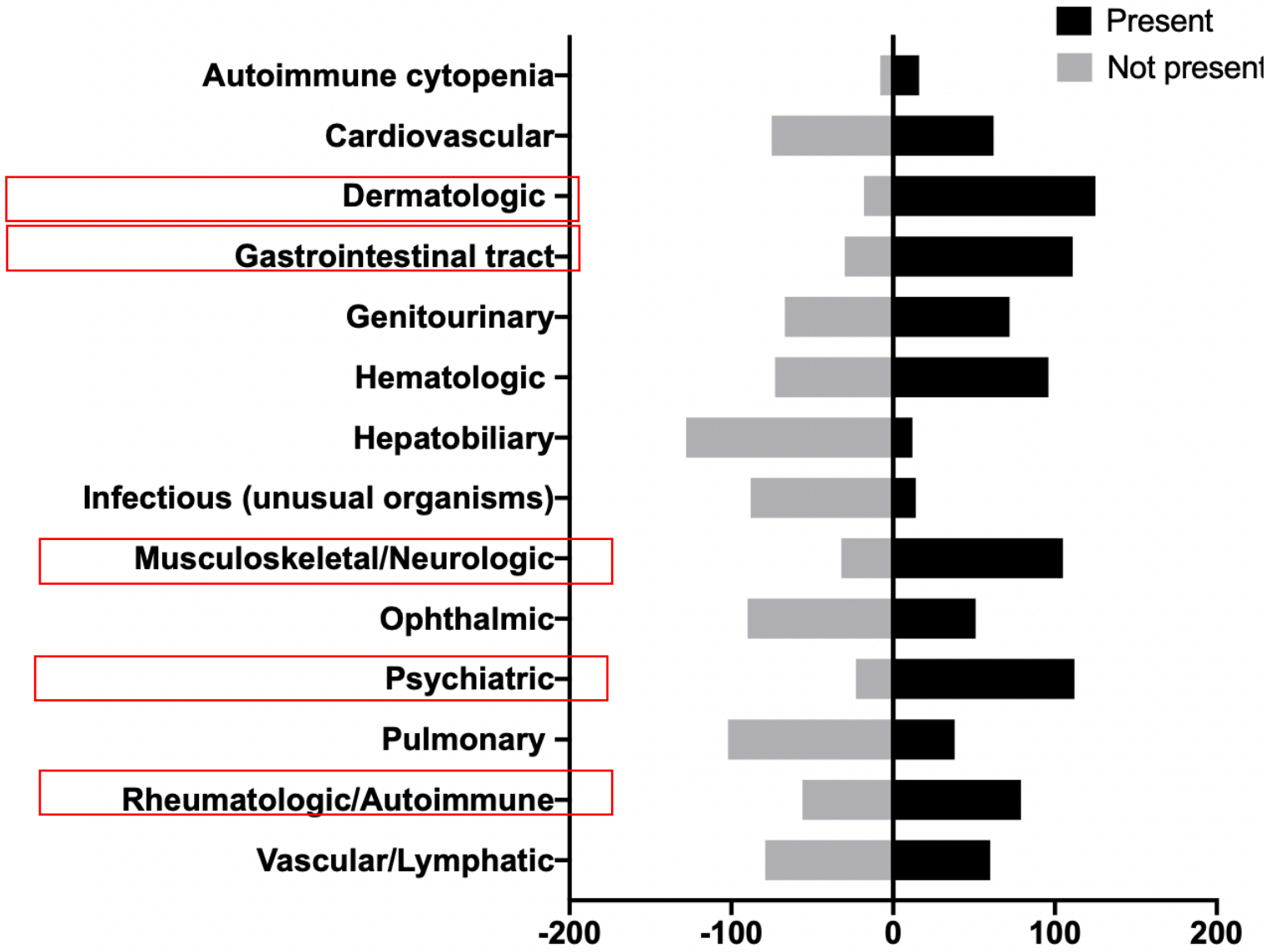


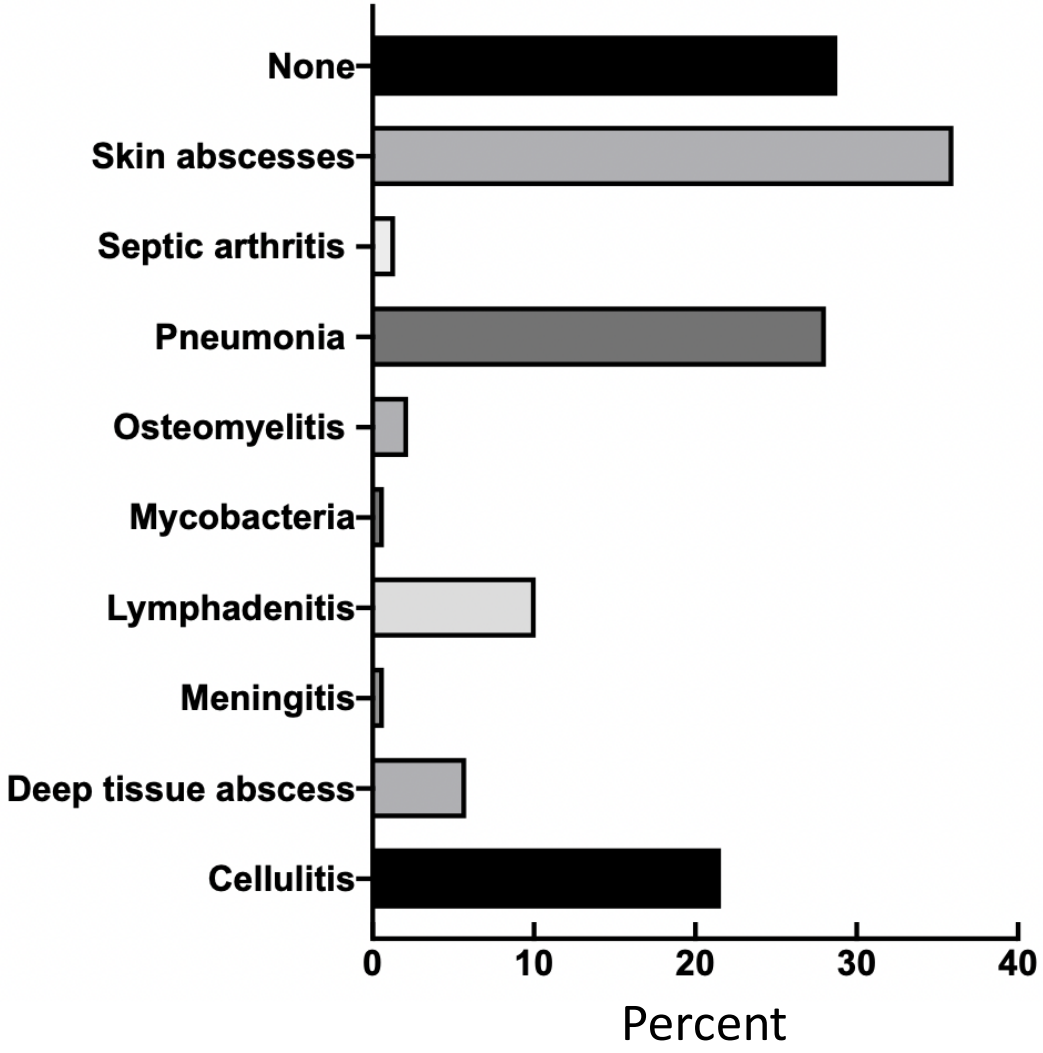
Figure 2E: Reasons for Restriction in Work Hours of XL-CGD Female Carriers



