FDA Patient Listening Session

Chronic Granulomatous Disease

CGD ASSOCIATION OF AMERICA

11th August, 2025

Participants

Partner Organization

CGD Association of America (CGDAA)

Felicia Morton - Founder and Executive Founder

Colton - Communications Consultant

Anissa - Senior Communications Consultant

Denise Proffitt - Executive Board Member

Barbara Morton - Executive Board Member

Immune Deficiency Foundation

Eric Feigen - Regulatory Affairs Manager

FDA Divisions Represented

FDA Attendees

Office of the Commissioner (OC) – 2 offices

- OC/OEA/PES – Office of External Affairs/Public Engagement Staff (*organizer*)
- OC/OCMO/OPT – Office of the Chief Medical Officer/Office of Pediatric Therapeutics

Center for Biologics Evaluation and Research (CBER) – 10 offices

- CBER/OCD – Office of the Center Director
- CBER/OTP/OCE/DCEGM/GMB1 – Office of Therapeutic Products/Office of Clinical Evaluation/Division of Clinical Evaluation General Medicine/General Medicine Branch 1
- CBER/OTP/OPT/DPT1/PTB1 – Office of Therapeutic Products/Office of Pharmacology and Toxicology/Division of Pharmacology and Toxicology 1/Pharmacology and Toxicology Branch 1
- CBER/OTP/PSPS – Office of Therapeutic Products/Policy and Special Projects Staff
- CBER/OVRR – Office of Vaccine Research and Review
- CBER/OVRR/DBPAP - Office of Vaccine Research and Review/Division of Bacterial Parasitic and Allergenic Products
- CBER/OVRR/DBPAP/LMPCI - Office of Vaccine Research and Review/Division of Bacterial Parasitic and Allergenic Products/Laboratory of Mucosal Pathogens and Cellular Immunology

- CBER/OVRR/DCTR/CRB1 – Office of Vaccine Research and Review/Division of Clinical and Toxicology Review/Clinical Review Branch 1
- CBER/OVRR/DCTR/CRB2 - Office of Vaccine Research and Review/Division of Clinical and Toxicology Review/Clinical Review Branch 2
- CBER/OVRR/DCTR/CRB3 - Office of Vaccine Research and Review/Division of Clinical and Toxicology Review/Clinical Review Branch 3

Center for Drug Evaluation and Research (CDER) – 6 offices

- CDER/OND/OII/DG – Office of New Drugs/Office of Immunology and Inflammation/Division of Gastroenterology
- CDER/OND/OII/DPACC - Office of New Drugs/Office of Immunology and Inflammation/Division of Pulmonology, Allergy and Critical Care
- CDER/OND/OII/DRTM - Office of New Drugs/Office of Immunology and Inflammation/Division of Rheumatology and Transplant Medicine
- CDER/OND/ORDPRUM/DRDMG - Office of New Drugs/Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine/Division of Rare Diseases and Medical Genetics
- CDER/OTS/OB/DBIII – Office of Translational Sciences/Office of Biostatistics/Division of Biometric III
- CDER/OTS/OB/DBIV - Office of Translational Sciences/Office of Biostatistics/Division of Biometric IV

Center for Devices and Radiological Health (CDRH) – 11 offices

- CDRH/OPEQ/OHTI - Office of Product Evaluation and Quality/Office of Health Technology I
- CDRH/OPEQ/OHTI/DHTIB – Office of Product Evaluation and Quality/Office of Health Technology I/Division of Health Technology IB
- CDRH/OPEQ/OHTI/DHTIC – Office of Product Evaluation and Quality/Office of Health Technology I/Division of Health Technology IC
- CDRH/OPEQ/OHTIII - Office of Product Evaluation and Quality/Office of Health Technology III
- CDRH/OPEQ/OHTIII/DHTIIIA - Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology IIIA
- CDRH/OPEQ/OHTIII/DHTIIIB - Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology IIIB
- CDRH/OPEQ/OHTIII/DHTIIIC - Office of Product Evaluation and Quality/Office of Health Technology III/Division of Health Technology IIIC
- CDRH/OPEQ/OHTIV/DHTIVB - Office of Product Evaluation and Quality/Office of Health Technology IV/Division of Health Technology IVB

- CDRH/OPEQ/OHTIV/DHTIVC - Office of Product Evaluation and Quality/Office of Health Technology IV/Division of Health Technology IVC
- CDRH/OPEQ/OHTV/DHTVB - Office of Product Evaluation and Quality/Office of Health Technology V/Division of Health Technology VB
- CDRH/OPEQ/OHTVIII/DHTVIIIC - Office of Product Evaluation and Quality/Office of Health Technology VIII/Division of Health Technology VIIIC

Non-FDA Attendees

Reagan Udall Foundation

National Institutes of Health (NIH)

- NIH/NCATS – National Center for Advancing Translational Sciences

Session Goals and Topics

- Provide the FDA a clear understanding of the real-world impact of CGD, the experiences of patients and caregivers and the importance of the inclusion of patient-centered outcomes in clinical trials and research design to ensure that research for CGD better addresses CGD patient needs.
- Help the FDA understand the current gaps in treatment and access and the need for continued innovation in CGD treatment.

