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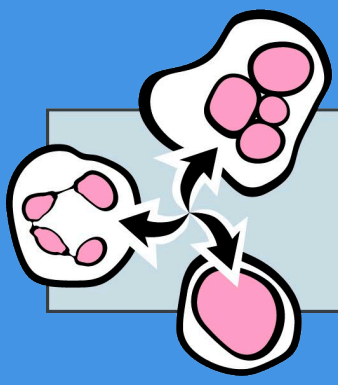

Primary Immune Deficiency Treatment Consortium

PIDTC Annual Workshop

March 18–20, 2026

Salt Lake City, Utah

Meeting Abstracts

JHI Journal of Human Immunity

Abstracts from the 2026 PIDTC Annual Workshop

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All abstracts were reviewed and approved by the Primary Immune Deficiency Treatment Consortium Program Committee, which held full responsibility for the abstract selections

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PIDTC MEETING ABSTRACTS 2026

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Outcomes After Allogeneic Hematopoietic Cell Transplant in Patients with GATA2 Deficiency

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Background: GATA2 deficiency syndrome is an inherited immune and bone marrow failure disorder with predisposition to myeloid malignancies. Allogeneic hematopoietic cell transplantation (allo-HCT) is a potential curative treatment. However, patients usually enter transplant with significant comorbidities, rendering them at a high risk for early transplant complications. Available reports on outcomes following HCT are scarce.

Design/Methods: The Center for International Blood and Marrow Transplant Research (CIBMTR) registry was used to evaluate outcomes of patients with GATA2 deficiency who received allo-HCT. Primary outcome was overall survival (OS) at 1 and 3 years post-HCT. Causes of death were described. Frequency of acute graft-versus-host disease (aGVHD) and cumulative incidence of chronic GVHD (cGVHD) was assessed. Regression analysis was performed to determine factors associated with developing aGVHD and cGVHD.

Objective: To evaluate outcomes of patients with GATA2 deficiency who received allo-HCT.

Results: We identified 127 patients that received allo-HCT at 46 centers (median age 23 years [0.7-61]; 63% were adults). Most (64%) had a high comorbidity index (HCT-CI >3) with infection (40%), prior solid tumor (35%), and moderate/severe pulmonary disease (26%) being the most common comorbidities. Immune deficiency and bone marrow failure were the indications for transplant in 76% of patients, with the remaining indication being myelodysplastic syndrome (MDS) or leukemia. Most received myeloablative conditioning regimen (76%) and received HCT from unrelated donors (56%). The median follow-up was 4 years (0.3-12 years). OS was 93% (95% confidence interval [CI] 89-97%) at 1 year and 82% (95% CI 77-91%) at 3 years. OS didn't differ when stratifying for age or transplant indication. Main cause of death was organ failure followed by infection. Subgroup analysis of 40 patients with post-HCT infectious data showed a high frequency of post-HCT infectious complications (87%), the majority being viral (67%). Endothelial complications (transplant-associated thrombotic microangiopathy [TA-TMA; 2%] and veno-occlusive disease [VOD; 5%]) were rare. All patients had primary engraftment. GVHD was frequently observed post-HCT: 60% of patients developed aGVHD, of which 60% were grade II-IV; cumulative incidence of cGVHD was 44% (95% CI 34-54%) at 1 year, with the majority (84%) experiencing extensive disease. GVHD was a contributing cause of death in 6 patients. Regression analysis did not identify any variables that significantly affected development of GVHD.

Conclusions: In patients with GATA2 deficiency, mortality related to transplant was low. However, the incidence of GVHD was high, adding to post-HCT–related morbidity. Future research should be directed toward assessing risk factors for GVHD and optimizing prevention strategies.

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Autologous Ex Vivo Lentiviral Gene Therapy for Severe Leukocyte Adhesion Deficiency-I Achieves Durable Immune Reconstitution and Reduction of Infection-Related Morbidity: Updated 3.5-5.5-Year Results from a Phase I/II Study

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Background: Severe leukocyte adhesion deficiency-I (LAD-I) is caused by biallelic deleterious variants in *ITGB2*, resulting in <2% CD18 expression and impaired leukocyte extravasation, particularly neutrophils. Affected infants and children experience recurrent, life-threatening bacterial and fungal infections, poor wound healing, and significant mortality in the absence of allogeneic hematopoietic stem cell transplantation (alloHSCT). Although alloHSCT can be curative, many patients lack suitable donors and remain at risk for graft-versus-host disease (GvHD), graft failure, and transplant-related morbidity and mortality. Treatment with a durable autologous hematopoietic stem cell (HSC) gene therapy was developed to address these limitations.

Aims: To evaluate the long-term safety and efficacy of RP-L201 (marnetegragene autotemcel), an autologous CD34+ HSC gene therapy using a Chim-CD18-WPRE lentiviral vector incorporating *ITGB2*, we investigated restoration of CD18 expression, normalization of neutrophil function, and reduction in infection-related morbidity in children with severe LAD-I.

Methods: Children ≥3 months old with severe LAD-I were enrolled in the phase I/II study (NCT03812263). CD34+ cells obtained via G-CSF/plerixafor mobilization and apheresis were transduced ex vivo with RP-L201 and infused following therapeutic drug-monitored myeloablative conditioning. Endpoints included survival without alloHSCT, restoration of peripheral blood (PB) polymorphonuclear (PMN) CD18 expression, peripheral blood mononuclear cell (PBMC) vector copy number (VCN), integration site analysis, resolution of baseline leukocytosis, and incidence of infection-related hospitalizations. All treated patients entered the long-term follow-up (LTFU) study (NCT06282432).

Results: Nine patients (age 9.8-117.4 months at infusion) received RP-L201 and were followed for a median (range) of 50.92 (42.6-67.9) months as of the June 18, 2025, LTFU data cut. AlloHSCT-free survival was 100% with no cases of graft failure. PBMC VCN/cell rose to 0.42-2.4 at month 3 and remained stable through month 12 (mean 1.73) with persistent long-term VCN levels across months 42-60. All patients achieved sustained PB PMN CD18 expression within or approaching the target levels, maintained through >3.5 years post-infusion. Longer-term results demonstrate markedly lower annualized incidences of pre-specified serious infections, infection-related hospitalizations, and prolonged infection-related hospitalizations after RP-L201 treatment relative to pre-treatment incidences. No new skin or oral infections occurred in the LTFU period. RP-L201 was well-tolerated; no RP-L201-related adverse events occurred. Integration site analyses demonstrated polyclonal integration patterns without dominant or expanding clones.

Summary/Conclusion: RP-L201 conferred durable engraftment, sustained CD18 restoration, and significant reductions in infection-related morbidity in nine children with severe LAD-I, with at least 3.5 years of follow-up. All nine patients are alive without alloHSCT. There were no RP-L201-related adverse events. These updated results support autologous HSC gene therapy as an effective alternative to alloHSCT with a favorable risk-benefit profile for severe LAD-I.

