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ADVANCEMENTS IN ADA-SCID: A DETAILED COMPILATION WITH DIAGNOSTIC APPROACHES AND PROPOSITIONS OF NOVEL TREATMENT MODALITIES

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ABSTRACT: The aim of the study is to evaluate the prevalence and impact of advancements in the diagnosis and treatment of Adenosine Deaminase Severe Combined Immunodeficiency (ADA-SCID) and propose novel strategies for improved management and therapeutic outcomes. A comprehensive review was conducted according to PRISMA guidelines, focusing on advancements in ADA-SCID. Gene variant data were analysed using databases like dbSNP and ClinVar, with pathogenicity assessed using tools such as SIFT and PolyPhen. The methodology includes a comprehensive review of studies from 1970–2024 was performed, emphasizing diagnostics (e.g., TREC screening, genomic sequencing) and therapies (e.g., enzyme replacement therapy, HSCT, and gene therapy). The study highlighted the pathogenic variants of the ADA gene contributing to ADA-SCID, diagnostic challenges, and the associated vaccination risks. Current therapeutic approaches, including enzyme replacement therapy, hematopoietic stem cell transplantation, and gene therapy, were reviewed, emphasizing their benefits and limitations. Novel therapies, such as CRISPR-Cas9 base editing, in-utero stem cell transplantation, and iPSC-derived treatments, demonstrated promising potential for future management of ADA-SCID. The review consolidates insights into ADA-SCID diagnosis and therapeutic strategies, proposing innovative approaches to enhance patient outcomes. Emerging treatments like gene editing and stem cell advancements hold significant promise, necessitating further research to address existing gaps and optimize care for ADA-SCID patients.

INTRODUCTION: Primary Immunodeficiency Disorders (PIDs) constitute a group of conditions where one or more elements of the immune system function inadequately or are entirely absent, resulting in a broad spectrum of disorders. Affected individuals encounter distinct challenges related to immune system functioning, including heightened susceptibility to severe infections, autoimmune conditions, abnormal inflammation, and an increased risk of cancer.

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This group encompasses over 250 identified genetic disorders, with new ones regularly emerging [1]. Notably, Severe Combined Immunodeficiency (SCID) stands out as the most severe form, characterized by profound anomalies in both cellular and humoral immunity. It presents with stunted growth, and diarrhoea and fatal opportunistic infections, typically leading to death within the first two years of life [2].

The primary cause of SCID is gene mutation. Some of the common SCID-related genes include IL2RG, JAK3, IL7RA, PTPRC, CD3D, CD3E, CD3Z, CORO1A, DCLRE1C, PRKCD, AK2, ADA, RAG1, RAG2, XLF/NHEJ1, LIG4, PNP, and ZBTB24 [3]. One of the most prevalent forms of SCID is caused by gene variants resulting in deficiency of the enzyme adenosine deaminase (ADA) [4]. It is located on the chromosome 20 (20q13.12), The ADA gene was isolated in 1983. It codes for the enzyme adenosine deiminase [5, 6]. It is a key enzyme in the purine salvage pathway, catalysing the irreversible deamination of adenosine and 2′-deoxyadenosine. Therefore, deficiency of ADA enzyme results in the accumulation of these substrates both intra and extracellularly resulting in several immunodeficiencies. While ADA is distributed throughout the body, it is most active in specialized white blood cells known as lymphocytes [7]. Absence of this enzyme therefore primary impacts the lymphocytes ultimately resulting in the immunodeficiency condition known as the ADA-SCID. This deficiency syndrome poses a significant threat to paediatric patients, with estimated occurrences ranging from 1 in 200,000 to 1 in 1,000,000 births (small variation in the incidence ratio may be due to newborn screenings) [8]. A limitation of proper diagnostic methods and treatment options is a major concern which needs to be addressed as quickly as possible considering the severity of the disease.

The current review is an attempt to investigate ADA-SCID, emphasizing the associated gene, its specific mutations and pathogenic variants associated with it. Various diagnostic techniques currently available to detect the disease are also outlined, along with the few therapeutic approaches. The review highlights potential complications, particularly those related to vaccinations and underscores the importance of careful management protocol for the condition. It also explores current treatment options such as Enzyme Replacement Therapy (ERT), Hematopoietic Stem Cell Transplantation (HSCT), and Gene therapy, with an emphasis on the promising approach of gene therapy. Further, the review discusses emerging therapies and novel treatment possibilities for ADA-SCID patients.

METHODOLOGY: This comprehensive review was conducted according to a predetermined protocol aligned with the PRISMA guidelines, focusing on advancements in ADA-SCID diagnosis and treatment. The novel strategies to improve patient outcomes are represented in **Fig. 1**. The study utilized data sourced from articles published in indexed journals up to the most recent year. Insights into various aspects of the review were drawn from pertinent findings of case studies. Gene variant data were sourced from databases like dbSNP, ClinVar, OMIM, UniProt/Swiss-Prot, ClinGen, and Ensembl. Pathogenicity was assessed using functional prediction and annotation tools, including SIFT, PolyPhen, REVEL, and MetaLR.

Objectives: To evaluate the prevalence and impact of diagnostic and therapeutic advancements in ADA-SCID. To propose innovative strategies to enhance the management and treatment of ADA-SCID.

Search Strategy: The systematic review utilized reputable databases, including PubMed and Google Scholar, for studies published from 1970 to 2024. Additional manual searches and cross-referencing ensured comprehensive literature exploration.

Search Methodology:

- Both free-text and Medical Subject Headings (MeSH) terms were used to capture relevant literature.
- Focused solely on articles published in English.

Research Themes: The search strategy was structured around the following themes:

a) **Disease and Pathophysiology:** Terms included "ADA-SCID," "Primary Immunodeficiency Disorders," and "Adenosine Deaminase Deficiency."

b) **Diagnosis:** Terms included "TREC screening," "Genetic Sequencing," and "Diagnostic Techniques."

c) **Therapy:** Terms like "Gene Therapy," "Hematopoietic Stem Cell Transplantation (HSCT)," and "Enzyme Replacement Therapy (ERT)" were prioritized.

The Boolean operator “AND” was employed to refine the search results.

Manual Search: A manual search was performed in leading immunology and genetics journals, focusing on publications from 2000 onward. Reference lists of all relevant articles were reviewed to identify additional studies not indexed in electronic databases.