Summary of Topics Discussed

- Patient and Caregiver Experiences:
    - Living with CGD: Daily challenges, emotional and psychological impact, and quality of life issues.
    - Caregiving Burden: The role of caregivers, the impact on family dynamics, and the financial and emotional toll on families, such as the high cost of treatment, the loss of income to care for a sick child, and hospital travel/accommodation costs; we will touch on these topics briefly
    - Impact of Current Treatments: Patient experiences with existing therapies, including benefits, limitations, and side effects.
- Gaps in Current Treatment Options:

    - Unmet Medical Needs: Areas where current treatments fail to address critical aspects of the disease, such as infection management, inflammation control, and long-term health risks.
- Patient Preferences for Patient-Centered Research
    - Prioritizing Patient-Reported Outcomes: The need for clinical trials to focus on outcomes that matter most to patients, such as improving quality of life, reducing treatment burden, and minimizing long-term side effects.
        - Improving quality of life: Patients' lives would be improved dramatically by minimizing their constant worry of contracting an infection with high mortality, especially when diagnosis of an infection has advanced past a dangerous stage. That's number one. The issue is that even with daily prophylactic treatment, they are still vulnerable to life threatening infections. So, they can never live a normal life. Plus, taking large daily doses of antibiotics and antifungal medications is onerous. Furthermore, they have their own side effects. Meanwhile, curative treatments as they stand now are risky. They carry a ten percent risk of death and the risk of life-long side effects, like infertility.
- Barriers to clinical trial participation
    - Current clinical trial and experiences
    - Participation barriers:
        - Traveling to clinical trial sites
        - Preference for decentralized clinical trials
        - Length of clinical trial follow-up
        - Willingness to participate in a clinical trial that has a treatment arm and a placebo (non-treatment) arm

Disclosures

CGD Association of America receives funding from a variety of sources, including sponsors such as Ensoma, Amgen, Memorial Health Services/ Joe DiMaggio Children's Hospital, Jeffrey Modell

Foundation, and John Hartford Foundation. However, none of these funds were used for the purposes of organizing or participating in this Session. None of the participants in this meeting are receiving compensation for attendance or participation.

Former CGDAA sponsors and disclosures include Sanguine Biosciences, Prime Medicine, Orchard Therapeutics, The Immune Deficiency Foundation, and Horizon.

CGD Association of America would like to disclose that Dr. Jennifer Leiding receives funding from a variety of sources, including sponsors, for research. She is a paid consultant for Amgen. Additionally, she was the chair of the Data and Safety Monitoring Board (DSMB) for Prime Medicine until June 2025 when they shuttered the CGD gene therapy pipeline.

The Immune Deficiency Foundation receives funding from a variety of sources, including sponsors. However, none of these funds were used for the purposes of organizing or participating in this Session. None of the participants in this meeting are receiving compensation for attendance or participation.

Meeting Summary

CGD Association of America – Organization Overview

- The CGD Association of America is committed to advocating on behalf of patients, carriers, and families by providing clear, accurate, and independent news and information about CGD and advancing CGD research.
- Brief introduction of speakers

Clinical Overview

Dr. Jennifer Leiding, M.D.,

Associate Professor, Division of Allergy and Immunology, Johns Hopkins University

Associate Director, Institute for Clinical and Translational Research, JHACH

Associate Director, Center for Cell and Gene Therapy for Non-Malignant Conditions, CBDI, JHACH

Dr. Leiding described how Chronic Granulomatous Disease (CGD) is an inborn error of immunity that affects neutrophils, otherwise called phagocytes. This is due to any of the 5 components of the NADPH complex experiencing a defect or any of the genes that encode for them lead to the same disease - CGD.

This disease is characterized by:

- Recurrent, severe life threatening (up to life-ending) infections with a subset of oxidase-positive bacteria and fungi
- Granuloma formation
- High rates of inflammatory disease

The infections are due to a subset of very common bacteria that most people in the world encounter on a daily basis, but CGD patients are uniquely susceptible to them. Things as simple as swimming in rivers and ponds could be life ending due to infections or bacteria that they might encounter.

The inflammatory disease includes autoimmune disease, especially of the gut (“CGD colitis”), lungs, and liver. X-linked CGD, resulting in defects from gp91phox is the most common type of

CGD in North America and affects about ⅔ of patients. Women often pass this type of CGD on to their sons, so there are also female carriers who can be affected by their carrier status. Recessive CGD is the next most common type of CGD in North America, primarily due to defects in p47phox affecting about 20% of patients.

Dr. Leiding then shared a schematic of inflammatory manifestations that occur in CGD patients, and every organ system can be affected. This is referred to as autoimmunity or autoinflammatory, which is hyper-inflammation in sites that are not currently infected. The three major organ systems that are affected the most are the lungs, the liver, and the gut. The gut causes inflammatory bowel disease that is reminiscent of Crohn's Disease, protein-losing enteropathy is common, and interstitial lung disease ("Granulomous Lung Disease"), and nonregenerative hypoplasia of the liver can be irreversible if not adequately treated.