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Implementing a First-in-Human Clinical Trial of Prime-Editing Gene Therapy in p47-CGD: Clinical Data and Site Perspectives

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In April 2025, CHU Sainte-Justine performed the world's first gene therapy using prime editing. The patient was an 18-year-old male with autosomal recessive p47phox chronic granulomatous disease (CGD). Infectious history included osteomyelitis, abscesses, and *Burkholderia cepacia* pneumonia. He also had an active colitis with intermittent oral ulcers, managed with Pentasa. An allogeneic hematopoietic cell transplantation (HCT) had been dismissed during childhood in the absence of a compatible donor. At fall 2024, the opportunity arose for the patient to enroll in this gene therapy clinical trial to achieve a permanent cure for his disease. After completing the screening, apheresis, and busulfan conditioning phases, the patient received the investigational product, PM359, manufactured from autologous CD34+ cells in which the GT deletion in NCF1 was corrected using prime editing. Aside from mild adverse events related to busulfan conditioning, no serious events occurred. Neutrophil engraftment was achieved on Day 16 and platelet engraftment on Day 19. NADPH oxidase activity in neutrophils, measured by dihydrorhodamine (DHR), increased from less than 1% pre-infusion to 69% by Day 30. To this day (9 months post-infusion), the DHR remains stable at 77%, and the patient has no CGD manifestations and is no longer on medication. Another 57-year-old patient with a long history of infections of lung, liver, and lymph nodes plus inflammatory bowel disease (IBD) received the same treatment at the National Institutes of Health (NIH), and the outcome was also excellent and uneventful. The DHR normalized for 83% of neutrophils, and this result was stable after 6 months. He is no longer on prophylactic antibiotics, and his IBD has significantly improved. While our patient's clinical course was simple, setting up the clinical trial required acrobatics and coordination worthy of a hyperactive octopus. Implementing a first-in-human therapy for patients whose lives are not immediately at risk represents a high degree of complexity. This success required nearly two years of preparation, from initial contact with the trial sponsor to PM359 administration. Through the preparation of the site qualification and audit days, it was essential to surround ourselves with the right resources—within the cell therapy laboratory, the apheresis unit, and the quality assurance team. Beyond having those resources in order, one must know how to present them, clarify them, and adapt to the sponsor's requests, while ensuring compliance with existing procedures. We orchestrated the treatment plan with our clinical teams to align as closely as possible with standard practice while anticipating tools to mitigate uncertainty when deviations were necessary and making sure no one was overlooked: nurses, physicians, nutritionists, laboratories, pharmacy, imaging, and more. In parallel, we had to prepare a robust ethics submission and a consent form that says everything—without being overwhelming. Finally, it culminated in presenting the trial to the patient and his parents and guiding their decision-making, leading to the results presented above. Our objective is to present the outcome of those patients together with the description of all the steps of the clinical trial, likely including a video testimony of our patient.

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Base Editing Hematopoietic Stem/Progenitor Cell Gene Therapy for Treatment of X-Linked Severe Combined Immunodeficiency

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X-linked Severe Combined Immunodeficiency (XSCID) due to IL2RG loss-of-function mutations typically cause a severe combined cellular and humoral immunodeficiency that is diagnosed and transplanted in infancy. Hypomorphic *IL2RG* variants with milder phenotypes are generally diagnosed later in life. Early stem cell transplants (allogeneic or autologous gene therapy) performed without conditioning often results in partial immune reconstitution with limited donor engraftment in T cell lineage alone. Defective host B, natural killer (NK), and other cell lineages remain and can cause progressive multi-organ disease. Ex vivo gene therapy using lentivector-transduced autologous hematopoietic stem/progenitor cells (HSPCs) has provided clinical benefit for many previously transplanted older XSCID patients (NCT01306019) and transplant-naïve infants (NCT01512888, NCT03311503). Lentivector transduction functionally corrects XSCID stem cells by semi-random insertion of IL2RG cDNA under the regulation of an engineered promoter. A conversion to gene-corrected immune cells in their respective compartment can take years, particularly in older adult patients. The exact mechanism for this slow progression, whether this is attributable to a relatively weak promoter in the transgenes, is unclear. CRISPR/Cas9 base editing provides the potential for precise gene mutation correction that is devoid of random virus integrations and, critically, restores physiological gene regulation by endogenous promoter. We developed a highly efficient base editing strategy using adenine base editor and respective guide RNAs to repair respective IL2RG mutations (*IL2RG* p.289X, *IL2RG* p.Gln235X, *IL2RG* p.Q144X, and *IL2RG* p.R226H). Preclinical efficacy and safety data supported a Phase I/II clinical trial to treat XSCID patients with base-edited HSPCs (IND 31037; NCT 06851767). Three patients have been treated to date with base-edited (BE) HSPCs (25 million to 50 million cells per kg/weight). BE HSPC products were well tolerated, with early myeloid recovery within 3 weeks after cell infusion. Gene correction frequencies in the study cell products averaged >80%. Follow-up data at 6 months in the first patient showed robust levels of gene correction in myeloid (70%), B (94%), NK (100%), and, surprisingly, in his T cell compartment (65%) as well, with a corresponding decline in donor T cell chimerism (99% at baseline, 47% at 6 months). Monitoring of the other treated patients is ongoing. We conclude from our preliminary data that gene therapy using BE HSPCs appear very promising for achieving an earlier and more robust multi-lineage immune reconstitution in adult patients using BE HSPCs.

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Post-HCT Autoimmunity in Patients with Primary Immunodeficiency or Immune Dysregulation

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Background: Patients undergoing allogeneic hematopoietic cell transplant (HCT) for nonmalignant conditions may be at higher risk for post-transplant autoimmunity (AI). The precise risk factors for these events remain unclear.
Methods: Retrospective review was performed of 92 patients with primary immunodeficiency (PID) or immune dysregulation who received HCT at our institution between 2000 and 2024.
Results: 17 of 92 patients (18%) developed AI at a median of 9 months post-HCT (HCT details in supplementary table 1; AI details in supplementary table 2). Majority received our institutional standard Bu2/Flu/ATG conditioning. There were no differences in primary diagnosis, donor type, graft source/composition, conditioning, or rates of graft-versus-host disease (GVHD) between AI and non-AI patients. Hematology AI diagnoses were most common. Antibody-positive rheumatologic disease was reported in 3 patients: mixed connective tissue disease (MCTD) with erosive arthritis, systemic lupus erythematous (SLE)/juvenile idiopathic arthritis (JIA) overlap, and immune-mediated necrotizing myositis. Patients with severe combined immunodeficiency (SCID) were overrepresented in the non-hematologic AI group (heme SCID = 1, nonheme SCID = 6). There was no relationship between immunosuppressive therapy (IST) and development of AI: 11 patients off IST and 6 on IST at time of AI diagnosis. Of AI patients, 14 (82%) developed an infection by day (D) 100 compared to 49 non-AI patients (65%; p = 0.17). Of AI patients, 24% developed acute GVHD (all skin GVHD), and one patient developed limited skin chronic GVHD; these patients all developed hematologic AI. Patients who required cell boost or second HCT were more likely to develop AI: 4 AI patients (24%) vs. 8 non-AI patients (11%, p = 0.16). Two of three AI patients requiring repeat intervention later developed rheumatologic disease. AI events were not associated with

subsequent decline in chimerism (Fig. 1). One patient experienced a drop in chimerism >20% following AI event. AI patients were less likely to achieve CD4+ >50 cells/μL by D+100 and CD19+ >200 cells/μL by D+360 than non-AI patients (CD4+: AI 65% vs. non-AI 89%; CD19+ AI 59% vs. non-AI 89%).