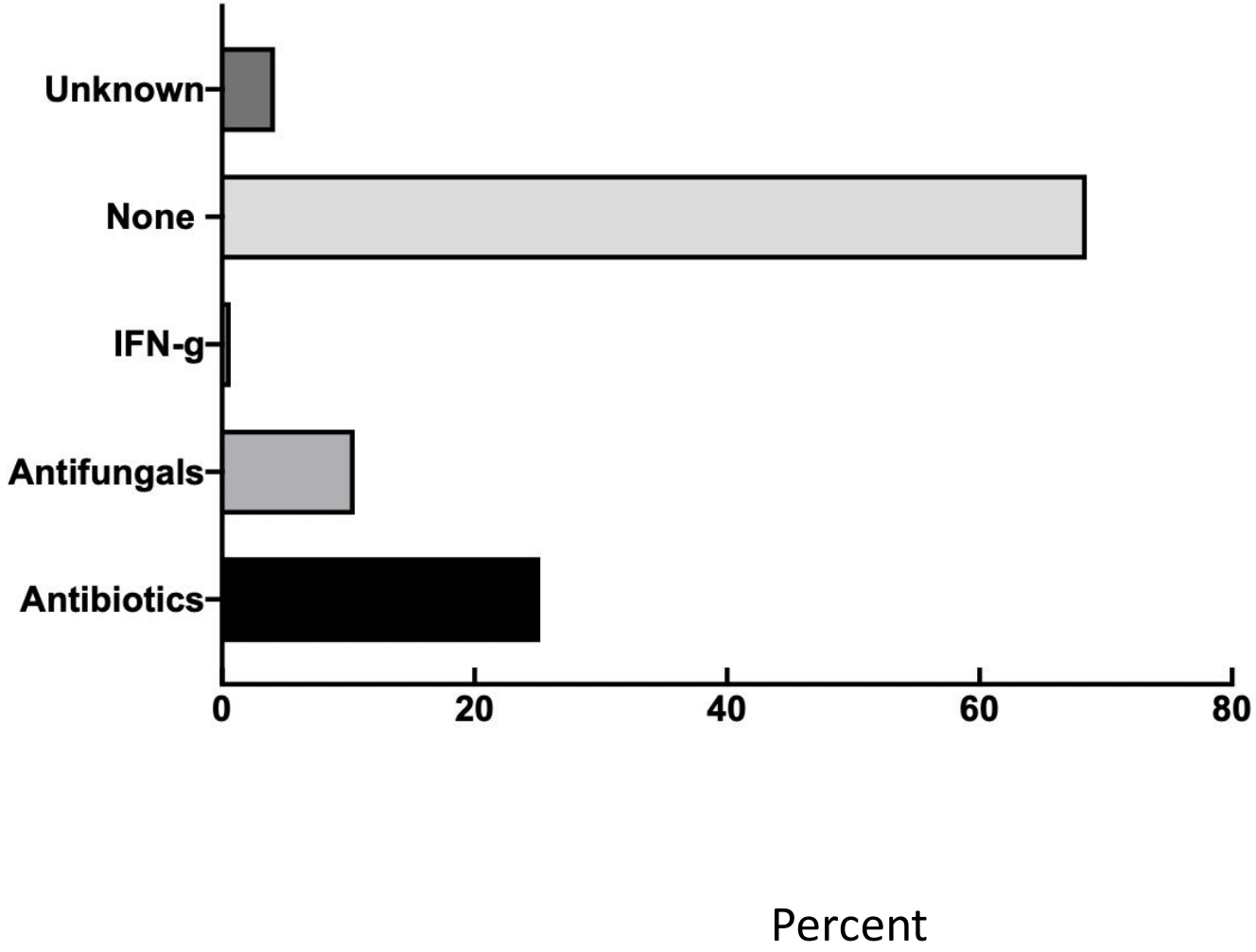
Overall Clinical Manifestations



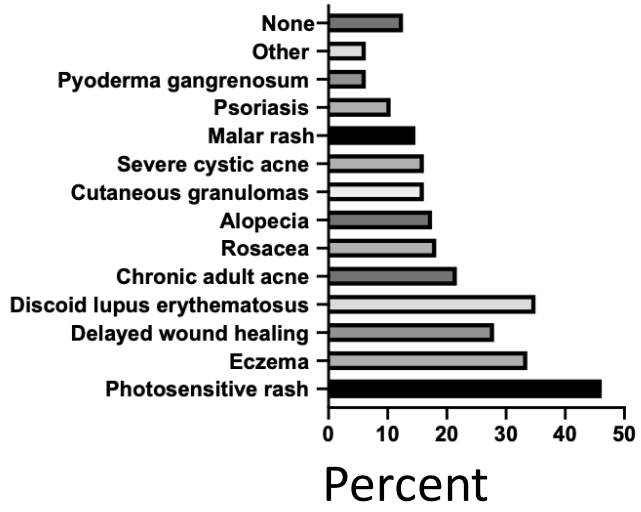
Infections in XL-CGD Female Carriers (n=139)