Gastrointestinal inflammation disease affects about 88% of CGD patients in some form or another while lung inflammation affects around 26% of patients. The probability of remaining free of an inflammatory manifestation is close to 0 by the age of 30. This is like compounding interest - once a patient has an inflammatory manifestation then the list of problems grows.

According to an NIH study, patients who have the lowest amount of superoxide production are at the highest risk for death. The majority of patients with X-linked CGD have the lowest survival rate as they have the lowest superoxide production, with about 50% survival by age 30.

There are no currently available FDA-approved therapies to treat the underlying causes of CGD. There is an FDA-approved therapy (ActImmune) that helps with infection prevention but does not prevent inflammatory disease, does not treat infections, does not treat inflammatory disease and does not have any kind of curative therapy for CGD.

Clinicians are left to help prevent infections with life-long antibacterial, antifungal prophylaxis, and the use of interferon gamma. There are no currently available therapies for inflammatory disease in CGD. Every therapy is used off-label and has never been studied in CGD patients, such as steroids and biologics that are approved for other indications. For curative options, there is allogeneic hematopoietic stem cell transplant (HCT) or gene therapy, neither of which are FDA-approved.

She then shared about a study she led along with the Primary Immune Deficiency Treatment Consortium (PIDTC) and 47 institutions across North America for hematopoietic stem cell transplant (HCT) or bone marrow transplant. This study showed that the medium age of CGD patients who have undergone a transplant was 5 years old with a survival rate of about 82%. While that success rate looks great, that still means that 1 in 5 people die due to transplant. Transplant has a high rate of success but there is a high rate of graft failure at around 18% in North America. The most likely cause of death in these CGD patients is graft failure.

Gene therapy can offer a definitive, one-time therapy for many hematopoietic disorders including CGD. This is where stem cells undergo gene transfer or gene induction leading to life-long daughter cells that produce the functional protein. This has been shown to be effective in CGD as a study published in *Nature* showed that 9 patients who did have durable engraftment with gene therapy for treatment of CGD.

However, there are many limitations to these options. Stem cell transplant has a lack of well matched donors, a risk of failure or death, and risk of graft-versus-host disease. Gene therapy is still under investigation and there are no approved therapies in this space. Earlier trials have been plagued with adverse events such as malignancies It is unclear if gene therapy will cure all manifestations of CGD in addition to being relatively expensive and difficult to access.

Patients & Caregivers Represented

Speaker 1: An entrepreneur describes their journey with Chronic Granulomatous Disease (CGD), leaving them with low pulmonary function and other treatment-induced complications.

- Disease status: Active CGD
- Treatments: Daily medication regimen of antibiotics, antifungal, corticosteroid, secondary Rx to manage side effects
- Clinical Trials: Original clinical trial for Actlmmune

Speaker 2: Parent of 9-year-old diagnosed with CGD in 2017 who had a bone marrow transplant in 2018. The child now has mixed chimerism as a result.

- Disease status: Child still has inflammatory manifestations.
- Treatments: Currently daily medication of anti-inflammatory medications for gut problems. Before transplant: daily medications of antibacterials and antifungals, and also Actlmmune.
- Clinical Trials: None

Speaker 3: Former CGD patient who underwent a successful BMT at NIH nearly 4 years ago.

- Disease status: Cured
- Treatments: Currently none. Before transplant, antibacterials and antifungals, steroids, blood thinners, Humira
- Clinical Trials: High Dose Peripheral Blood Stem Cell Transplantation with Post Transplant Cyclophosphamide for Patients with Chronic Granulomatous Disease

Speaker 4: Caregiver to 5-year-old child diagnosed with CGD. Also has physical symptoms as a result of being an X-linked carrier of CGD.

- Disease status: Child has active CGD
- Treatments: Returned to prophylaxis medication post unsuccessful BMT. Posaconazole and Bactrim.
- Clinical Trials: Yes but study is now closed because it was not a success for most participants.

Speaker 5: Caregiver to child who was diagnosed with CGD and underwent successful unrelated umbilical cord transplant at age 4. Also has physical symptoms as a result of being an X-linked carrier of CGD.

- Disease status: cured
- Treatments: CGD prophylaxis prior to unrelated umbilical cord blood transplant and not no treatments other than what might be necessary from time to time for a normal, healthy child
- Clinical Trials: none

Speaker 6: CGD patient

- Disease status: Active CGD
- Treatments: FDA Approved CGD treatment protocol
- Clinical Trials: Yes

Summary of Key Points:

- The immune system of a patient with CGD does not work properly, leaving the body prone to bacterial and fungal infections.
- CGD patients on average experience a life-threatening illness every 3.5 years
- The medicinal combinations of antibiotics, antifungals, and interferon gamma-therapy 1-b (Actimmune) are like a moat around a castle: things can still get over the moat.
    - CGD patients also have to avoid everyday bacteria and fungi such as dirt, construction areas, caves, grass cuttings, decaying leaves, dust, garden mulch, fresh water (lakes, ponds, rivers), jacuzzis/hot tubs, and potting soil.
- Funding for CGD research is limited, so CGD families have a hard time finding clinical trials nearby.
- The CGD community needs more than just managing and best efforts of infection prevention.