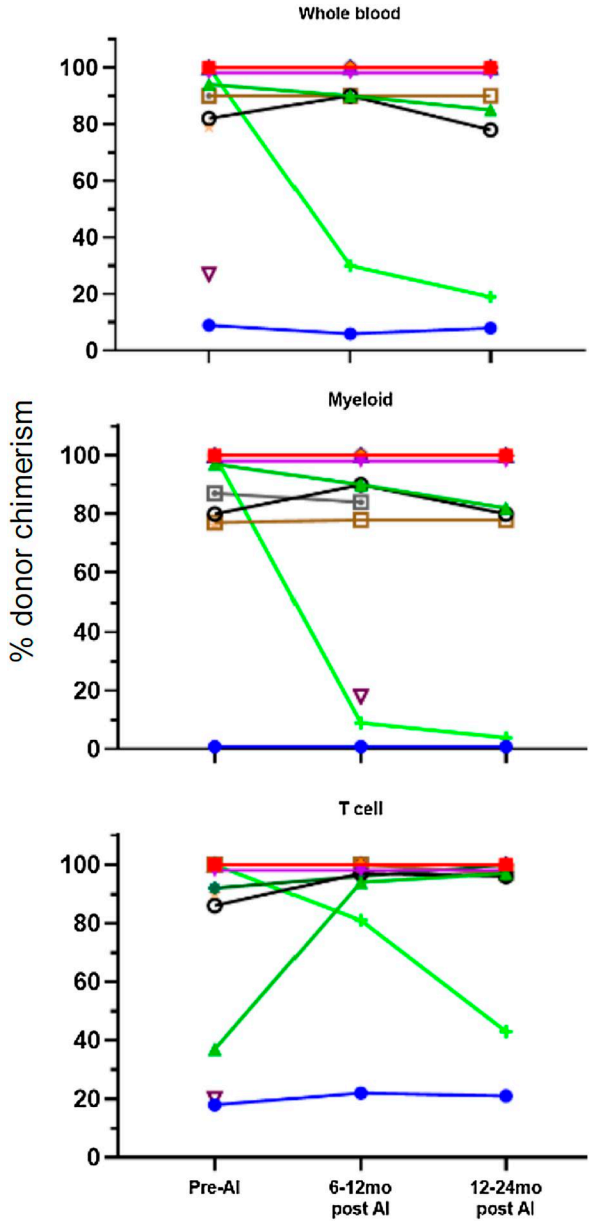

Figure 1. **Donor chimerism pre- and post-AI diagnosis.**

Conclusions: We report post-HCT AI of 18% in our PID/immune dysregulation population, including multiple patients with rheumatologic AI manifestations. We saw no impact of graft source, donor type, GVHD, or post-HCT immunosuppression on development of an AI complication. Patients with infection by day 100 were likely to develop post-HCT AI, which may be related to early immune activation. Second intervention increased risk of developing AI. Further studies are needed to determine if this is related to extensive immune system modulation or predisposition to both post-HCT AI and graft rejection.

Tabular data are included as downloadable supplement files.

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T Cell Exhaustion in Patients with Severe Combined Immunodeficiency Transplanted Without Conditioning or Graft-Versus-Host Disease Prophylaxis: The Duke Experience

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Introduction: Our large cohort of patients with severe combined immunodeficiency (SCID) underwent bone marrow transplantation (BMT) without pre-transplant conditioning or graft-versus-host disease prophylaxis and has an overall survival exceeding 70% at 43 years of follow-up. It is important to determine whether immune reconstitution in these patients is sufficient for normal life expectancy.
Methods: Flow cytometry was performed to longitudinally study the reconstitution of CD4 and CD8 T cells among 59 patients with different molecular types of SCID at Duke for up to 30 years post-BMT. The flow cytometry panel was optimized to identify and quantify both PD-1+CD57+ senescent and PD-1+CD57- exhausted T cells.
Results: Data collection occurred at various time points and was not consistent across the cohort with median (min, max) number of samples per patient being 2 (1, 7). We found a strong negative correlation between the CD4 T cell count and percentage of CD4 exhausted T cells (ρ = -0.67, confidence interval [CI]: -0.56 to -0.76, $p < 0.001$) and a moderate negative correlation between the CD4 T cell count and the percentage of CD8 exhausted T cells (ρ = -0.48, CI: -0.34 to -0.60, $p < 0.001$). Through an unadjusted regression, we found that each additional year from time of transplant was associated with a mean increase in the percentage of CD4 exhausted T cells by 0.7 (CI: 0.4 to 1.0, $p < 0.001$). Recipients of HLA-identical BMT had less CD4 and CD8 exhaustion.
Conclusions and Ongoing Work: We identified a negative correlation between CD4 T cell counts and the accumulation of exhausted T cells in a Duke cohort of 59 patients with SCID. Ongoing work aims to characterize the factors that might contribute to T cell exhaustion, including peri-transplant course, infections, molecular type of SCID, degree of T cell immune reconstitution, and impact of aging in comparison to healthy controls. Examining the mechanisms and relevant variables contributing to T cell exhaustion may help improve long-term transplant outcomes for SCID as well as other diseases requiring hematopoietic stem cell transplantation.

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Prognostics Markers for CGD Hematopoietic Stem Cell Transplant Outcomes

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Chronic granulomatous disease (CGD) is an inborn error of immunity (IEI) caused by genetic mutations impairing function of the phagocyte NADPH oxidase, leading to frequent severe bacterial and fungal infections. While allogeneic donor hematopoietic stem cell transplant (alloHSCT) is curative, identifying factors predictive of post-transplant morbidity and mortality would be helpful to design individualized best management of patients. The immune deficiency and dysregulation activity score for IEI (IDDA) (1), developed to predict transplant outcome, is a weighted scoring system assessing pre-transplant disease burdens. We assessed whether the IDDA scoring system is a valid prognosticator for CGD patients by performing a retrospective analysis of the IDDA scoring of CGD patients who underwent alloHSCT at the National Institutes of Health (NIH) Clinical Center. The cohort received a busulfan- and alemtuzumab-based alloHSCT from 2016 to 2022. We calculated the IDDA, pre-transplant and preconditioning, for the total cohort of 40 patients with a median follow-up of 54 months (range 0.5–115). For IDDA, inpatient hospitalization days were counted during the time of 100 days before Day -14 of transplant. Acute graft-versus-host disease (GvHD) of grades III and IV, any grade of chronic GvHD, graft rejection early or late, graft failure, or death from any cause were defined as post-transplant events. We found a significant difference in the median IDDA scores between the survived and expired patients (survived = 13, range 6–56; expired = 30, range 21–37; $p = 0.001$). Also, median pre-transplant IDDA scores between patients who had no post-transplant event and those who had one differed (no event = 12, range 6–56; event = 29, range 12–37; $p = 0.01$). From this, we performed a receiver operating characteristic analysis to find the optimal threshold for low vs. high IDDA. We categorized the patients with IDDA below 20 as low IDDA patients; equal to or above 20 as high. The 3-year overall survival rate

(OSR) in the low IDDA patients was 100% compared to 50% for the high ($p < 0.0001$). The 3-year event-free survival (EFS) in the low IDDA patients was 92% compared to 57% for the high ($p = 0.007$). We have also determined that a C-reactive protein (CRP) level ≥100 mg/dL in the 45 days before initiation of transplant conditioning delineates high-risk patients from standard risk in our CGD transplants using our conditioning regimen. The 3-year OSR in the standard risk patients was 97% compared to 0% for the high risk ($p < 0.0001$). The 3-year EFS in the standard risk patients was 91% compared to 0% for the high risk ($p < 0.0001$). The R-squared value for IDDA vs. CRP was 0.34, indicating no significant correlation between the two values. Although IDDA scoring can predict outcomes of HSCT for CGD patients, we believe that CRP is as good if not a better predictor, and that given the ease of IDDA vs. CRP calculation, CRP is the more useful marker in CGD transplant patients.