Inclusion Criteria:

a) Studies focusing on ADA-SCID, including clinical trials, case reports, and reviews.

b) Articles discussing advancements in diagnostics (e.g., genomic sequencing, TREC screening) and therapies (e.g., ERT, HSCT, and gene therapy).

c) Study populations involving patients with ADA-SCID.

Exclusion Criteria:

a) Articles in languages other than English.

b) Studies involving conditions unrelated to ADA-SCID.

c) Articles requiring subscription or with incomplete data.

d) Studies on other forms of SCID that do not involve ADA deficiency.

Data Collection and Analysis:

Quality Assessment: The study synthesized evidence on ADA-SCID diagnostics and therapies, following PRISMA guidelines. Three reviewers analysed articles, integrating findings on genetic advancements, CRISPR, and iPSC therapies to bridge management gaps and propose innovative pathways for future ADA-SCID research.

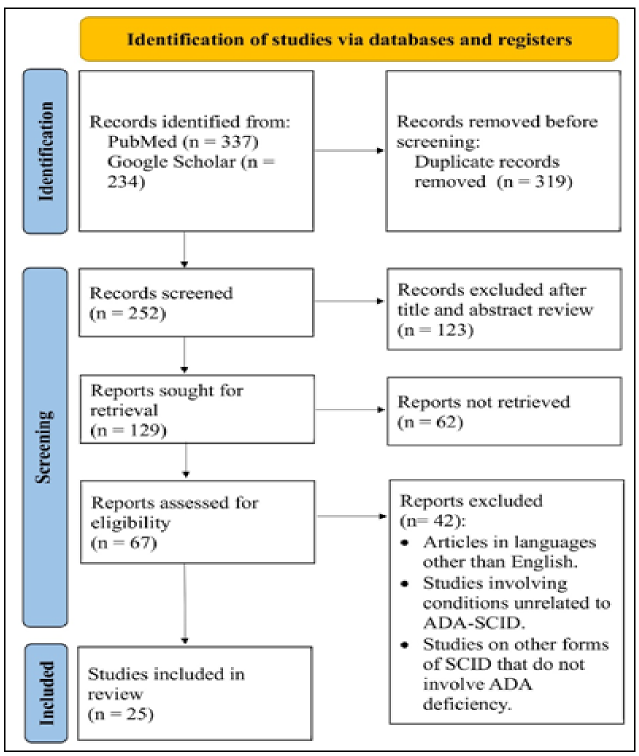

FIG. 1: FLOWCHART ILLUSTRATING THE SELECTION PROCESS OF STUDIES FOR DIAGNOSTIC METHODS AND NOVEL TREATMENT APPROACHES

Gene Variants Associated with the Development of ADA-SCID: Structural and functional characteristics of ADA gene: First isolated and characterized in 1983, the human ADA gene is located on chromosome 20 at the locus 20q13.12. The gene spans approximately 32 kilobases (kb) and consists of 12 exons. Notably, the gene's promoter region is about 135 bases long and lacks the typical eukaryotic promoter specific "TATA" and "CAAT" sequences. The ADA gene is characterized by a high G/C content of around 82% and consists of three inverted repeats along with two direct repeats of 10 and 16 base pairs that enable in the formation of cruciform structures which are crucial for functional activation of the gene including its replication, recombination, transcription regulation of gene expression, and the organization of the genome as a whole [9, 10, 52]. Functionally, ADA, encodes the adenosine deaminase, an enzyme crucial for catalysing the irreversible deamination of adenosine and deoxyadenosine in the purine catabolic pathway which is important for the formation of uric acid and deoxyadenosine triphosphate (dATP) in the purine salvage pathway were represented in **Fig. 2** [11, 52].

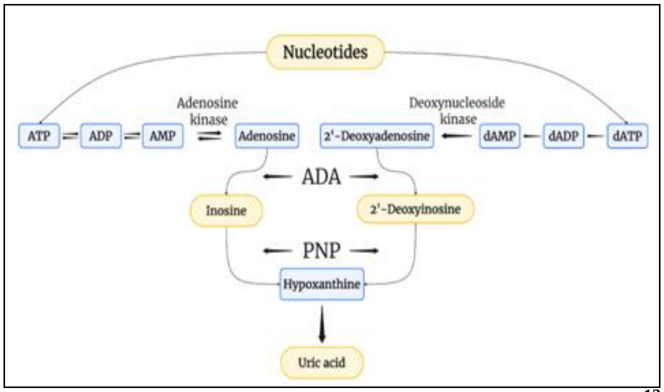

FIG. 2: METABOLIC PATHWAY OF ADA ENZYME [12]

ADA enzyme plays a crucial role in the purine salvage pathway by irreversibly deaminating adenosine and 2′-deoxyadenosine, converting them into inosine and 2′-deoxyinosine, respectively. Adenosine mainly comes from intracellular ATP breakdown, RNA degradation, or external uptake through widely expressed nucleoside transporters. In contrast, 2′-deoxyadenosine primarily stems from DNA degradation and is mainly processed by ADA [12].

Following further conversions, inosine nucleosides are transformed into hypoxanthine, which can either irreversibly convert to uric acid or be reutilized in other mononucleotides. In the absence of ADA, alternative pathways, known as "bypass" pathways, maintain normal levels of ADA's breakdown products in individuals with ADA-SCID. Conversely, elevated levels of ADA substrates, such as adenosine and 2′-deoxyadenosine, not only accumulate in extracellular fluids but also divert into additional pathways that are typically underutilized. This overflow contributes to the disease's pathogenicity [12].

ADA SCID Specific Gene Mutations: Numerous ADA gene mutations were identified in ADA-SCID affected children aged 2 months to 2 years [13]. A mutation that causes ADA-SCID includes Missense Variant, Intron Variant, Splice Donor Variant, Initiator Codon Variant and more, were represented in **Table 1**.

Consequences of Mutations in ADA-SCID: The mutations in the ADA gene lead to a sequence of events for the development of disease were represented in **Fig. 3**.