- We need more safe and effective treatment options.

Open Discussion

FDA Question: How could clinical trials be better tailored for patients and caregivers living with CGD?

- **Dr Leiding:** Therapies for CGD patients need to actually *be* for CGD patients. There are no FDA-approved therapies currently for treating the inflammatory manifestations of CGD. Other drugs that are approved for other purposes in an off-label way have many concerns such as not knowing the risk-benefit profile or the efficacy and safety profile. As private insurers get more picky about what is covered, they are less likely to provide coverage on medications that are not specifically FDA-approved for CGD. Until it is able to be shown that the medications are safe and effective in the CGD patient population, this problem will only amplify. Funding for clinical trials and education about CGD is another issue. The National Institutes of Health is a mecca for knowledge of CGD but many places outside of this need to learn about these patients. No patient should have to wait until they are 30 or 40 years old to receive a correct diagnosis.
- **Speaker 5**: When the speaker's son was ill, the family had been living in Manhattan with all of the best medical care around but still no one was able to give a correct diagnosis until the speaker had the idea to see an immunologist. Immunologists need to be part of the dialogue from the beginning when patients have "strange" manifestations without explanation. Additionally, the CGDAA would like to be a part of the dialogue when it comes to clinical trials. We can help advise on what patients need and what would be important to them. We can raise awareness of the clinical trial and help remove barriers to entry.
- **Speaker 6**: Patients are thinking about their health and obviously want to be healthy, but want to live as close as possible to a "normal" life. Some of the treatment protocols or requirements might come across as unrealistic for CGD patients. Patients want to be partners in their care and the patient communities have so much wisdom to offer due to living with the disease day-to-day. Symptoms that should be addressed are inflammation, especially how it impacts vomiting and bowel issues in addition reducing fatigue and inflammation that impacts mobility and joints. Not needing so many antibiotics and antifungals would be ideal. A tertiary concern would be addressing reducing issues related to breathing.
- **Speaker 4**: After the unsuccessful bone marrow transplant for their son, they realized that the ongoing studies for gene therapy are no longer an option due to undergoing chemotherapy as preparation for transplant.

- **Speaker 5**: If it is possible to be added to a list or be reached out to directly, we would relish the opportunity to partner. It can be a burden to find out about clinical trials and the clinicaltrials.gov website can be hard to navigate. Patients have shared that it is difficult to see if they qualify for a clinical trial for CGD.
- **Speaker 3:** As a member of the LGBTQ community, many people are excluded from clinical trials due to HIV or AIDS positivity. The speaker would like to have more research and funding to be able to include these people across the world. Most CGD people are diagnosed as a child, but the speaker was diagnosed with Lupus, which often is a blanket diagnosis given. This should be a red flag to test further for rare diseases and immune diseases.
- **Speaker 6**: The speaker knows other CGD patients and X-linked CGD carriers who have chosen not to have children due to not wanting to pass on the disease. It cannot be overstated how much this disease affects lives and while finding joy to move forward in life, CGD patients are pragmatic and want to be involved with the people making clinical trials and providing funding to share their experiences directly. Additionally, moving across the country, having to live at your facility for 4-5 months is not something available to every patient and their family. What happens if you have multiple kids, or one parent/caregiver can't move for the duration? How can you maintain a mortgage and an apartment at the facility? A lot of things fall out of the practice of medicine but are still pertinent if you want to have a positive outcome from a treatment, whether curative or not.

FDA Question: One challenge in designing clinical trials for rare diseases like CGD are end points to look at in trials to show that something is effective. In a disease like CGD the presentation can be so variable (age of onset, age of diagnosis, types of symptoms). What would be a clinically meaningful outcome in your daily life (e.g. something that could be measured in clinical trials)?

- **Speaker 5**: The CGDAA invests in research and has co-authored a paper on a related subject which is the first-ever multicenter outcome for CGD patients who have gone through bone marrow or stem cell transplant. We looked at those endpoints and successful transplant patients do incredibly well - some have gone on to father children, there were very few co-malignancies, and continue to do well 5-10 years later. This is a great opportunity to talk about those end points and having a sanguine approach with investment and partners who will see our community as a great partner. We are tracking outcomes ourselves but we need more research like with X-linked carriers. It is newer research that shows women who give birth to CGD patients can become CGD patients but we don't know why. As many as 20-40 other diseases now also show that women can

have symptomatic X-linked carriers. Could those endpoints we are working on impact other women, not just for CGD? One endpoint is how patients are doing post-transplant is just the tip of the iceberg and there is much more to learn about how other treatments are affecting our population.