Reference

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Characterizing and Overcoming Barriers to PIDTC Research Participation and Compliance in Canadian Rural and Low German Mennonite Communities

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Background: In Canada, rural populations, especially Low German Mennonite (LGM) communities, constitute a substantial demographic of patients with inborn errors of immunity (IEI), but several interconnected barriers affect their inclusion in Primary Immune Disease Treatment Consortium (PIDTC) studies. Geographic isolation, language and literacy, culture and religion, technology, and logistics are key themes most associated with the involvement of LGM communities in research. LGM communities experience unique barriers stemming from historical experiences of persecution, discrimination, stigma, and fear of judgment, leading to distrust for government and medical systems, and extending to research. LGM culture, religion, and social structure place emphasis on privacy and confidentiality, also influencing engagement with research.
Objective: This study aims to characterize barriers and identify facilitators for participation and compliance for rural populations, especially LGM communities in PIDTC studies.
Methods: A focus group of PIDTC researchers at the Alberta Children's Hospital identified key themes to inform a literature review. With few available publications for this population, the literature review will identify key barriers and corresponding facilitators in similar populations and disease groups. These will be validated and expanded through open-ended interviews with an LGM community representative and patient advisory committee. Collaborative thematic analysis will synthesize findings from the literature review and interviews.
Results: This is an ongoing study. A pre-study focus group identified several preliminary themes to guide the pending literature review and interviews. Geographic isolation shapes nearly every aspect of rural healthcare, including access to research. Rural populations depend heavily on local primary care, as long travel distances of up to 8 hours and limited transportation options reduce accessibility to PIDTC research hospitals. This distance translates into fewer opportunities for study visits and sample collection for enrolled patients, resulting in poor compliance and diminished data quality. Many LGM families lack the devices or adequate internet connection for video calls, making real-time telehealth research visits nearly impossible. Low health literacy affects almost half of rural patients, and gender disparities in education, language, and reading skills are common within LGM communities. Limited literacy skills of LGM mothers, who are typically the primary caregivers, are a barrier to informed written consent and meaningful engagement with written questionnaires offered in English, French, or Spanish. Translation services for Low German are not always accessible. Privacy concerns around data sharing, especially across borders, and potential industry involvement in research are other common concerns of LGM families, rooted in distrust for institutions. Differing electronic medical record (EMR) systems between sites limits access to patient information for data collection. In provinces like Alberta, a provincial Epic EMR and unified public laboratory facilitate access to clinical and laboratory data, while public health insurance allows equal access to healthcare facilities.

Conclusions: Rural populations face complex, overlapping barriers to inclusion and compliance in health research, and LGM communities are additionally impacted by unique cultural factors. Implementation of culturally, linguistically, and demographically informed care, community health representatives, flexible consent and questionnaire formats, tailored technology, and logistic solutions can facilitate rural and LGM community representation in research.

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The Clinical and Economic Burden of Severe Leukocyte Adhesion Deficiency-I: A Lifetime Cost-of-Illness Modeling Analysis

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Background and Aims: Leukocyte adhesion deficiency-I (LAD-I) is an ultra-rare inborn error of immunity (IEI), with severe cases characterized by recurrent, life-threatening infections, hyperinflammation, and high mortality rates. Treatment options are limited to allogeneic hematopoietic stem cell transplantation (allo-HSCT) and best supportive care (BSC). Without allo-HSCT, infection risk remains high despite antimicrobial prophylaxis. Even with allo-HSCT, patients are at risk of graft failure, graft-versus-host disease (GvHD), and transplant-related morbidity and mortality. Outcomes after allo-HSCT are strongly influenced by donor compatibility, with poorly matched grafts associated with higher complication rates. This study aimed to quantify the lifetime health economic burden associated with severe LAD-I and to compare outcomes across currently available treatment modalities.

Methods: A de novo Markov model estimated lifetime outcomes for patients with severe LAD-I receiving allo-HSCT (up to two rounds) or long-term BSC. Health states included initial/long-term BSC, engraftment success (with/without chronic GvHD), graft failure (primary [PGF] or secondary [SGF]), and death. Severe LAD-I complications and acute GvHD were modeled as one-off events. Allo-HSCT outcomes were explored by age (<13 months and ≥13 months at transplant) and donor type (matched sibling donor [MSD] and non-MSD). Clinical effectiveness and natural history inputs were sourced from real-world data via the European Society for Bone and Marrow Transplantation (EBMT) registry and observational studies. Due to limited utility data, health-state utility values were derived from published literature on proxy IEIs and supplemented by expert opinion. Costs were estimated for a U.S. healthcare payer perspective. Health state and one-off acute GvHD (aGvHD) event costs were obtained from an OPTUM claims analysis using clinically validated proxy IEIs and adjusted to 2024 prices. Model outcomes are reported as mean values using undiscounted costs and outcomes.

Results: Patients receiving allo-HSCT were projected to live 44.2 years (35.9 quality-adjusted life years [QALYs]) at an estimated lifetime cost of $2.0 million. An "average" patient is based on 39% receiving an MSD, with 16% experiencing graft failure (3% PGF, 13% SGF), 10% chronic GvHD, and 23% aGvHD; outcomes may vary substantially if these rates change. Age at transplant also affects outcomes. Patients receiving long-term BSC had shorter survival (16.1 years), substantially impaired quality of life (7.1 QALYs), and higher lifetime costs ($9.0 million), driven by high annual healthcare costs and low health-state utility from frequent severe LAD-I-related complications. Lifetime burden was also assessed for an "average" severe LAD-I cohort, comprising both allo-HSCT and long-term BSC recipients, acknowledging ratios may vary by transplant center and region.

Conclusions: Long-term BSC is associated with substantial cumulative lifetime costs and poor clinical outcomes. Allo-HSCT offers the potential for cure and significantly reduces long-term management costs compared with BSC; however, it entails high upfront costs and carries risks of serious, potentially life-threatening complications, which contribute to both short- and long-term healthcare expenditures. Lifetime burden under allo-HSCT varies by rates of transplant-related complications, age at transplant, and donor type. Overall, these findings highlight that current treatment options for severe LAD-I remain suboptimal, underscoring a critical unmet need for alternative therapies.

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Interleukin 7 Receptor Alpha-Associated Severe Combined Immunodeficiency: Impact, Clinical Course, and Outcomes Following Hematopoietic Stem Cell Transplantation

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Introduction: Newborns with genetic variants in interleukin 7 receptor (IL7R) resulting in severe combined immunodeficiency (SCID) are commonly identified after an abnormal newborn screen. These patients experience profound T cell lymphopenia with varied humoral findings and are at risk for infection prior to definitive therapy. Definitive therapy includes hematopoietic stem cell transplant (HCT) and can result in immune reconstitution.