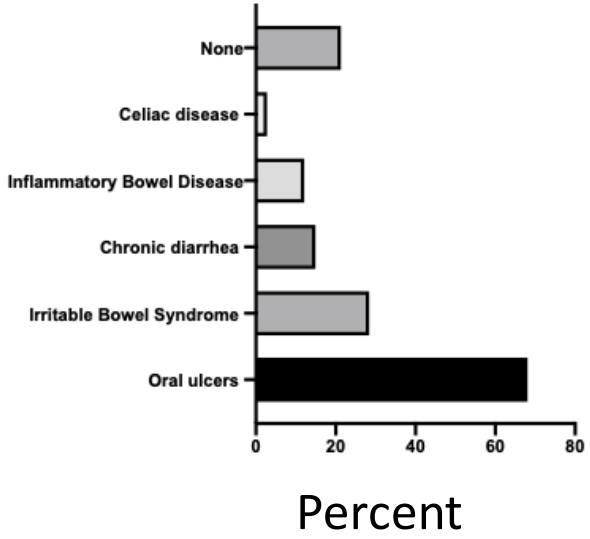
Use of Prophylactic Agents (n=143)



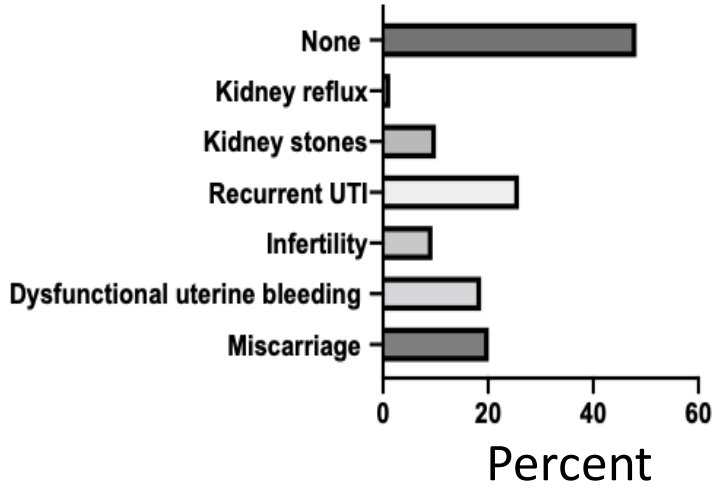
Cutaneous Manifestations (n=143)



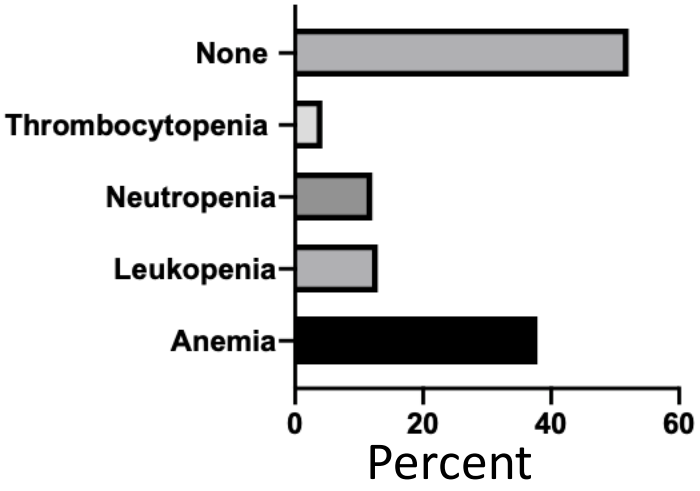
Gastrointestinal(n=155)



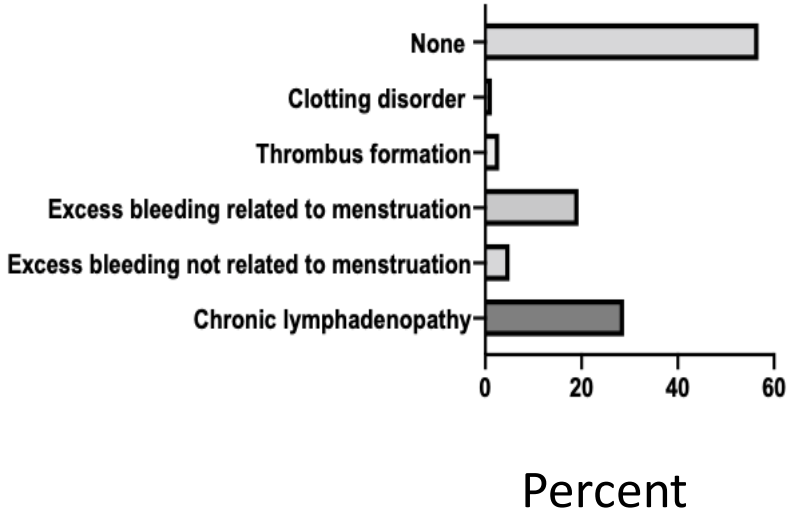
Genitourinary / Fertility (n=139) Manifestations (n=139)