- **Dr. Leiding:** Where CGD is different from other inborn errors of immunity, you have a really good biological objective test that quantifies disease activity which is the dihydrorhodamine (DHR). It has been validated over and over with its ability to give prognostic information regarding risk of infections and survival. While it is not a clinical endpoint it is a biologic endpoint that is really strong. When looking at clinical endpoints, infections are hard to measure as not everyone gets infected. Looking at response to medication or need for medication is better. Clinicians use the DHR in a transplant which mirrors gene therapy to determine whether someone is at risk for medication. An endpoint could be withdrawal of medicine or the withdrawal of immune-suppression. The PIDTC (an NIH-funded consortium) along with Dr. Leiding have created their own validated score system that quantifies disease activity in CGD. Gene therapy companies should use these types of scoring systems. The DHR as an endpoint may not be the primary endpoint but should certainly be a secondary endpoint at least. I would discourage using the "lack" of something as an endpoint. Some companies have used the absence of a symptom as an endpoint but that is very difficult to measure. Instead, the presence of a pre-existing symptom should be used.
- **Speaker 5**: Chimerism could also be used as an endpoint. Generally, if transplant is successful, it is 99.9% chimeric cells in long-term follow up visits.
- **Speaker 6 (shared in the Zoom chat)**: Addressing Inflammation, especially with how it impacts vomiting and bowel issues; reducing Fatigue; and inflammation that impacts mobility/joints. Of course, improving consistency reduces infections. Magic bullet would be to do all of that without needing so many antibiotics and antifungals, etc. Tertiary: reducing issues related to breathing.

Disclaimer

Discussions in FDA Patient Listening Sessions are informal. All opinions, recommendations, and proposals are unofficial and nonbinding on FDA and all other participants. This report reflects the CGD Association of America's account of the perspectives of patients and caregivers who participated in the Patient Listening Session with the FDA. To the extent possible, the terms used in this summary to describe specific manifestations of Chronic Granulomatous Disease (CGD), health effects and impacts, and treatment experiences, reflect those of the participants. This report is not meant to be representative of the views and experiences of the entire Chronic

Granulomatous Disease (CGD) patient population or any specific group of individuals or entities. There may be experiences that are not mentioned in this report.

APPENDIX: Patient & Caregiver Experiences

There were 3 patients and 3 caregivers who spoke about their lived experiences with Chronic Granulomatous Disease (CGD).

Speaker 1: CGD Patient

Speaker 1 is a CGD patient who was diagnosed at age 4.

Only 3 years before this patient was born, CGD was referred to as “Fatal Granulomatous Disease” as almost no children survived it. While the speaker is now in their 60’s, this is quite rare for CGD patients and does not come without its own challenges.

Before diagnosis, the speaker was regularly treated for infections throughout the first few years of life, starting at the age of six weeks. But these treatments were simply reactive -- long hospital stays for surgeries and IV antibiotics as infections reoccurred. The speaker detailed how they were diagnosed at Boston Children’s Hospital - fortunately in the right place at the right time to be treated by expert medical teams - including Dr. David Nathan, a NIH-trained hematologist. Dr. Nathan used the speaker’s white cells to help create the first diagnostic test - NBT Blue - which has remained the standard for decades.

The speaker shared how they were constantly ill throughout school-age years, at one time during high school set a personal record of staying out of the hospital for 18 months. The speaker noted that infections from CGD would strike suddenly and escalated to lengthy hospital stays. For instance, a simple sharp breathing pain could mean pneumonia requiring IV antibiotics with chest PT, a neck muscle ache with a fever was usually a lymph node infection requiring surgical intervention, an achy twisted ankle turned out to be osteomyelitis, and even a skin scrape or bug big was a source for invasion by bacteria or fungi.

Speaker 1 shared how they spent significant weeks across many semesters of college in the hospital, often crafting complicated setups in their dorm to hang IVs and swap out heparin locks.

The speaker was able to still graduate college summa cum laude while as an inpatient at the hospital with a four hour pass to attend commencement. After graduating college, the speaker had to stay in Boston for follow-up care while starting a new job as soon as possible to have group health insurance. By staying in the area, the speaker was able to frequently provide blood samples to Dr. David Nathan and his team which then allowed the researchers help map the CGD gene and later develop the drug interferon gamma. The speaker then became the first patient in its clinical trial - now known as ActImmune.

While newlywed, the speaker developed disseminated aspergillosis - a fungal infection that spread from the skin, to the lungs, and then to the ribs. Knowing that the aspergillosis survival rate for CGD patients was only 50%, the speaker started on a brutal 20-week course of amphotericin.

In recent years, the speaker's lung function has sharply declined and doctors have recommended a double lung transplant. Dr. David Nathan and his network were able to come to the speaker's rescue and provide the care needed from CGD specialists at NIH.

"With CGD, vibrancy is relative and always cautious."

However, the speaker shares how they still suffer from chronic kidney disease and ringing in the ears as side effects of high dosages of IV antibiotics and antifungals. It is extremely difficult to get the veins to cooperate with nominal blood draws because they have been used so often. Despite a full schedule of daily prophylactic antibiotics, antifungals, and corticosteroids, the speaker must avoid everyday situations that present even modest risks.

"Still embracing every day, sometimes even every hour, as a remarkable gift is not a cliche for me. It's just my way of life."