Methods: Retrospective chart review of four patients with IL7R SCID who were diagnosed through newborn screening in Maryland, Virginia, or Washington, D.C., and received HCT at Children's National Hospital.

Results: All four patients were found when the newborn screening identified abnormal T cell receptor excision circle (TREC) values and were evaluated by immunology between 8-13 days of life. Each patient had markedly reduced CD3+ T cells at presentation (CD3+ 5-23 cells/mcL), variable B cells (CD19+ 354 cell/mcL–1,948 cells/mcL), and natural killer (NK) cell counts (CD16/56+ 288 cells/mcL–946 cells/mcL). Humoral profiles varied, with all patients exhibiting normal immunoglobulin G (IgG) and M (IgM). Two patients had absent immunoglobulin A (IgA) levels. Antifungal prophylaxis was initiated between days of life (DOL) 14-41. *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis was initiated between DOL 30-41, and immunoglobulin replacement was initiated between DOL 30-53. Maternal CMV IgG was positive in three mothers. All mothers who had positive CMV IgG were asked to stop breastfeeding. One mother with detectable CMV stopped breastfeeding. All patients experienced pre-transplant infections ranging between upper respiratory infections, including parainfluenza, rhino/enterovirus, and respiratory syncytial virus (RSV), and fungal infections, including candidal intertrigo of axilla and pityrosporum folliculitis. Transplant strategies encompassed haploidentical peripheral blood HCT (3 patients) and matched sibling donor marrow HCT (1 patient). One patient received anti-CD117 monoclonal antibody conditioning with graft failure necessitating subsequent HCT. Three patients received a preparative regime of busulfan, fludarabine, and rabbit antithymocyte globulin (rATG), and one patient received busulfan and fludarabine preparative regime. Post-transplant complications included CMV disease (retinitis, pneumonia, and enteric involvement) requiring virus-specific T cell therapy, hypertension, transaminitis, norovirus, and poor oral intake. All four patients demonstrated full donor T cell chimerism and mixed myeloid chimerism. Post-transplant immune assessments showed T cell reconstitution, improved lymphocyte proliferation to mitogens, and appropriate immunoglobulin values. Vaccine responses were protective to diphtheria, tetanus, and pneumococcal serotypes, and all patients were off chronic IgG replacement between 106–244 days after transplant.

Conclusion: In this cohort of four patients with IL7R SCID, newborn screening was essential for diagnosis and implementation of prophylactic treatment. Despite early intervention, patients with IL7R SCID may still experience pre-transplant complications such as upper respiratory infections or fungal infections. Early definitive therapy is essential and can lead to immune reconstitution.

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A Wolf in Sheep's Clothing: CAEBV and Lymphoproliferative Immune Dysregulation

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19-year-old previously healthy female with infectious mononucleosis complicated by recurrent fevers and persistent EBV viremia. Approximately three months later, she presented with quotidian fevers, hepatosplenomegaly (HSM), pancytopenia, and rising EBV viremia. Laboratory studies revealed elevated ferritin, lactate dehydrogenase (LDH), transaminases, triglycerides, and hypercytokinemia (sIL-2R, CXCL9, IL-18, IL-10, IL-8, ADA2, and serum amyloid A [SAA]). Initial bone marrow (BM) biopsy showed atypical lymphocytosis consistent with acute EBV infection, histiocytes with marked increase in hemophagocytosis, and significant EBV-encoded small RNA (EBER) staining of T and natural killer (NK) cells. B cells were absent in BM. Cerebrospinal fluid (CSF) did not show evidence of inflammation. Treatment was initiated for chronic active EBV-T cell lymphoproliferative disease (CAEBV-TLPD) with improvement in symptoms and viremia. One month later, there was rebound EBV viremia, worsening fevers, hepatosplenomegaly (HSM), and patchy pulmonary infiltrates progressing to respiratory failure requiring intubation, hepatic, and renal failure with coagulopathy. Quantitative EBV analysis in different cell subsets showed florid increase in EBV within the B cell compartment suggestive of EBV-driven B cell lymphoproliferation/malignancy. EBV was positive in T and NK cell subsets but less significantly. Treatment was transitioned to focus on the B cell lymphoproliferative process (Fig. 1). Quantitative EBV DNA methylation was performed at 25 EBV loci and found to have intermediate EBV methylation (47%). Methylation pattern was consistent with lymphoproliferative disease/lymphoma. Immunophenotyping in blood revealed increased activated CD4+ and CD8+ T cells (HLA-DR+CD38+++). There were also increased CD5+CD38++ T cells. There was also increased exhausted (LAG3+) and senescent (KLRG1, CD57+) T cells in the CD4+ T cell subset. PD1 expression was not increased on CD4+ or CD8+ T cells due to prior treatment with nivolumab. An atypical B cell subset (CD19+CD20-) was identified prior to EBV infection in B cells. Additional phenotyping revealed numerous B cell marker anomalies consistent with aberrant differentiation, prior to rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) (RTXx2). There was rebound of CD19+CD20+ and CD19+CD20- B cells within 2+ weeks of treatment. At this time, there was evidence of central nervous system (CNS) involvement with expressive aphasia and volume loss. CSF analysis demonstrated CD19+CD20- B cells as well as T cells along with elevated cytokines. She developed warm autoantibodies against RBCs without hemolysis. She also had anti-smooth muscle antibodies suggestive of active endogenous production, rather than passive administration via immunoglobulin replacement. Rapid genome sequencing was performed and negative, despite evaluation for EBV predisposing genes. A single maternally inherited variant in *MEFV* was present, which could have contributed to the overall clinical phenotype, albeit indirectly. Despite numerous therapies, there was continued decompensation, resulting in fulminant liver failure and severe metabolic acidosis, resulting in irreversible organ failure and death.

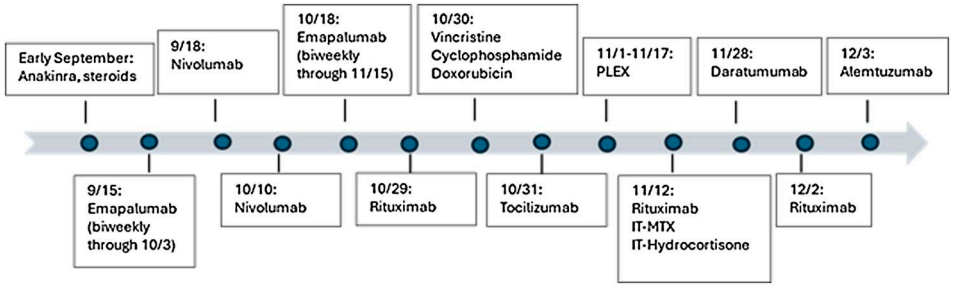

Figure 1.

Take-Home Points: With no prior history of immune dysregulation, this patient developed rapid and fulminant course of EBV-LPD (lymphoproliferative disease), which was refractory. While the aggressive course of disease is not fully understood, the atypical CD19+CD20- B cells could have contributed to disease pathogenesis, along with EBV strain and replicative potential, and possible uncharacterized host genetic contributions. Most cases of biclonal (B and T cell) EBV-LPD are associated with significant immune compromise, often in the setting of solid organ transplantation. This case illustrates CAEBV evolving to B cell-EBV-LPD with the inability to pursue hematopoietic cell transplant (HCT) due to clinical instability and exemplifies the need to understand the molecular and immunological underpinnings of EBV-LPD.