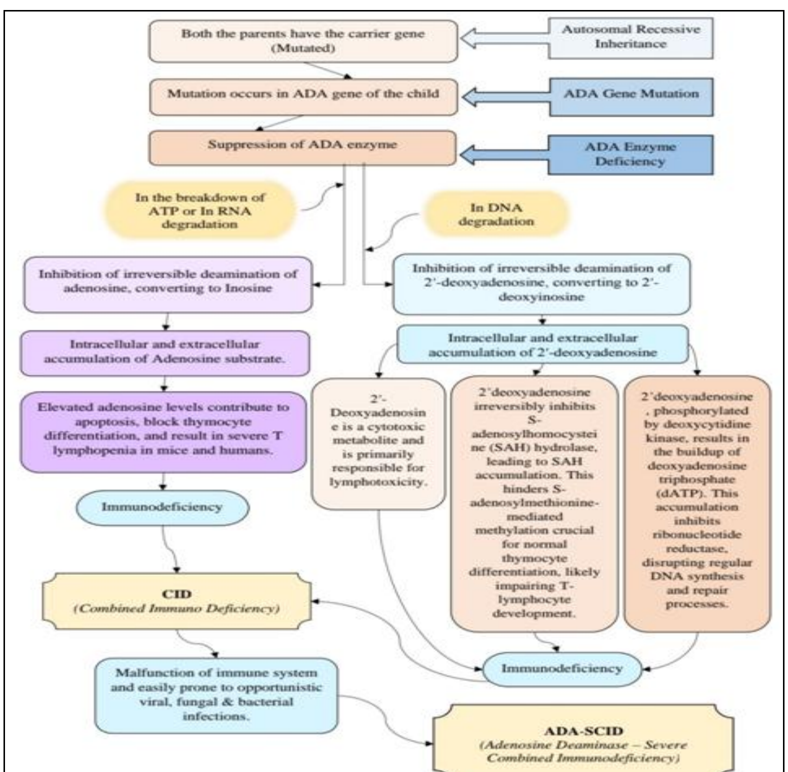

FIG. 3: FLOW DIAGRAM DESCRIBING DEVELOPMENT OF ADA-SCID INITIATING FROM MUTATION [12, 14, 15, 16]

Pathogenic Gene Variants of ADA SCID: Pathogenic Mutations are responsible for the acute clinical condition, ADA-SCID. With the advent of high throughput technologies and Next-generation Sequencing, it is possible to know gene variants that have pathogenic effects in ADA deficient individuals [17].

Not all ADA gene variants exhibit pathogenic effects. It is identified that single nucleotide polymorphisms (SNPs) associated with the ADA gene from the CliniVar database, which consolidates a collection that is publicly accessible for research and analysis. Details regarding these variants are collected from dbsnp, CliniVar, OMIM, UniProt/Swiss-Prot, ClinGen, and Ensembl.

Alterations in the ADA gene result in SNPs, leading to changes in the amino acid residue, ultimately giving rise to mutant enzymes. In the present study, the pathogenicity of these variants is assessed using functional prediction and annotation tools such as SIFT, Polyphen, Revel, and MetaLR.

Sorting Intolerant from Tolerant (SIFT): The score can range from 0 to 1, wherein values below 0.05 are considered deleterious [18].

Polymorphism Phenotyping (PolyPhen-2): The score can range from 0 to 1, wherein values about 0.5 are interpreted as deleterious and values below 0.5 is considered non-pathogenic [18].

Rare Exome Variant Ensemble Learner (REVEL): The REVEL score for an individual missense variant can range from 0 to 1, with higher scores reflecting the greater likelihood that the variant is disease-causing [19].

MetaLR: MetaLR is a logistic regression (LR) based ensemble prediction score that integrates 10 scores (SIFT, PolyPhen-2 HDIV, PolyPhen-2 HVAR, GERP++, Mutation Taster, Mutation Assessor, FATHMM, LRT, SiPhy, PhyloP) and considers the maximum frequency observed in the 1000 genomes populations. The score varies from 0 to 1, with higher values indicating a higher likelihood of being deleterious [18].

TABLE 1: LIST OF PATHOGENIC ADA GENE VARIANTS CAUSING SCID. ABBREVIATIONS: PROTEIN CHANGE: R – ARGININE; Q – GLUTAMINE; G – GLYCINE; S – SERINE; H – HISTIDINE; L/LEU – LEUCINE; A – ALANINE; V/VAL – VALINE; P – PROLINE; W – TRYPTOPHAN; C/CYS – CYSTEINE; M – METHIONINE; TYR – TYROSINE; D – ASPARTIC ACID; CHR – CHROMOSOME. REFERENCE ALLELE/VARIANT ALLELE: ADENINE (A); CYTOSINE (C); GUANINE (G); THYMINE (T)

S. no.	Variants	Protein change	Consequence	Reference Allele/Variant allele	Clinical significance	Sift	Polyphen	Revel	MetaLR	Genomic position
1	rs121908717	R101W	Missense Variant	G>A / G>C	Pathogenic	0	1	0.939	0.961	chr20:44626517
2	rs121908714	R101Q, G5S	Missense Variant	C>A / C>G / C>T	Pathogenic	0	1	0.947	0.967	chr20:44626516
3	rs121908716	R211H, R76H	Missense Variant	C>T	Pathogenic	0	0.873	0.955	0.938	chr20:44623053
4	rs199422327	L304R, L280R, L169R	Missense Variant	A>C	Pathogenic	0	0.78	0.962	0.963	chr20:44621082
5	rs121908715	A329V, A305V, A194V	Missense Variant	G>A	Pathogenic	0	0.993	0.925	0.949	chr20:44620391
6	rs121908739	L107P, W11R	Missense Variant	A>G	Pathogenic	0	0.996	0.924	0.928	chr20:44626498
7	rs121908723	G216R, G81R	Missense Variant	C>T	Pathogenic	0	0.995	0.94	0.981	chr20:44623039
8	rs121908735	R156C	Missense Variant	G>A	Pathogenic	0	0.995	0.937	0.936	chr20:44625581
9	rs121908721	S291L, S267L, S156L	Missense Variant	G>A / G>C	Pathogenic	0	0.977	0.964	0.953	chr20:44621121
10	rs199422328	G74V	Missense Variant	C>A	Pathogenic	0	0.999	0.91	0.921	chr20:44626597

11	rs267606634	L106V; LEU106VAL	Initiator Codon Variant	T>A / T>C	Pathogenic	0	1	0.931	0.956	chr20:44626528
12	rs267606635	M1V; TYR97CYS	Missense Variant	G>C	Pathogenic	0	0.658	0.714	0.849	chr20:44626502
13	rs121908722	R156H	Missense Variant	C>A / C>G / C>T	Pathogenic	0	0.989	0.942	0.946	chr20:44625580
14	rs121908725	H15D	Missense Variant	G>C	Pathogenic	0	1	0.962	0.993	chr20:44636279
15	rs121908731	V129M	Missense Variant	C>A / C>T	Pathogenic	0	0.998	0.942	0.96	chr20:44625662
Ref.	11, 17, 21	23	24	24	23	20	22	22	22	24

Clinical Presentations of SCID: Clinical presentations of ADA vary with respect to age. Infants with severe combined immunodeficiency (SCID) phenotype fail to thrive due to the absence of lymphoid tissue, leading to susceptibility to opportunistic infections. They may present with symptoms such as persistent diarrhoea, dermatitis, and recurrent pneumonia. In childhood and adulthood, individuals with combined immunodeficiency disorder (CID) may experience conditions like frequent otitis media, sinusitis, upper respiratory infections, chronic pulmonary insufficiency, allergies, or autoimmune disorders[70, 71].