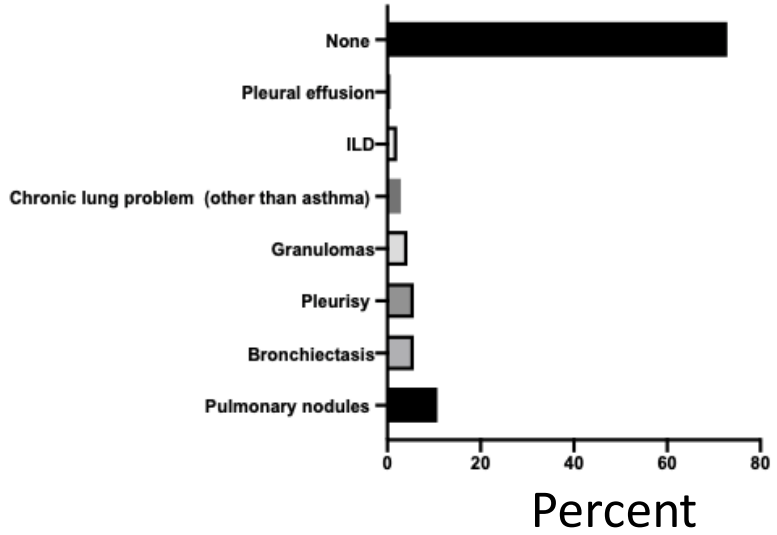
Hematologic Manifestations (n=140)



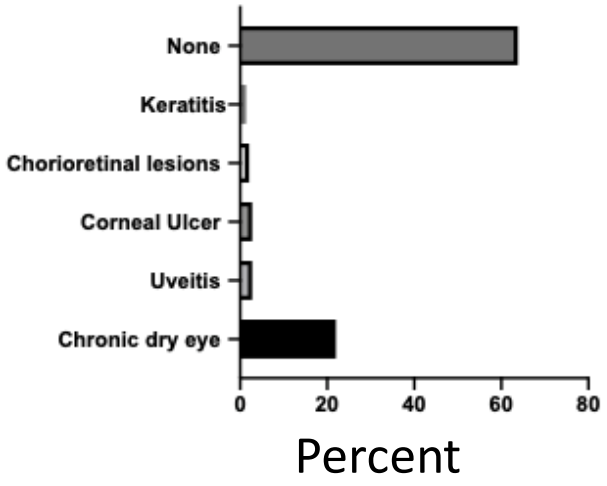
Lymph / Bleeding (n=140)



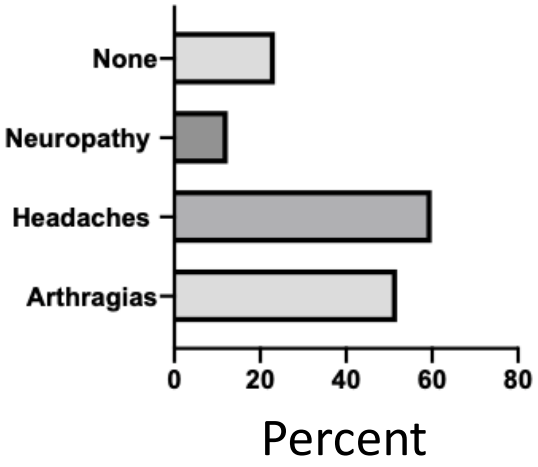
Pulmonary Manifestations (n=140)



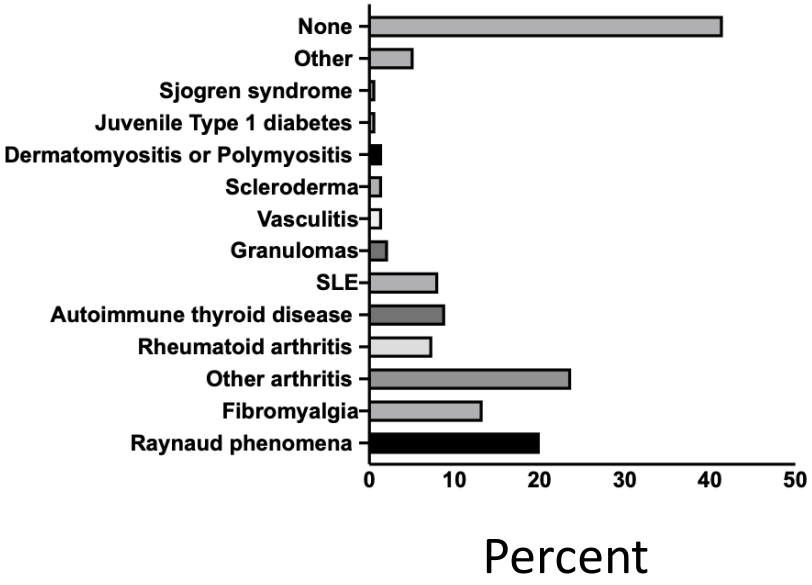
Ophthalmic Manifestations (n=141)