Speaker 2: Caregiver to CGD patient

Speaker 2 is a mother of a 9-year-old boy who was diagnosed with CGD. In 2018, her son underwent a bone marrow transplant to cure CGD - this was only semi-successful. The son now has mixed chimerism, meaning he is part himself and part donor cells.

The speaker shares how any parent knows that taking care of a child is like having a second job. But when caring for a chronically ill child, it becomes almost a third full-time job. She detailed how you imagine your life will look like with a child (e.g. going to baseball games, vacations, when the child goes to school, etc.). There is emotional and physical strain as a caregiver, the speaker notes that she is also a carrier of CGD so she has physical ailments as well.

As a parent and caregiver, trying to decide if the child should stay on prophylactic medication for the rest of his or her life while reducing exposures versus putting the child through a bone marrow transplant is an extremely difficult decision. She shares how dealing with a chronic illness results in changes in sleep patterns for the caregiver and the patient. This often results in fatigue and additional physical health problems due to fatigue. She went on to share about the emotional implications of caregiving for the patient, oneself, the rest of the family, and other caregivers.

There are significantly more stressors and things to create anxiety when caring for someone with a chronic illness, especially CGD. Common things like playgrounds with mulch chips, going swimming in a lake or river, or going to daycare could all lead to the child becoming sick. With CGD, patients rapidly escalate from being sick to requiring hospitalization for life-threatening infection - a constant worry as a caregiver.

The constant state of stress and worry becomes a heavy mental load on top of keeping track of a multitude of appointments and medications. As the speaker previously mentioned, she is a carrier of CGD and carries a sense of guilt for passing the CGD gene to the child. There is a regular thought pattern of “Why is my child going through this?” and “Is my child going to die?”

When someone in the family has CGD, this affects the whole family unit as they must become socially isolated. The speaker shared how when the pandemic hit in 2020, the rest of the world became more used to isolating, using masks, and using more hand sanitizer. But for families like the speaker’s, this is their everyday “normal” life. She detailed how they see everyone else living life and going where they please but she is worrying if it is safe to send their child with CGD to public school. The feeling of being socially isolated is further compounded by not having others in one's life who can understand as this is a rare disease.

As previously mentioned, the speaker’s child underwent a bone marrow transplant which required even stricter isolation and additional stress. Not only as a caregiver but also as a parent she had to find additional time in the day to research what hospital to go to for transplant. Not every hospital has the same protocol when it comes to transplant and uses different drugs. Additional considerations were how far away the hospital was (would the family need to live in another city during this time?), the parent’s jobs, the other children in the household, and ultimately what is the best decision? All the decisions made as the caregiver are stressful.

Speaker 3: Caregiver to CGD patient

As a Chronic Granulomatous Disease carrier, this causes physical symptoms that compound the difficulty of being a caregiver for someone that has CGD. The speaker notes that even choosing

to move forward with a bone marrow transplant, things don't always go as planned and [we] are left to navigate the world of CGD is a difficult situation.

The speaker's son was diagnosed with CGD when he was 1.5 years old in 2021. This is the speaker's first child and dealing with the learning curve as a first-time parent, navigating COVID, and a medical diagnosis of a life-threatening disease was an earth-shattering experience. The speaker notes she is very fortunate to have a supportive community around her family, including the CGD Association of America.

Multiple long-term hospitalizations and health incidents left the family feeling rushed into a bone marrow transplant at their local hospital. After connecting with a CGD expert at the NIH, they decided to hold off on the bone marrow transplant until the speaker's son was 4 years old so that the procedure could take place at the NIH. The speaker's family moved cross-country, leaving their family and friends, and everything familiar, in order to join a clinical trial study that would allow for less chemotherapy in hope of a successful bone marrow transplant.

It was a different world after leaving a children's hospital to go to an adult hospital with a children's floor. The difficulties from this added to the strain of being away from their support system. Unfortunately, the transplant was not a success. The speaker's son must now return to a prophylactic treatment to protect from harmful bacteria and fungus. After going through this process, the speaker learned it is not uncommon for patients to get a second bone marrow transplant. The speaker also learned after the transplant occurred that the chemo used in preparation for transplant now makes her son ineligible for gene therapy.

The speaker hopes that the testimonies given today will help the FDA understand the need for approving new drugs for CGD and more successful treatments.

Speaker 4: CGD patient

Speaker 4 is a CGD patient who lived for over 20 years with symptoms that no one could fully explain as doctors suspected Lupus, Behcet's Disease, and other conditions. Meanwhile, the speaker was battling persistent infections and severe inflammation, managing symptoms that no 20-year-old should face while being "treated" with medications that were doing more harm than good.

Starting from the moment the speaker was born, they had symptoms. They stayed in an oxygen tent for over a week after they were born - delaying their parents' ability to hold them for the first time. As a child, they were constantly sick and contracting serious infections, one of which was an infection in a lymph node in their neck that eventually had to be removed. This was only the beginning. Over the years they suffered recurring infections that also impacted their liver and

lungs. These infections required surgical intervention and continued drug therapy — some of the most painful experiences of their life.