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Identification of a Shared CD3D Variant Among a Severe Combined Immunodeficiency Cohort of Cabo Verdean Ancestry

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Identifying patient populations with recurring and potentially targetable genetic variants is crucial to develop innovative therapeutics such as gene editing. However, many patient populations remain underrepresented in genetic databases, highlighting an unmet need in diagnosis and treatment of immunodeficiency. Cabo Verde is an island country off the coast of West Africa that was uninhabited until the 15th century, now with a unique genetic admixture of Portuguese and sub-Saharan African descent. Despite a sizable population (500,000 citizens and a global diaspora of nearly 1 million), genomic data from Cabo Verdeans remains limited and genetic conditions among Cabo Verdean patients under investigated. Our institution has now diagnosed and treated 3 non-consanguineous patients of Cabo Verdean ancestry with $T^-B^+NK^+$ severe combined immunodeficiency (SCID) secondary to the homozygous variant *CD3D*: c.279C>A (p.Cys93*). This variant results in a premature stop codon, with associated loss of CD3δ protein and absent T cell development. All three infants were diagnosed by newborn screening and received busulfan-based conditioning prior to successful hematopoietic cell transplant (HCT). Patient 1 was a male with family history notable for two older siblings who were not assessed by newborn screening but died of pneumonia at 4 months of age. He received a matched unrelated donor transplant at 2 months of age, with transplant course complicated by acute respiratory distress syndrome (ARDS) requiring mechanical ventilation and transverse myelitis at 2 years of age. By 9 months post-HCT, he was off exogenous immune suppression with full donor chimerism and T cell and B cell reconstitution. Patient 2 was a female who was a first cousin once removed of patient 1. She received a haploidentical T cell–depleted graft from her mother at 18 weeks of age. Her HCT course was complicated by polymicrobial sepsis requiring intensive care unit (ICU) admission and EBV viremia requiring rituximab therapy. By one year post-HCT, she had stably discontinued exogenous immune suppression with full donor chimerism, T cell reconstitution, and recovering B cell reconstitution post-rituximab. Patient 3 was a female without family history of immunodeficiency, severe infections, or early infant death, nor a relation to patient 1 or 2. She received a matched unrelated donor HCT at 12 weeks of age, complicated by EBV viremia (requiring rituximab), veno-occlusive disease (VOD), transplant-associated thrombotic microangiopathy (TA-TMA), and cutaneous graft-versus-host disease (GvHD). By one year post-HCT, she was off exogenous immune suppression with full donor chimerism, full T cell reconstitution, and recovering B cell reconstitution post-rituximab. These cases signal the possibility of a *CD3D* founder variant among Cabo Verdean populations, for which further prevalence studies are warranted. If increased allele frequency is found, it would be appropriate to evaluate gene editing approaches as a potential alternative to stem cell transplant, especially for this SCID variant believed to require more intensive conditioning relative to other forms of SCID.

Conflict of Interest: S. Prockop receives support for the conduct of clinical trials through Boston Children's Hospital from Pierre Fabre and Cabaletta. Inventor of IP related to third-party VST program with all rights assigned to MSKCC. Consulting Atara Biotherapeutics, Ensoma, HEOM, Pierre Fabre. DSMB Stanford University and NYBC. Equity share Regatta Biotherapy (a non-excluded organization).

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A Diagnostic Dilemma in a Lymphopenic Infant: Congenital Cytomegalovirus Infection vs. Primary Immunodeficiency

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Introduction: Cytomegalovirus (CMV) infection and severe combined immunodeficiency (SCID) can both present with T cell lymphopenia in infancy complicating early diagnosis. We present a unique case of profound lymphopenia in a newborn initially attributed to CMV infection, later found to be a novel RAG–associated SCID based on evolving immunologic and genetic findings.

Case Description: A full-term female infant was identified on Florida newborn screening (NBS) to have low T cell receptor excision circles (142 copies/μL) on day of life 2. Flow cytometry at 2 weeks of age confirmed profound T cell lymphopenia (CD3 122 cells/μL; CD45RO+ 20%) with low CD4 and CD8 counts. Notably, B cells, natural killer (NK) cells, and immunoglobulin (IgG, IgA, IgM) levels were within normal limits, contributing to a T-B+NK+ phenotype. Genetic studies with INVITAE SCID and combined immunodeficiency (CID)

gene panels were negative. Chromosomal microarray detected a duplication at 15q13.1-q13.2 classified as a variant of uncertain significance (VUS), prompting whole-exome sequencing (WES), which was negative. At 1 month of age, she was admitted with fever and found to have CMV viremia (141,000 IU/mL). Brain imaging, ophthalmologic exam, and hearing screen showed no signs of congenital CMV. Valganciclovir was initiated; however, 2 weeks later, she required admission for intravenous ganciclovir induction following discovery of worsening titers (315,000 IU/mL). CMV genotyping demonstrated no UL97, UL54, or UL56 mutations. Lymphocyte proliferation testing demonstrated normal responses to anti-CD3 alone and anti-CD3 with IL-2 but decreased proliferation to anti-CD3 with anti-CD28 costimulation. CD3 counts improved over time (1,081 cells/μL at 1 month; 1,292 cells/μL at 2 months; 1,313 cells/μL at 3 months), along with decreasing viremia (1,790 IU/mL), suggesting CMV-related immune suppression. However, T cell abnormalities persisted. Despite increasing CD3, CD4 counts remained low (~200 cells/μL). External evaluation at the National Institutes of Health (NIH) demonstrated a block in T cell development with absence of $CD3^+$ $TCR\alpha\beta^+$ cells and present but aberrant $CD4^+CD8^+$ double-positive cells, which lack CD3 expression and the typical $CD1a^{++}$ $CD7^{dim}$ phenotype. External WES at NIH identified a heterozygous RAG1 variant (NM_000448 c.908C>A; p.P303H), raising concern for a novel form of autosomal recessive RAG-associated SCID. At 9 months of treatment with valganciclovir, CMV viral load is still present at 595 IU/mL, and the patient is currently admitted for repeat ganciclovir induction, bone marrow biopsy, TCR repertoire analysis, RAG protein analysis, and assessment for future hematopoietic stem cell transplantation. Of note, the patient's clinical course has been complicated by Salmonella and Norovirus enteritis, multiple central line–associated bloodstream infections (CLABSIs) with *Staphylococcus epidermidis*, *Serratia marcescens*, *Bacillus cereus*, and *Salmonella enterica*, recurrent candidal skin infections, thrush, and an undifferentiated dermatitis, further supporting a diagnosis of primary immunodeficiency. She is otherwise currently on prophylaxis with immunoglobulin replacement therapy, azithromycin, and trimethoprim-sulfamethoxazole.

Discussion: This case illustrates the diagnostic complexity in distinguishing CMV immune suppression from primary immunodeficiency and highlights the importance of longitudinal immune assessment. RAG defects impair V(D)J recombination, resulting in decreased T cell diversity and immune dysregulation. While congenital CMV can disrupt immune function, the persistence of T cell abnormalities despite viral control supports an underlying primary immunodeficiency.