Cellular abnormalities include lymphopenia and depletion of T-, B-, and NK cells. Additionally, there are typically low levels of immunoglobulins, increased release of deoxyadenosine triphosphate (dATP), reduced activity of S-adenosylhomocysteine hydrolase (SAHase) in erythrocytes, and elevated levels of adenosine in urine and dried blood spot extracts, which are clinically significant [25, 36].

Vaccinations and Scid-Associated Infections:

Caution with Vaccination in SCID: The risk of vaccination in Severe Combined Immuno-deficiency (SCID) is a critical consideration in the healthcare management of individuals with SCID. While vaccinations are essential for preventing many diseases, they can pose significant risks to SCID patients due to their compromised immune systems. The various vaccination risks include:

a) **Contraindication of Live Vaccines:** Live vaccines, such as the rotavirus vaccine, pose a significant risk for undiagnosed SCID patients, potentially causing untreatable diarrhoea [35, 36].

b) **BCG Vaccine and Risks:** SCID infants are at increased risk of disseminated BCG infection. Monitoring is crucial to mitigate these risks [35, 36].

c) **Breastfeeding Considerations and CMV (Cytomegalovirus):** Before considering breastfeeding, evaluate maternal CMV serological status. Breastfeeding is discouraged if the mother is CMV seropositive and the infant is CMV PCR negative [35, 36]

d) **BCG-Related Issues:** BCG vaccination can lead to site ulceration and disseminated BCGosis. The absence of microbiological confirmation has impacted the rates of these complications [35, 36].

e) **Vaccine-Associated Paralytic Poliovirus:** A child with a RAG1 defect in Mumbai presented with persistent diarrhoea, developmental delay, and hypotonia, highlighting the risks of vaccine-associated paralytic poliovirus [35, 36].

Diverse Infectious Challenges in Severe Combined Immunodeficiency: Individuals with SCID face an extensive and intricate spectrum of infectious challenges, ranging from bacterial and viral pathogens to fungal and parasitic invaders. Key observations include:

a) **Opportunistic Infections:** Most SCID patients present with opportunistic infections, including pneumonia (82%), diarrhoea (43.7%), oral thrush (18.4%), BCG site ulceration (17%), otitis media (12.6%), and meningitis (4%) [36, 37].

b) **Blood Culture-Proven Septicemia:** Common bacterial isolates in septicemia cases include

Candida sp., *Staphylococcus* sp., *Escherichia coli*, *Acinetobacter* sp., *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Enterococcus* sp., *Enterobacter* sp., and *Streptococcus* sp. [36, 37].

c) **Respiratory Tract Bacterial Infections:** Isolates include *Mycobacterium bovis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *M. tuberculosis*, *Escherichia coli*, and *Staphylococcus aureus*. SCID patients are at constant risk of recurrent infections with encapsulated bacteria [36, 37].

d) **Renal System:** Renal abnormalities in ADA deficiency, such as nephrotic syndrome, have been reported. Renal involvement is also noted in Omenn syndrome (OS), including diffuse mesangial sclerosis [36, 37].

e) **Viruses:** SCID patients are prone to disseminated CMV infection, which can cause CMV retinitis and intestinal lymphangiectasia. Adenovirus can lead to viral pneumonia, bronchiolitis, hepatitis, and gastroenteritis, with potentially fatal outcomes. The rotavirus vaccine is associated with severe diarrhoea and should be avoided. Epstein-Barr virus increases the risk of reactivation, herpes zoster, retinal necrosis, and death. Parvovirus-B19 also poses similar risks [36, 37].

Diagnosis Techniques: The diagnosis of ADA deficiency in neonates with depleted T-B-NK- cells and reduced TRECs is crucial. It is diagnosed by ADA activity below 1% in hemolysates or DBS extracts, confirmed by biallelic pathogenic ADA variants [25].

In 2003, the U.S. Secretary's Advisory Committee on Heritable Disorders in Newborns and Children (SACHDNC) established criteria for routine neonatal screening, including [26, 27]:

a. The condition must be medically significant.

b. Pilot data from population-based screening is required.

c. The disorder's range must be well-documented in medical literature.

d. The screening test must be reliable, with a low false-negative rate.

e. For broad-spectrum disorders, the most treatable population should be identifiable.

f. Treatment must be effective if administered before symptoms appear.

The existing and alternative diagnostic techniques for ADA-SCID are crucial for its treatment and are detailed in **Table 2** for further discussion.

TABLE 2: EXISTING AND ALTERNATIVE DIAGNOSTIC TECHNIQUES OF ADA-SCID

Authors	Method	Description	Advantage	Challenges	Reference
		Existing Techniques			
Buckley (2012) Cassani et al. (2008)	TREC, CBC, & Flow Cytometry Screening Method	Detects Severe Combined Immunodeficiency (SCID) by identifying absent T-cell receptor excision circles (TRECs) and lymphopenia using PCR, CBC, and flow cytometry	Reliable for detecting SCID-related lymphopenia in newborns	Low TREC levels may indicate other conditions; positive results require confirmatory tests	27, 73
Moore and Meuwissen (1974)	Filter Paper ADA Screening Method	Blood sample placed on filter paper with pH indicators to detect ADA presence through ammonia release	Cost-effective and reliable for ADA detection	Considered outdated for ADA-SCID detection	28
La Marca et al. (2013)	Dried Blood Spot (DBS) Sample method	Extraction of adenosine and its metabolites from a dried blood spot sample using mass spectrometry with Multiple Reaction Monitoring (MRM)	Convenient, cost-effective, and simplifies therapy monitoring for ADA-SCID	Requires specialized mass spectrometry equipment	29
Ziegler et al. (1981)	Amniocentesis for Intrauterine Diagnosis	Amniocentesis to measure ADA levels in amniotic fluid, used to confirm ADA deficiency in a fetus	Reliable prenatal diagnosis for ADA-SCID	Invasive procedure; limited use and requires confirmation with	33