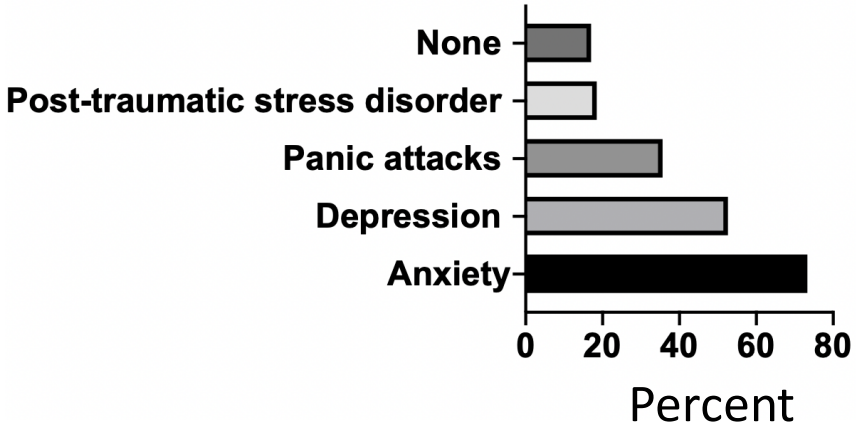
Musculoskeletal / Neurologic Manifestations (n=139)



Rheumatic Manifestations (n=135)



Psychiatric Manifestations (n=135)



Conclusions

- Limitations
  - Self reported symptoms that can’t be validated
  - No healthy control group
- XL-CGD Female Carriers
  - Can have CGD-related infections and many require use of anti-microbial prophylaxis
  - Symptoms in every organ system
    - Autoimmune/Rheumatic Disease
    - GI disease
  - High amount of psychiatric conditions

Acknowledgements

- **PIDTC Working Committee:**
  - **Jennifer Leiding – (JHU)**
  - **Dani Arnold – (NIH)**
  - **Harry Malech – (NIH)**
  - **Elizabeth Kang – (NIH_**
  - **Suhag Parikh – (Emory)**
  - **Rebecca Marsh – (CCHMC)**
  - **Eyal Grunenbaum – (Sick Kids)**
  - **Kanwal Mallhi – (U Washington / Seattle)**
  - **Deepak Chellapandian - (JHACH)**
  - **E. Liana Falcone – (Montreal)**
  - **Fabien Touzot – (Montreal)**
- **CGDAA**
  - **Felicia Morton**

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  - **Kate Sullivan**
  - **Rebecca Marsh**
  - **Jennifer Leiding**
  - **Harry Malech**

THANK YOU!

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Infectious Diseases & Immunology