In high school, the speaker developed severe deep vein thrombosis blood clots in their legs, prompting a long journey of using blood thinners. Regardless of the medication, the speaker still experienced breakthrough clots, including some that eventually reached their brain and nearly required emergency surgery. After this, the speaker's doctors decided to use Lovenox, the only drug known to work given the speaker's health issues, and the speaker had to inject this drug two times, daily, for ten years.

While working at a summer camp, the speaker started experiencing what could be a lung infection or pulmonary embolism. The local hospital doctors were not able to determine what it was and recommended the speaker take a medical helicopter back home. While the speaker would have preferred to drive the 8+ hours home, the doctor informed the speaker that they might not survive the drive home. The speaker agreed to fly but was left with an $80,000 medical bill. Once arriving at the home hospital, it was determined that there was an infection but no culture taken was able to provide a positive diagnosis of what infection or illness was going on. This is a common symptom - serious infections with no clear diagnostic markers making it nearly impossible to determine the right treatment.

After being prescribed Humira to treat an eye inflammation that was threatening the speaker's vision, the immunosuppressant triggered multiple severe infections that left them hospitalized for weeks.

Eventually, the speaker was able to get diagnosed with CGD which came after doctors repeatedly refused to test the speaker, saying the disease was "too rare." While getting a diagnosis brought relief, it brought a new slew of questions - "What are the treatment options?", "Is there a cure?", "Will my life be cut short?", and "What medications are needed and for how long?" The speaker was told they wouldn't live past the age of 40 and if they did, the quality of life would be extremely limited.

While trying to determine if a bone marrow transplant was the right decision, the speaker crossed paths with another CGD patient who had undergone the procedure but was still very sick and eventually died. After attending the funeral on Zoom, the speaker was unable to stop thinking, "If I go through with this, it could be me (dying)." This decision wasn't a simple one - it is gambling with one's life. Nearly 20% of CGD patients don't survive a bone marrow transplant and another 20% don't have a successful outcome.

The speaker did move forward with the bone marrow transplant at the National Institutes of Health with a successful result - ultimately saving their life. Before transplant, the speaker was told they would need to be on blood thinners for life. The speaker's world revolved around

mediations, specialist appointments, and emergency stays. The quality of life wasn't just limited, it was defined by CGD. The speaker had to drop out of school, quit their job, and move back in with their parents; every decision centered on survival.

Today, the speaker is free from the fear of life-threatening infections and no longer needs to take any CGD or transplant-related medications. In the speaker's experience, quality of life is the single greatest impact of current CGD treatments. A bone marrow transplant comes with its own risks but for those who are successful, it offers a cure and allows people to focus on the future. No infections, no inflammation, and no decreased life expectancy.

But transplant isn't available or desirable for everyone; for those patients antifungal and antibacterial therapies are essential for reducing the risk of life-threatening infections and creating a foundation for health stability. These medications allow people to live, survive, and sometimes thrive but these medications only work if taken consistently and as prescribed. Without them, CGD patients would face constant risk of death.

Another option is interferon gamma (ActImmune) which can be used alongside prophylaxis. It helps the immune system respond to infections and has been shown to reduce serious symptoms and infections by up to 65%. CGD also causes inflammation complications, especially gastrointestinal. Immunosuppressive medications can help but they also increase the risk of infection so managing them is a constant balancing act.

Current treatments, though not perfect, have allowed patients to live longer and better lives. Antibacterials, antifungals, and interferon gamma help CGD patients prevent serious infection and bone marrow transplant can offer a cure for some. Continued research and expanded access to these medications are critical to improving outcomes for everyone with CGD. We cannot allow budget cuts or political agendas to undermine access to these life-saving treatments and their continued advancement. Doing so will result in devastating consequences for patients and countless lives will needlessly be lost.

Speaker 5: Caregiver of CGD patient

Speaker 5 is a caregiver to her son who was diagnosed with CGD at 5 months old and the speaker notes she was diagnosed as an X-linked carrier of CGD after her son's diagnosis. The speaker's mother is a highly-lionized carrier meaning she has to take traditional CGD prophylaxis medication.

The unbearable burden: deciding whether to face the risks of a life-threatening infection and a shortened life span with CGD prophylaxis treatment vs deciding whether to face the risks associated with a stem cell transplant.

The speaker's introduction to CGD was their son's diagnosis at almost six months old after a harrowing journey in and out of ER. Once diagnosed, began the trauma of caregiving for a CGD patient including administering daily medications / CGD prophylaxis.

The harsh reality: CGD patients face life-threatening infections every 3.5 years despite taking prophylactic treatment. There is a huge emotional impact on caregivers due to balancing life-saving treatments with side effects in addition to the emotional impact on the patients themselves.

Alternatively, one can face the realities of a bone marrow transplant, the only curative option. However, not everyone has a good donor source; the speaker's son lacked a bone marrow match and they had to choose a 4/6 unrelated umbilical cord blood match - the lowest possible match rate. With that increased risk due to low match rate, they then faced the arduous process of an unrelated umbilical cord transplant, which involves harsh pre-transplant conditioning (fully ablative chemotherapy), the risk of severe complications such as graft-versus-host disease, and a demanding recovery period (almost a year for the speaker's son).