				postnatal tests	
Aitken et al. (1986)	Fetal blood sampling and fetoscopy	Invasive techniques to obtain fetal blood for direct metabolic analysis	Allows direct analysis of ADA deficiency when a metabolic error is suspected	Invasive procedure requiring specialized expertise	38
Śmigiel et al. (2020)	Next-Generation Sequencing (NGS), Whole Genome Sequencing (WGS), and Whole Exome Sequencing (WES)	NGS targets specific disease-related genes, while WGS/WES comprehensively assess genetic variants in both coding and non-coding regions for clinical and research purposes	NGS enables targeted analysis, while WGS/WES offer comprehensive genetic insights, improving diagnostics and research in genetic disorders like ADA-SCID.	These methods are time-intensive, resource-heavy, and technically complex, limiting accessibility.	40
Alternative Techniques					
Azzari et al. (2011) Kahwash et al. (2021)	Tandem Mass Spectrometry for Neonatal ADA-SCID Diagnosis	Mass spectrometry used to diagnose ADA-SCID in newborns by analysing adenosine and 29-deoxyadenosine	Lower cost compared to TREC tests, integrates seamlessly into newborn screening programs	Limited availability of mass spectrometry equipment, with a risk of false-negative results in rare cases	32, 31
Linch et al. (1984)	Comprehensive Fetal Testing for ADA Deficiency	Combines leucocyte phenotyping and purine pathway metabolism analysis on fetal blood samples, assessing ADA and purine nucleoside phosphorylase activity	Provides increased diagnostic confidence due to broader antibody range for leucocyte differentiation	Invasive technique requiring fetal blood sampling via fetoscopy; radiochemical enzyme assessment is needed	34
Monk and Kathuria (1977) Benson and Monk (1988)	Novel Techniques for Early Detection (Mouse Model)	Microassay method developed for detecting ADA deficiency in pre-embryos using blastomere or trophectoderm biopsy, tested on a mouse model of ADA deficiency	Enables early detection of ADA-SCID before implantation, reducing the risk of disease transmission	Still experimental and requires validation in humans; high technical complexity	41, 42

ADA SCID Therapies: Conventional and Evolving Interventions: Successful management of ADA-SCID, involves careful analysis of basic criteria underlying a successful therapy. Since, enzyme deficiency is the root cause of the syndrome there is an accumulation of toxic metabolites due to which there is an impact on different organ systems especially the immune system.

Replacing the deficient enzyme is the guiding principle for the detoxification of harmful metabolites which aids in immune recovery. Though the available enzyme therapy is proven to show marked immune recovery, the decision of correct order of treatment shall guide in treating ADA SCID patients with existing comorbidity while considering varied donor options. Currently available treatment options include:

Enzyme Replacement Therapy: Enzyme Replacement Therapy (ERT) with PEG-ADA, designated as an orphan drug for ADA deficiency, provides an alternative treatment approach for ADA SCID, though it is not curative like HSCT or gene therapy. It requires regular intramuscular administration but significantly improves metabolic and immunological parameters, enhancing patient well-being [75]. PEGylation, developed in the 1970s, involves attaching PEG to ADA, increasing molecular weight and circulation time while reducing immunogenicity and clearance. This modification extends the therapy's effectiveness and reduces the frequency of administration [43].

Prognosis for ERT: In a study involving patients undergoing enzyme replacement therapy (ERT), several key observations were noted:

Lymphocyte Reconstitution: Total lymphocyte counts generally increased or remained stable with elapegademase therapy compared to pegademase. By study end, patients showed a 1.2- to 2.1-fold increase in total lymphocytes, with higher CD3+, CD4+, and CD19+ counts in all six patients, and increased CD8+ counts in five out of six patients and four out of six patients experienced increased CD16+/56+ counts [44].

Immunogenicity: None developed neutralizing antibodies, though three of seven patients had transient, non-neutralizing anti-drug antibodies, and two had anti-PEG antibodies. These antibodies did not affect therapeutic outcomes [44, 75].

Safety: Mild to moderate adverse events (AEs) occurred, including injection-site pain and discomfort in two patients. One patient withdrew due to severe injection-site pain. Severe or serious AEs were mostly related to comorbidities, not elapegademase [44, 75].

Challenges in Enzyme Replacement Therapy: Despite recent advancements, few enzyme therapies are FDA and EMA-approved due to challenges like short *in-vivo* half-life, lack of tissue specificity, and immunogenicity. Enzymes can lose function quickly through interactions or degradation, and while fast clearance may benefit short-window treatments, metabolic deficiencies require solutions for rapid enzyme clearance. Enzymes' high catalytic activity can cause off-target effects and toxic side effects. Immune responses also reduce efficacy by producing anti-drug antibodies that alter enzyme activity or clearance. Factors influencing immune responses include genetic variations, age, and enzyme immunogenicity, potentially leading to autoimmune risks [45].

Hematopoietic Stem-Cell Transplantation (HSCT): Haematopoietic stem cell transplantation (HSCT) treats haematological conditions like leukaemia, lymphoma, multiple myeloma, and inherited or metabolic disorders. HSCT uses autologous or allogeneic HSCs sourced from bone marrow (BM), peripheral blood (PBSC), or cord blood, following a conditioning regimen of chemo- or radiotherapy and immunosuppressants [46, 49]. BM harvesting is performed under anaesthesia from the posterior iliac crests [46, 76]. Compared to PBSC, BM transplants result in lower graft-versus-host disease (GvHD) rates but slower neutrophil and platelet engraftment [46, 76].

Prognosis for Hematopoietic Stem-Cell Transplantation (HSCT): HSCT is a curative therapy for ADA deficiency with survival rates comparable to gene therapy (GT) and matched sibling/family donor (MSD/MFD) transplants. When HLA-matched siblings are unavailable, alternative donor HSCT should be considered, particularly if GT is not an option. Reduced-intensity chemotherapy and enzyme replacement therapy (ERT) show excellent survival rates, and conditioned transplants result in better long-term chimerism and reduced ERT dependence. Long-term morbidity, including autoimmunity and neurodevelopmental outcomes, requires further research [47]. MSD/MFD transplants have significantly higher survival rates, partly due to faster CD3+ cell recovery without serotherapy, aiding viral infection resolution [48, 49]. Matched unrelated donor (MUD) transplants show less favourable outcomes compared to MSD/MFD but outperform mismatched unrelated (MMUD)/ haploidentical (HAPLO) procedures. Advances in conditioning may improve MUD outcomes [48, 49]. Long-term immune reconstitution is robust across donor types, with near-normal recovery post-HSCT [48].

