

REVIEW

Congenital Disorders of Glycosylation (CDG): State of the Art in 2026

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Received: 18 August 2026 | **Revised:** 14 September 2026 | **Accepted:** 23 September 2026

Academic Editor: Julien Park

Keywords: congenital disorders of glycosylation | glycomics | inherited metabolic diseases | molecular diagnosis | targeted therapy

ABSTRACT

Congenital disorders of glycosylation (CDG) are a rapidly expanding group of inherited metabolic diseases affecting glycoconjugate glycan biosynthesis and attachment. This review provides a structured overview of major advances in human CDG reported from 2023 to 2026, including newly recognized CDG, emerging biochemical and pathophysiological insights, advances in diagnostic strategies and biomarkers, and progress in treatment. Recent developments include the recognition of RPN1-CDG, UGGT1-CDG, and DHRSX-CDG, refinement of phenotypes in established disorders, including PMM2-CDG, ALG13-CDG, ALG8-CDG, GMPGA-CDG, TRAPPC11-CDG, and PGAP3-CDG, and increasing use of glycomics, glycoproteomics, cellular models, and multi-omics approaches. Therapeutic progress remains uneven: no FDA/EMA-approved disease-modifying therapy is currently available for any CDG, and most interventions remain off-label, experimental, or supported by limited observational evidence. Despite substantial progress, most CDG still lack disease-modifying treatment, validated biomarkers, and prospective natural history data.

1 | Introduction

Congenital disorders of glycosylation (CDG) are inherited defects of glycoconjugate glycan synthesis, modification, and attachment. Glycosylation is essential for protein folding, intracellular transport, receptor function, cell–cell communication, immune regulation, and extracellular matrix biology; consequently, CDG may present with neurological, hepatic, endocrine, hematologic, immunologic, skeletal, ocular, cardiac, or multisystem disease.

The field has changed substantially since the first descriptions [1, 2]. Initially, most recognized disorders affected N-linked protein glycosylation and were detected through abnormal serum transferrin (Tf) isoforms. Current CDG nosology includes defects of N- and O-linked glycosylation, lipid and glycosaminoglycan synthesis, glycosylphosphatidylinositol (GPI)-anchor

biosynthesis, dolichol metabolism, nucleotide-sugar transport, vesicular trafficking, endoplasmic reticulum quality control, and related cellular processes.

A previously published state-of-the-art review summarized the CDG field up to 2022 [3]. The present review focuses on major human CDG advances reported from 2023 to 2026.

2 | Materials and Methods

A structured literature search was performed in PubMed/MEDLINE for articles published from 1 January 2023 to 31 July 2026. The search strategy combined disease-group terms with pathway, diagnostic, and therapeutic terms, including congenital disorders of glycosylation, CDG, glycosylation, N-glycosylation,

O-glycosylation, glycomics, glycoproteomics, glycosphingolipid, biomarker, diagnosis, treatment, therapy, natural history, genotype–phenotype, and the names of specific CDG genes identified during screening. Reference lists of relevant articles and reviews were searched manually to identify additional eligible publications.

Inclusion criteria were: (i) original human studies, patient reports or patient series describing novel CDG, expanded CDG phenotypes or genotype–phenotype correlations; (ii) diagnostic, biochemical, glycomic, glycoproteomic or functional studies with direct relevance to human CDG; (iii) natural-history studies, cohort studies, consensus recommendations and treatment studies; and (iv) major reviews published during the search period that summarized rapidly evolving CDG subfields.

The OMIM database [4] was used to extract information related to human genotype–phenotype relationships and their characteristics, whereas the UniProt database [5] was consulted to collect information related to protein function and biochemical pathways.

3 | Results

3.1 | Novel CDG and Phenotypic and Genotypic Expansion

Most CDG are complex multisystem disorders. Every organ with a glycosylation system can be involved, and CDG may present as recognizable syndromic patterns such as dystroglycanopathies, cardiomyopathy, skeletal dysplasia, cutis laxa, congenital myasthenic syndromes, immunodeficiency, liver disease, or endocrine dysfunction [3, 6–8]. However, the clinical spectrum is not limited to multisystem disease. Several disorders now included within the broader CDG spectrum may present with predominantly mono-organ or pauci-organ involvement, such as DHDDS-related retinitis pigmentosa, GNE-related myopathy, or GANAB-related polycystic kidney or liver disease [3, 9].

For this review, the 2024 nosology table of 200 CDG was converted into a structured organ-involvement dataset and updated with three established 2025–2026 additions: RPN1-CDG, UGGT1-CDG, and DHRX-CDG [9–13], resulting in 203 CDG. B4GALT5 deficiency is discussed below as an emerging glycosphingolipid-biosynthesis CDG but was not included because current evidence is limited to a single report that described it as a potential new CDG [14].