Felicia Morton
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of America

Horizon Therapeutics

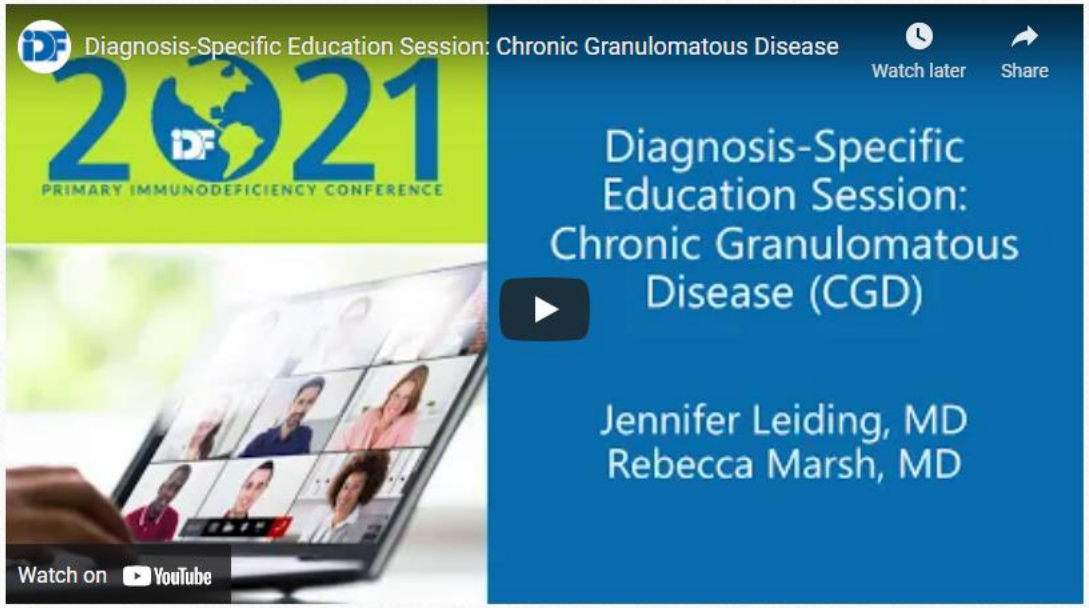
Q&A SESSION:
YOUR QUESTIONS ANSWERED

Additional IDF Resources for CGD

To view all CGD Resources and Materials, visit: www.primaryimmune.org and search "CGD"

- CGD- focused Blogs
- CGD Videos
- Real stories from patients & families
- CGD: An Official IDF Facebook Group
- Peer Support and Get Connected

IDF CGD Videos & Media



Reel Stories

IDF Reel Stories Playlist on YouTube →

Have more Questions?

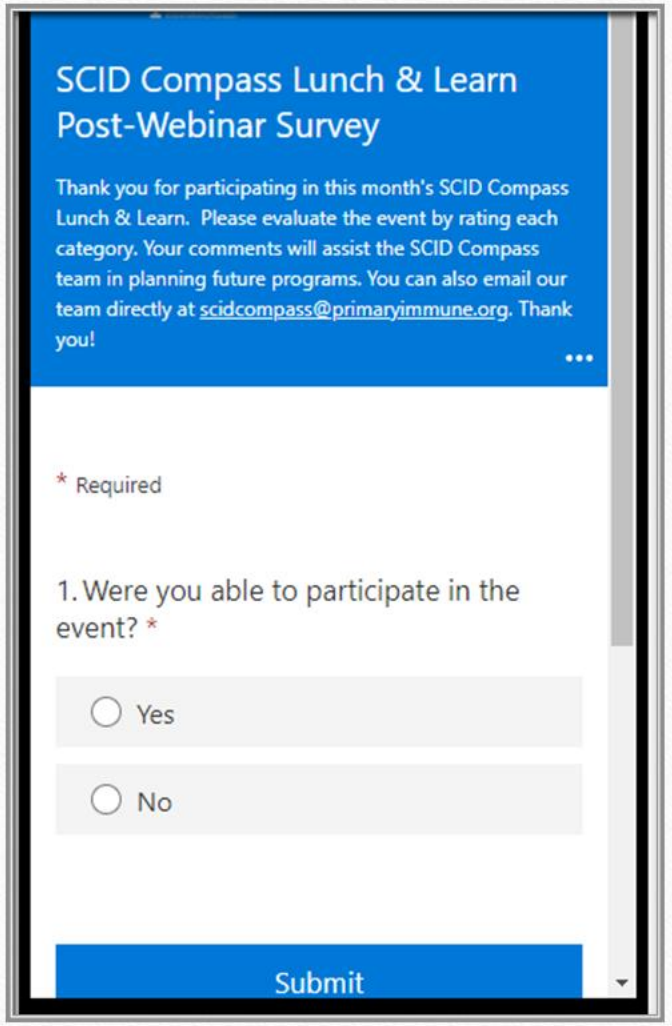
www.Primaryimmune.org/ask-idf

800-296-4433

Immune Deficiency Foundation

WE VALUE YOUR FEEDBACK!

Please take a moment to complete our Program Evaluation Survey



NEXT PROGRAM

Wednesday, June 22nd
1:00 PM ET

IDF Lunch & Learn: Congenital Athymia 101

Elena Hsieh, MD
Children's Hospital Colorado

https://community.primaryimmune.org/s/events?language=en_US