Limitations of HSCT: Complications following bone marrow transplantation are classified as acute or chronic, influenced by factors like patient age, baseline health, stem cell source, and conditioning regimen. Acute complications, occurring within 90 days, include myelosuppression (neutropenia, anemia, thrombocytopenia), sinusoidal obstruction syndrome (SOS), mucositis, acute graft-versus-host disease (GVHD), and infections. Chronic complications encompass chronic GVHD, encapsulated bacterial infections, and varicella-zoster virus reactivation [49].

- Sinusoidal Obstruction Syndrome (SOS) manifests within six weeks post-transplant with symptoms like hepatomegaly and jaundice, diagnosed by hyperbilirubinemia >2 mg/dL. Treatment options include ursodeoxycholic acid and defibrotide [49].

- Idiopathic Pneumonia Syndrome (IPS) occurs within 90 days; steroids are commonly used, though their efficacy is uncertain, and etanercept provides no additional benefits [49].

- Graft Rejection or Failure arises when bone marrow function does not return post-transplant, with higher HLA disparity increasing risk, particularly with cord blood and haploidentical donors [49].

- Graft Versus Host Disease (GVHD) typically develops within three months, with prophylaxis using calcineurin inhibitors and methotrexate. Chronic GVHD affects multiple organs over three months, requiring long-term treatment [49].

- Toxicity from the preparative regimen causes severe pancytopenia, raising infection risk, as chemotherapy destroys normal bone marrow. Recommended vaccinations include pneumococcus, tetanus, diphtheria, pertussis, Haemophilus influenzae, meningococcus, polio, Hepatitis B, influenza, measles, mumps, and rubella. Various prophylaxis regimens are guided by patient risk assessment tools [49].

Late Effects of Transplantation in Patients with SCID: According to a report from the Center for International Blood and Marrow Transplant Research, patients with SCID experience a considerable incidence (7%) of late deaths, defined as occurring more than two years after hematopoietic cell transplantation (HCT). In their study, the primary reasons for late mortality in SCID patients were infection, organ failure, and chronic GVHD [50].

Gene Therapy: Gene therapy involves introducing corrected genes into an individual's somatic cells to cure or alleviate genetic disorders. These lab-synthesized genes compensate for DNA abnormalities, modifying the DNA or RNA involved in protein synthesis to rectify the disorder [51, 77].

Autologous Hematopoietic Stem Cell Gene Therapy: Autologous gene therapy was first used to treat ADA deficiency, demonstrating safety and efficacy. Research using gamma-retrovirus vectors to deliver the ADA gene emphasized the importance of conditioning for long-term correction across multiple cell lineages. Since then, advancements in hematopoietic stem cell gene therapy (HSC-GT) for ADA deficiency have treated over 100 patients, with all surviving. However, 10–20% required resuming enzyme replacement therapy (ERT) or undergoing HSCT/HSC-GT [52].

Retroviral: Over 40 ADA SCID patients have safely undergone gene therapy using gamma retroviral vectors without leukaemia-like complications. Initial studies at TIGET in Milan, followed by research at University College London and UCLA, led to the European Medicines Agency's approval of Strimvelis, marketed by GSK [53].

Limitations of retroviral therapy:

- Moderate efficiency in gene transfer to human HSC due to low titres at clinical scale.

- Potential risk of insertional oncogenesis from insertion near proto-oncogenes.

- Lentiviral vectors (LV) may be safer with minimal enhancer activity.

- LV may offer more efficient gene transfer and better stem cell engraftment capacity [54].

Lentiviral: A new generation of lentiviral vectors (LV), developed as "self-inactivated" (SIN) vectors, has shown improved safety by minimizing the activation of nearby cellular genes [53]. Autologous CD34+ cells modified with the EFS-ADA LV following non-myeloablative busulfan conditioning have proven effective and well-tolerated [54].

a) **Case Studies:** In three studies, 50 ADA-SCID patients underwent gene therapy: 30 in the U.S. (median age 10 months) and 20 in the U.K. (median age 11.6 months). The overall survival rate at 12 months was 100%, remaining at 100% at 24 months for all studies and 36 months for the U.K. study[55].

b) **Advantage of Lentiviral with Cryo-preservation:** Cryopreservation of transduced cells allows for better product characterization and flexibility in treatment logistics, enabling patients to remain in local hospitals. It also facilitates busulfan level adjustment before infusion and reduces the need for extended hospital stays at specialized centers [52].

Gene Therapy, A Step Ahead of HSCT and ERT: HSCT is recommended as the initial curative treatment for ADA-SCID, but success rates are lower in patients with infections. PEG-ADA has been used to stabilize patients before HSCT, but long-term effects are partial due to thymic output reduction, apoptosis, and oligoclonal B cells, along with high costs [56]. HSCT using a matched sibling or family donor (MSD/MFD) reduces graft-versus-host disease risk, while unrelated donor transplants carry higher risks. PEG-ADA enzyme replacement therapy (ERT) has variable T-cell recovery and long-term complications, reducing the 20-year survival rate to 78% [49, 56, 78].

Strimvelis, approved in 2016, offers a one-time gene therapy option for ADA-SCID patients without suitable donors, as recommended by ESID and EBMT guidelines [49, 57, 78]. No leukemic or myelodysplastic events were observed with Strimvelis or other gene therapy approaches [49, 78]. Gene therapy is now explored as a curative option for ADA-SCID due to HSCT and ERT limitations [56, 57].

Exploring New Horizons in ADA–SCID Treatment:

p73-Mediated ADA Regulation Mechanisms: The ADA gene is activated by the p73 gene when there is an imbalance in dNTP pools due to a deficiency in the ADA enzyme. This deficiency leads to the accumulation of dAdo and causes cells to halt in the G1 and S phases while activating p73. The study proposes that p73 might aid in cell recovery by triggering the expression of the ADA gene through a feedback regulation process, possibly with the involvement of other regulatory factors that control the gene's basal expression. Additional research could investigate the potential connection between p73 and ADA SCID, simultaneously investigating the role of p73 gene in controlling ADA gene expression in response to dNTP pool imbalances due to ADA enzyme deficiency [58].