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Steroid-Refractory Grade 4 Gut Graft-vs.-Host Disease Responding to Multimodal Anti-GVHD Medications in a 3-Year-Old with Combined Immunodeficiency: A Story of Perseverance and Exceptional Supportive/Nursing Care

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Introduction: Grade 4 steroid refractory gut graft-versus-host disease (GVHD) is associated with significant mortality and morbidity. We successfully managed a patient with multiple anti-GVHD medications, ultimately achieving a positive response with combination of ruxolitinib, vedolizumab, and supportive care. Effective nursing care played a crucial role, providing the necessary time for these medications to take effect.

Case: A 3-year-old girl with combined immunodeficiency presented with severe *Pneumocystis jirovecii* pneumonia, eczema, failure to thrive, recurrent respiratory viral infections, and CMV viremia and colitis at 12 months. Immune investigations revealed hypogammaglobulinemia. Definitive genetic is testing still ongoing. Due to the absence of a matched sibling donor, she underwent an unrelated (9/10) peripheral blood stem cell transplant. The conditioning regimen included treosulfan, fludarabine, and cyclophosphamide, with GVHD prophylaxis involving antithymocyte globulin (ATG), methotrexate, and tacrolimus. On Day +12, she experienced engraftment syndrome, presenting with fever, rash, and increased oxygen requirement, which was managed with three days of methylprednisolone. Successful engraftment occurred on Day +17. However, by Day +21, she developed diarrhea, escalating to grade 4 gut GVHD within 72 hours. Her stool output peaked at approximately 4 liters per day, including blood, necessitating three daily infusions of albumin (0.5g/kg) to maintain serum albumin levels above 20 g/L. Despite initiating standard treatment with methylprednisone at 2 mg/kg/day, there was no response by day five. Therefore, multiple anti-GVHD agents were administered, including infliximab, etanercept, basiliximab, alpha-1 antitrypsin, ATG, ruxolitinib, and vedolizumab. Throughout 8-10 weeks, she received comprehensive care, which included fluid and electrolyte management, transfusion support, opioids for pain management, total parenteral nutrition, and exemplary supportive

and nursing care. Remarkably, she did not develop sepsis despite being on immunosuppression, nor did she have bed sores or perianal abscesses. During this period, she experienced reactivation of both EBV and CMV, requiring treatment with rituximab and ganciclovir. Ultimately, her condition began to improve, and her stool output decreased. By Day +180, she was discharged from the hospital. Immunosuppression was fully discontinued by Day +270. One year post-transplant, she demonstrated full donor CD3/CD33 chimerism and 50% CD19 donor chimerism. She is no longer on intravenous immunoglobulin (IVIG), has begun her immunizations, and shows no signs of chronic GVHD.

Conclusion: Despite the high mortality associated with grade 4 gut GVHD, dedicated perseverance, relentless persistence, and exceptional nursing care can lead to positive outcomes, providing sufficient time for immunosuppressive medications to take effect.

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Rare Clinical Presentation of Incomplete X-Linked Chronic Granulomatous Disease: A Case Report

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A 9-month-old male initially presented with persistent left submandibular abscess, resistant to multiple courses of antibiotics, and required complete excision of affected tissue. No organisms were identified. At 10 months of age, the patient presented to their local emergency department and was admitted into the hospital with persistent high fevers of unknown etiology and concerns for antibiotic associated diarrhea. Shortly after admission, patient was transferred to the pediatric intensive care unit (PICU) for concerns of an acute abdomen with septic shock, in the setting of infectious colitis versus gastroenteritis. Gastrointestinal workup included an esophagogastroduodenoscopy/colonoscopy, which revealed a grossly abnormal colon in addition to small-bowel disease concerning for chronic granulomatous disease (CGD). Initial dihydrorhodamine (DHR) test demonstrated absent neutrophil oxidative bursts, suggestive for X-linked complete CGD. Genetic testing confirmed CYBB sequencing abnormalities with a mutation at c.389G.C(p.Arg130Pro). With persistent fevers, he developed a hyperinflammatory state consistent with CGD-related hemophagocytic lymphohistiocytosis (HLH) and he was treated with high-dose intravenous immunoglobulin (IVIg) and steroids. McLeod phenotype was sent and negative. The patient proceeded with a mismatched unrelated (DRB1) bone marrow transplant (BMT) after reduced-intensity conditioning. Although Day +30 chimerisms were 1.5% donor T cell and 93% donor CD33, by Day +60, he developed secondary graft failure with autologous immune reconstitution and had 0% donor chimerisms across all cell lines. A decision was made to plan for a second transplant, approximately one year after his first transplant. In preparation for a repeat BMT, DHR was sent demonstrating 30% function. Further confirmation testing was sent through the National Institutes of Health (NIH), which confirmed true neutrophil oxidative burst, and a second transplant was not needed as he developed no infectious or immune complications related to his graft-versus-host disease (GvHD). This case illustrates that in periods of neutrophil exhaustion, there may be additional loss of neutrophil function in patients with incomplete X-linked CGD. As a result, routine screening for incomplete X-linked CGD should be considered in all patients with X-linked CGD.

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IRF8-Associated Primary Immune Regulatory Disorder Complicated by Progressive Liver Failure: Implications for Natural History and Transplant Decision-Making

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Background: Primary immune regulatory disorders (PIRDs) caused by interferon regulatory factor 8 (*IRF8*) gene defects are rare, with limited cases reported worldwide. *IRF8* is essential for myeloid and lymphoid development, and its deficiency can lead to immune

dysregulation manifested by infections, cytopenias, lymphoproliferation, and organ injury. The natural history of *IRF8*-associated disease remains poorly characterized.

Clinical Case: A 25-year-old man presented for evaluation of immune deficiency and workup of an IRF variant of uncertain significance [c.1279dupT] in the context of liver failure. His disease course began in early childhood and was characterized by chronic lung disease, immune-mediated cytopenias with an autoimmune lymphoproliferative syndrome (ALPS)-like phenotype, and recurrent severe infections, including sepsis, pneumonias, and primary Epstein-Barr virus (EBV) lymphoproliferative disease controlled by periodic rituximab treatment. At age 4, he was diagnosed with combined immunodeficiency with lymphoproliferation and treated with immunoglobulin replacement therapy. At age 11, he underwent splenectomy for refractory thrombocytopenia. His subsequent course was complicated by portal vein thrombosis requiring emergent transjugular intrahepatic portosystemic shunt (TIPS) placement; the shunt later occluded, with progression to cavernous transformation and portal biliopathy. At age 20, his case was further complicated by progressive cholestatic liver dysfunction of unclear etiology. Post-splenectomy sequelae, chronic *Cryptosporidium* infection, and immune dysregulation were all considered as potential causes. At 25 years old, he developed end-stage liver disease characterized by severe hyperbilirubinemia. Biopsies revealed biliopathy consistent with sclerosing cholangitis, and his immune workup revealed combined immune defect with reduced natural killer (NK) cell cytotoxicity shown on ^{51}Cr release assay. Deceased donor liver transplantation (DDLT) was performed with the goal of stabilizing hepatic function to permit subsequent curative hematopoietic stem cell transplantation (HSCT). His post-transplant course was complicated by persistent graft dysfunction and biliary disease, necessitating repeat liver transplantation with a living sibling donor six months later. After the second transplant, he experienced significant infectious burden, including ongoing chronic infection with norovirus and COVID-19, *Cryptosporidium* infection, vancomycin-resistant enterococci (VRE) bacteremia, and *Candida glabrata* fungemia. Two months later, he proceeded to HSCT. His clinical course rapidly deteriorated with severe colitis, progressive hepatic and renal failure, and septic shock. Despite transient improvement with escalation of antimicrobial therapy, he developed refractory shock and respiratory failure, failed to engraft, and died approximately one month after transplant at age 26.