Transplants pose many barriers to entry, not just the daunting risks, but also the time and resources it takes for patients and caregivers to get through it. Plus it is generally considered too risky for patients over 40 because they've experienced too many debilitating infections to endure it.

For those who continue with CGD prophylaxis, the medications provide incomplete protection against life-threatening infections. In addition, there are side effects from treatments and the extreme burden of giving daily doses and injections lead to additional stress for families.

Specific Medications and Their Issues:

- Trimethoprim-Sulfamethoxazole (Bactrim) Daily dosage, known antibiotic side effects
- Antifungals: Daily dosage can have gastrointestinal and other side effects
- Interferon gamma: Potential burden to maintain injections three times a week; and side effects can include flu-like symptoms

Additionally, X-linked CGD carriers can be highly lionized and we (the CGDAA) have research that shows carriers can have similar physical symptoms of CGD patients. The speaker is an X-linked carrier but their mother is a highly lionized X-linked carrier who has had issues with cellulitis, a common physical ailment of X-linked carriers.

The consequences of ongoing infections include reduced growth rates and limited life expectancy (40-50 years). As previously mentioned, bone barrow transplants are an option but not everyone has the ability to undergo the procedure. Even if they can, there is a 10 to 20 percent risk they will not have the successful outcome that the speaker's son had.

Encouraging Biotech for Brighter Horizons Ahead

This is a call to action for the FDA and biotech/pharmaceutical companies to recognize the need for investment in rare diseases like Chronic Granulomatous Disease (CGD). We hope the FDA will foster innovation across various diseases and enhance therapeutic options. We encourage partnerships between academia and industry to speed up research to create a win-win opportunity.

Initiatives to drive more awareness, support, and investment in CGD can lead to breakthroughs applicable to larger populations with life-threatening monogenic disorders, such as: Sickle Cell Anemia, Cystic Fibrosis, Duchenne Muscular Dystrophy, Hemophilia and more.

We suggest the following strategies for the FDA to continue investing in CGD:

- Streamline regulatory processes to harness advancements in technology.
- Incentivize companies to invest in rare disease research and provide grants for investing in rare disease research.
- Encourage partnerships with biotech companies, academic institutions, and patient advocacy groups to leverage collective expertise and resources.
- Create more patient-centered guidelines so that patients can be included in the drug development process to ensure clinical trials and treatments meet the unique needs of the CGD community.
- Continue to monitor safety by establishing comprehensive post-approval monitoring systems to enhance patient safety.
- Increase awareness of CGD and innovative therapies to attract investment and collaboration.
- Drive more awareness for the success of FDA's Platform Technology Designation Program by encouraging the use of reusable frameworks to enable the development of a single approach across multiple rare diseases is especially important to encourage biotech investment in orphan diseases like CGD.

Speaker 6: CGD patient

Speaker 6 has a sibling who was in a medically-induced coma and the doctors were not sure what was wrong. Once tested, the speaker's sibling was diagnosed with CGD and so the rest of the family was tested. The speaker was then diagnosed with CGD at age 10. After diagnosis the speaker's doctors informed them that they would be lucky to live to age 18. This was an existential crisis for the speaker at only age 10 realizing they could have an early death and what to with the potentially limited time they had left. The doctors shared an incredible exception of a CGD patient who had lived to age 64 so that became the inspiration for living - determined to live past their 18th birthday.

Growing up as a person with CGD, adulthood presents challenges that childhood did not. There are issues with misdiagnosis and misunderstanding of symptoms. When the speaker was a child with CGD, the doctors at that time did not know that inflammation was tied to symptoms like vomiting. There was an instance where the speaker as a child was not able to keep a barium solution down and the doctor thought the speaker was being difficult, rather than understanding the vomiting was due to internal inflammation. Living with CGD is not just about "fixing" the body - it is a full, holistic health impact. Moms and primary caregivers are the unsung heroes of becoming a CGD expert to take care of the patient. However, it is still difficult for dads and secondary caregivers who may need to work extra hours or multiple jobs to pay the large medical bills. Siblings of CGD patients may miss out on parental interaction due to this and may also be limited in their social interactions as the family as a whole isolates to prevent infection.

The speaker and their wife created their own company as a way to be able to work while managing CGD as most regular jobs have limited or no sick time. However, running a business is a different level of hard work in addition to living with a chronic illness. When thinking about patient experiences and care, you have to think about the full patient journey - it impacts things like relationships, marriages, families, and partner relationships. Doctors are so concerned with treating CGD but don't often have time to support in these other areas. What is life if you can't experience *all* aspects that matter to you as an individual and as a family?

When thinking about designing clinical trials, patients should be asked questions like "What is the most important objective?" The objectives should extend far beyond what medical providers typically think about. For people who come from marginalized backgrounds, they bring additional insights and complexities to the patient experience.