In-Utero CD34 Hematopoietic Progenitor Cell Transplants: A Pre-Birth Lifesaver: In mice, genetic issues like moderate anaemia and severe combined immunodeficiency (SCID) have been effectively treated through in-utero transplantation of hematopoietic stem cells. This involves injecting the fetus intraperitoneally with CD34 hematopoietic progenitor cells obtained from the father's bone marrow, with T-cell depletion using E rosetting. In comparison to postnatal bone marrow transplantation, in-utero transplantation offers advantages because it occurs during the early development of the hematopoietic system, potentially allowing the donor's stem cells to establish themselves. This is because the immune system is still underdeveloped during early pregnancy, potentially enabling the tolerance of donor cells [59].

The study's scope can be expanded to encompass ADA SCID, along with the possibility of conducting additional research.

Enhancing Genetic Manipulation: CRISPR-Cas9-Derived Adenine Base Editing Techniques: Initially in a study, they established a disease model using Jurkat cells to evaluate suitable strategies for adenine base editor (ABE) application. Subsequently, they worked with CD34+ cells sourced from healthy donors, modifying them with a lentiviral vector (LV) carrying sequences of the 202C > T mutation as the target for ABE. These LV-modified and ABE-edited CD34+ cells demonstrated a high on-target base editing frequency (approximately 80%) and successfully engrafted in mice, producing all hematopoietic lineages, and persisting long-term (for 16 weeks) [59, 79].

Ultimately, the ABEmax-NRTH variant was selected for base editing of CD34+ cells from an infant with SCID, harbouring a biallelic CD3δ 202C > T nonsense mutation. These cells were cultured within artificial thymic organoids (ATO), an advanced in vitro differentiation assay mirroring various stages of human thymopoiesis. The study observed that unedited CD3δ-SCID cells remained arrested at the early double-positive stage, whereas the base editing-corrected cells differentiated into functional T-cells with a diverse TCR repertoire [59, 60, 79]. This promising research is expected to have a significant impact on the treatment of SCID.

Further investigations could potentially focus on specific types of SCID, such as ADA SCID.

iPSC and HSCT: An Optimal Duo for Advanced Medical Interventions: iPSCs are now routinely generated from various species, including human. and various tissue sources. While the specific combination of genes used to induce pluripotency may vary, resulting in iPSC lines share similarities with existing ESC lines in terms of their behaviour, epigenetic characteristics, transcription profiles, and proteomics.

Nevertheless, it is important to note that iPSCs can elicit an immune response upon transplantation, as demonstrated in a syngeneic teratoma model. Researchers have successfully repaired faulty genes within autologous iPSCs through homologous recombination, leading to the generation of genetically corrected HSCs. Transplanting these corrected HSCs has proven effective in treating sickle cell disease.

A similar strategy could potentially be applied to treat SCID, using iPSCs derived from fibroblasts to correct the defective gene locus through homologous recombination. In contrast to the transplantation of non-human leukocyte antigen-identical HSCs, which carries the risk of graft-versus-host disease, gene therapy for SCID has shown high efficacy, especially with the use of novel self-inactivating vectors. Additionally, ongoing research is exploring iPSC-based approaches.

As this rapidly advancing field becomes safer, harnessing autologous stem cells with repaired genes through iPSCs offers valuable insights into the mechanisms of blood-borne diseases and may, when proven safe, provide an innovative treatment approach [61]. iPSCs could serve as a revolutionary adjunct therapy alongside HSCT to address HSCT's limitations in the context of ADA SCID, with the potential for further investigation in the future.

Targeting Mutations for Therapeutic Breakthroughs in ADA-SCID: Exploring innovative treatments for Primary Immunodeficiency Disorders (PIDs) is paramount. The concept of mutation-targeted therapy, originally developed for non-PID genetic diseases, can now be adapted to address PIDs [62].

Correction of Splicing Mutations with Antisense Oligonucleotides (AMOs): In this research, AMOs have effectively reinstated normal splicing in the ATM gene for type II and type III mutations. AMOs have a proven track record of modulating RNA splicing in various genetic diseases like cystic fibrosis, β-thalassemia, and Duchenne muscular dystrophy. Given the prevalence of splicing mutations in PIDs, AMOs hold promise. Furthermore, the use of RVG-9R-mediated oligonucleotide delivery can breach the blood-brain barrier, which is particularly relevant for PIDs involving the central nervous system [62].

Approaches for Correcting Missense and In-Frame Mutations: Chimeric RNA/DNA oligonucleotides (chimeraplasts) offer an alternative strategy for addressing missense mutations. Well-designed chimeraplasts create a single base pair mismatch in the mutated region, activating the mismatch repair system to rectify the missense mutation. Chimeraplasts have demonstrated their effectiveness in rectifying point mutations, as observed in Duchenne muscular dystrophy.

In summary, antisense oligonucleotide-based methods for splicing redirection and exon skipping hold significant potential for treating PIDs. Anticipate progress in delivery and stability, particularly regarding blood-brain barrier penetration. Several antisense oligonucleotides are currently undergoing clinical trials and are poised for evaluation in PIDs [62].

Given the success of mutation-targeted therapy in ongoing clinical trials for PIDs, it holds promising approach for the treatment of ADA SCID with additional research.

Unlocking the Role of Alkylating Agents in Inducing ADA Gene Transcription: In a study, the Ada protein, which possesses methyltransferase activity, serves as a positive regulator, particularly when it is in its methylated state. This enhances the transcription of the ada gene in vitro.

Transcription initiation sites for the ada gene have been identified using nuclease S mapping and primer-extension cDNA synthesis. Near these sites, sequences resembling promoters have been found. However, these promoter-like sequences differ notably from the consensus sequences typically observed in E. coli promoters. They function as relatively weak promoters and often require the presence of the Ada protein, especially when methylated, to initiate transcription effectively [63].

The Ada protein plays a pivotal role in regulating the Ada regulon, which encompasses at least three operons: ada-alkB, alkA, and aidB. Normally, only a small amount of Ada protein is synthesized. However, exposure to alkylating agents triggers a significant increase in Ada protein production. Consequently, this leads to heightened expression of genes within this regulon. Activation of the Ada protein occurs when a methyl group from one of the stereoisomers of DNA methyl phosphotriester is transferred to cysteine residue 69 of the Ada protein, facilitated by its intrinsic methyltransferase activity. A similar activation can also occur when certain methylating agents directly methylate the Ada protein [63].