Discussion: Other reported *IRF8* cases reveal similar infectious and lymphoproliferative manifestations, and several patients have been successfully treated with reduced-intensity HSCT. However, none of these patients have exhibited liver disease of comparable severity.

Conclusion: This case expands the phenotypic spectrum of *IRF8*-associated PIRDs to include progressive liver failure and highlights the need for improved understanding of immune-mediated organ dysfunction in rare PIRD conditions. It also aligns with existing reports of increased morbidity and mortality among patients with inborn errors of immunity who undergo splenectomy. Early recognition of non-hematologic complications and further study of disease natural history are critical to optimizing timing and sequencing of solid organ and hematopoietic transplantation in this population.

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Evolution of Diagnosis and Management of Omenn Syndrome Using Multiple Immunosuppressive Strategies: A Case Series

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Rationale: Omenn syndrome represents a therapeutic challenge as a state of florid immune dysregulation born out of autoreactive oligoclonal T cells due to hypomorphic variants in genes associated with severe combined immunodeficiency (SCID). In the era of newborn screening, patients with Omenn SCID are often identified earlier in the disease course with a more subtle clinical presentation than is classically taught. With appropriate screening and subsequent management, outcomes of Omenn syndrome may be improved.

Methods: We analyzed the patients diagnosed with Omenn syndrome at the Children's Hospital of Philadelphia from 2007 to 2025 (n = 7). Data collected included initial presenting signs and symptoms, laboratory features at diagnosis and over time, and management strategy.

Results: The patients in this series were diagnosed with Omenn syndrome at a median age of 9 days (interquartile range [IQR] 7-12) and were 57% female, and six had *RAG1*-associated SCID (86%). Frequent signs at diagnosis included rash (100%), lymphadenopathy (43%), and hepatomegaly and/or splenomegaly (43%). Common laboratory features at diagnosis were greater than 80% of CD4 T cells with memory phenotype (100%), eosinophilia (86%), elevated IgE (71%), abnormal T cell receptor excision circles (TREC; 100%), and oligoclonal T cells (14%, only 1 patient with T cell receptor vβ repertoire analysis pre-transplant). Maternal engraftment was negative in the six patients for whom it was tested; the only patient not tested was born in 2009. All patients were treated with systemic corticosteroids,

86% with tacrolimus, 29% with cyclosporine, and 29% with antithymocyte globulin. Median age at transplant was 90 days (IQR 73-94). The median time from Omenn syndrome presentation to transplant was 70 days (IQR 64-82).

Conclusion: We describe seven patients with Omenn syndrome diagnosed and managed early in life at a single center. Patients demonstrated the characteristic clinical and laboratory findings consistent with Omenn syndrome, with all presenting with a rash and nearly half with lymphadenopathy and hepatomegaly and/or splenomegaly. Most patients had eosinophilia and elevated IgE levels, and all patients had abnormal TREC results and greater than 80% of CD4 T cells with memory phenotype. The majority were successfully managed with systemic corticosteroids and tacrolimus alone, without the need for cyclosporine or antithymocyte globulin. Early diagnosis of Omenn syndrome facilitated timely initiation of targeted therapy and progression to hematopoietic stem cell transplantation within the first three months of life.

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Relevance of a Computational Deep-Dive to Characterize the Molecular Biology of a Novel Cd40l Variant

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CD40L deficiency is a well-described inborn error of immunity (IEI). The disease is characterized immunologically by impaired class-switching and T cell costimulation. A male infant presented at 8 months of age with recurrent cellulitis. At 11 months, he was admitted for prolonged fever and leukopenia with vomiting and watery diarrhea, periorbital edema, back abscess, increased sIL2R at 50,598 pg/mL (<14,491), and normal CXCL9 at 22 pg/mL with mild to modest increases in IL-18 at 694 pg/mL (<185.4), IL-6 at 226.4 pg/mL (<10), serum amyloid A (SAA) at 1,413 mcg/mL (<373.8), IL-8 at 196 (<10), and IL-10 at 101pg/mL (<10). His IgG and IgA were low at <30 and <10 mg/dL, respectively. He developed *Pseudomonas* sepsis, palatal ulceration, jejunal perforation requiring repair, *Candida* peritonitis, persistent neutropenia, CMV, and *Parechovirus* viremia. Along with the hypogammaglobulinemia, class-switched memory B cells were decreased for age. Flow cytometry was performed for CD40L expression on activated CD4+ T cells along with functional evaluation of ligand binding to a soluble form of the receptor (CD40), using CD40-muIg. There was significantly diminished CD40L expression with essentially absent binding to the receptor. Genetic testing confirmed a diagnosis of CD40L deficiency due to a hemizygous variant in *CD40LG*, c.674T>C; p.Leu225Ser (NM_000074.2). We had previously evaluated a 4-year-old male with intermittent, non-bloody diarrhea, pneumonia, hypogammaglobulinemia, and significant neutropenia, and identified this novel variant, now also observed in this infant. We utilized advanced computational tools to evaluate the molecular impact of this variant on the structure and function of CD40L. The Leu225Ser variant is located within the trimerization interface of CD40L. Molecular modeling, mutagenesis alanine scanning, and molecular dynamic simulations revealed that the variant causes loss of critical intramolecular time-dependent interactions between hydrophobic molecules that would typically facilitate trimerization of wild-type CD40L for optimal interaction with the CD40 receptor. This analysis of the Leu225Ser variant revealed the molecular basis of the decreased CD40L protein expression (loss of contact to form trimers) and impaired CD40 binding (loss of intramolecular bonds affecting folding and impaired interaction at the trimerization interface). The patient also had immune paralysis due to decreased MHC class II (HLA-DR) expression on CD14+ monocytes, a result of a compensatory anti-inflammatory response syndrome (CARS). Assessment of neutrophil activation and granule markers (CD66b, lactoferrin, myeloperoxidase [MPO], and elastase) revealed low-normal CD66b and lactoferrin with slightly increased MPO and elastase, suggesting a complex and dysfunctional neutrophil response rather than simple activation or deactivation. This phenotype is consistent with the known pathology of CD40L deficiency, in which neutrophils are defective in their ability to respond effectively to infection, leading to chronic inflammation and tissue damage despite persistent signs of granule release. Treatment with rIFNg has been shown to reverse neutrophil dysfunction in X-linked hyper-IgM syndrome (XHIGM) but also restore HLA-DR expression on monocytes and reverse immune paralysis. He is currently being evaluated for hematopoietic cell transplantation (HCT). This case exemplifies the relevance of utilizing a variety of strategies to evaluate novel variants in IEI genes. Further, molecular and computational studies permitted an improved understanding of the impact of the Leu225Ser variant on CD40L protein expression and function.