Future research strategies hold potential for defining and expanding the appropriate use of alkylating agents in ADA SCID.

Revertant Cells:

Points to Ponder: In a case study, involving two patients who were diagnosed with ADA-SCID surprisingly, their B-cell lines had reduced ADA activity, while their T-cell lines displayed half-normal ADA activity. The suspicion of a reversion in one inherited ADA gene mutation in the T-cell lines was confirmed through RNA analysis, revealing both lines consisted entirely of revertant cells.

Initially, the ADA gene reversion in the patients went unnoticed until the T-cell lines were thoroughly examined. Supporting *in-vivo* evidence included notably lower dAXP levels in their red blood cells compared to typical ADA-SCID patients. Additionally, the impact of PEG-ADA replacement was observed in one patient, where lymphocyte counts increased, but PBMC ADA activity decreased, likely due to PEG-ADA abolishing the selective advantage of revertant cells. In another patient, an unexpected increase in T lymphocyte numbers indicated in vivo reversion of one ADA gene allele. Measurement of ADA activity showed some activity in red blood cells, lower than normal. The continued presence of modest dAXP levels suggested that revertant T cells contributed to improved immune function, enabling the patient to survive for four years. Furthermore, NK cell counts increased, indicating that the reversion might have affected NK cells too.

PEG-ADA administration in patients with somatic mosaicism has been shown to reduce the selective advantage of revertant cells. Sequencing genomic DNA before and after enzyme replacement therapy confirmed the elimination of revertant cells in their patient, underscoring the potential of ERT in managing such cases. While reverse mutations are considered rare, it is essential to remain vigilant and prioritize the detection of such events in certain genetic disorders as they hold significant implications for somatic gene therapy [64, 65].

ADA Structural Research Links Zinc Deficiency to Immune Impact: The Prior research consistently indicated that ADA functioned independently of bound cofactors. The unexpected discovery of a metal presence in the structure was noteworthy, given ADA's previously established cofactor-independent nature.

Understanding the three-dimensional structure of adenosine deaminase complexed with a transition-state analogue has provided valuable insights into the enzyme's catalytic mechanism and how point mutations associated with SCID can lead to functional loss. The newfound zinc cofactor not only plays a crucial role in catalysis but also helps in explaining many of the mutational effects. The necessity of zinc for ADA is particularly intriguing, considering that zinc deficiency significantly impairs immune function, potentially resembling ADA deficiency. These findings open the door to exploring the structures of mutants, including those mimicking ADA deficiency-related mutations and others designed to investigate structure-function relationships [66]. Further research into the genetic structure of ADA and the confirmation of Zinc deficiency as a cause of ADA SCID yield positive results, these findings could contribute to the better treatment of ADA SCID.

HSCT-Induced Microbiota Disruption and Potential Remedies: In a pilot study, the researchers investigated the gut microbiota in SCID patients before and after HSCT. The study included two IL2RG-deficient patients and one RAG1-deficient patient. Despite the limited number of patients, the research revealed significant changes in bacterial taxonomy over time. These changes led to distinct pre- and post-HSCT microbiota populations characterized by low microbial diversity and the dominance of various species, particularly Escherichia, Staphylococcus, and Enterococcus. For SCID patients, the presence of low-concentration microbiota offers potential therapeutic opportunities. This suggests that specific faecal microbiota transplantation (FMT) could be a viable therapy for intestinal diseases [67]. Similarly, in the treatment of ADA SCID using HSCT, there is a potential risk of microbiota damage. Therefore, combining FMT with HSCT could offer a solution, supported by further research.

vOrganoids, Strategy to Defeat GvHD: For long-term organoid graft survival within a host, vascularization is crucial for proper oxygen and nutrient supply. In a study, 60-day-old vOrganoids were intracerebrally implanted into cavities in the S1 cortex of NOD-SCID mice. vOrganoid grafts showed reduced cell death compared to nonvascularized grafts, indicating enhanced cell survival in the host brain. Steady blood flow in organoid grafts confirmed the development of a functional vascular connection between graft and host. Human HUVEC-derived HUN+ ECs and mouse HUN− ECs coexisted in vOrganoid graft blood vessels two months post-implantation. This suggests that our vascularized culture system has broad potential for improving survival and functional reconstruction in future 3D organoid transplantation *in-vivo* [68]. The success of vOrganoids in NOD SCID mice has the potential to revolutionize ADA SCID treatment, particularly with additional research, providing the advantage of mitigating GvHD.

Zebrafish Model's Role in Shaping Future Treatments: Understanding genetic defects' impact on immunological traits is vital for tailored treatments, enabling precise care for patients with Primary Immunodeficiency Disorders (PIDs). Zebrafish, a well-established genetic model, plays a pivotal role in studying immunity-related development and diseases. It has proven invaluable in researching blood and immune cell disorders, including over 100 publications on immuno-deficient zebrafish models linked to human PIDs. Crossbreeding PID models with optically transparent Casper zebrafish enhances immune cell characterization, facilitating advanced RNAseq transcriptome analysis. Zebrafish models have been instrumental in investigating the interplay between immunity and the gut microbiome, often through genomic DNA sequencing of dissected gut tissues.

Genetic similarities between zebrafish and humans, especially concerning immune cells and regulatory genes, make it an ideal platform for modelling various human PIDs, including Severe Combined Immunodeficiency (SCID). This approach allows precise analysis and insights into genetic disorders, offering the potential for tailored therapies and true precision medicine. Collectively, these findings underscore the relevance of zebrafish as a genetic model for human PIDs [69].

Through additional research, ADA SCID mutation could be mimicked in zebrafish establishing it as a genetic model for uncovering novel treatment approaches.

CONCLUSION: This review is an effort to consolidate and analyse the various aspects of ADA-SCID, including the treatment and diagnostic approaches, through insights gained from analogous conditions of the disease. It summarizes a balanced perspective on the supportive and key treatment strategies, suggesting their potential synergy with established therapies. The review aims to bring together the meticulous information of the disease while simultaneously integrating the significant resource for improving the lives of ADA-SCID patients with advanced treatment strategies. It throws light on further investigation needed on the proposed novel treatment methods, highlighting the positive outcomes that can lead toa better future management of ADA-SCID. Further the solicit aim of this comprehensive analysis is to foster advancements in treatment options and patient care strategies that shall bring hope in the patient group affected by ADA-SCID.

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