Neurological involvement remains the most prominent clinical category, documented in 164 disorders. Dysmorphic features, skeletal involvement, and ocular abnormalities were reported in more than 90 disorders each. Gastrointestinal, cardiovascular, and muscular manifestations formed the next major groups, whereas growth, skin, hematologic, endocrine, immune, respiratory, renal, genitourinary, dental, hair, and psychiatric features were less frequent.

CDG thus remain primarily neurodevelopmental and multisystem diseases but also comprise important organ-dominant presentations. Larger cohorts have clarified neurological and

developmental profiles in PMM2-CDG, ALG13-CDG, and TRAPPC11-CDG; endocrine, growth, and mortality data have become more informative in PMM2-CDG, and immunological manifestations have been revisited across CDG [6–8, 15–25].

The organ pattern depends partly on the glycosylation pathway involved. For example, O-linked glycosylation defects are enriched for skeletal muscle and ocular involvement, whereas N-linked glycosylation and GPI-anchor biosynthesis disorders more often combine neurological, skeletal, gastrointestinal, and ocular disease. These patterns are useful for clinical recognition but should not be interpreted as rigid rules, because individual CDG may show age-dependent, genotype-dependent, or organ-dominant presentations.

The period 2023–2026 brought several novel CDG.

RPN1-CDG is an oligosaccharyltransferase-complex disorder. *RPN1* encodes ribophorin I, an essential component of the OST complex that participates in co-translational N-glycosylation. The disorder was identified in two siblings with neurodevelopmental disease and a type 1 serum transferrin isoelectrofocusing profile. Both carried a homozygous nonsense *RPN1* variant predicted to truncate the protein. Studies in patient-derived lymphoblasts showed reduced RPN1 levels and secondary reduction of other OST-complex components, including STT3A, RPN2, and DDOST. Structural modeling suggested loss of a C-terminal four-helix bundle involved in interaction with the translating ribosome, supporting a mechanism in which impaired OST-A function leads to substrate-specific hypoglycosylation [10].

B4GALT5 deficiency affects glycosphingolipid biosynthesis. The reported patient carried compound heterozygous *B4GALT5* variants, p.Arg173His and p.Gly274Arg, and presented with microcephaly, mild cognitive impairment, and early-onset bilateral cataracts. Functional studies in B4GALT5/B4GALT6 knockout cell models showed that both variants lacked lactosylceramide synthase activity. Patient plasma and fibroblasts showed markedly reduced glycosphingolipid levels, with approximately 80% reduction compared with controls. The report is important because it supports B4GALT5 as indispensable for normal human glycosphingolipid synthesis and suggests that human B4GALT6 may not fully compensate for loss of B4GALT5 activity [14].

UGGT1-CDG represents a major addition to the group of endoplasmic reticulum quality-control disorders. *UGGT1* encodes UDP-glucose: glycoprotein glucosyltransferase 1, which reglucosylates misfolded glycoproteins and promotes their re-entry into the calnexin/calreticulin folding cycle. Biallelic *UGGT1* variants were reported in 15 individuals from 10 families. The phenotype was variable but centered on developmental disability, intellectual disability, seizures, characteristic facial features, and microcephaly. The most severe presentations included fetal or infantile multisystem disease [11].

DHRX-CDG illustrates how discovery of a human CDG can revise a biochemical pathway. DHRX is located in the pseudo-autosomal region and encodes an enzyme involved in the terminal steps of dolichol biosynthesis. Patients with biallelic *DHRX* variants had abnormal N-glycosylation and variable neurodevelopmental and multisystem manifestations. Functional work

showed that dolichol synthesis requires a previously unrecognized three-step route through polyprenal and dolichal intermediates, with DHRSX acting in two non-consecutive steps and SRD5A3 reassigned to an intermediate reductase step. Thus, the discovery of DHRSX-CDG was associated with a revised model of dolichol metabolism [12, 13].

3.1.1 | MAN2A2-CDG Expanded the Group of Golgi N-Glycan Processing Defects

MAN2A2 encodes alpha-mannosidase IIx, which contributes to the conversion of hybrid to complex N-glycans. A homozygous truncating variant, p.Val1101Ter, was reported in two affected brothers from a consanguineous family with neurological involvement and dysmorphism. Patient lymphoblasts showed decreased complex N-glycans and accumulation of hybrid structures, and complementation studies in *MAN2A1/MAN2A2* double-knockout cells supported complete loss of function. This disorder illustrates how redundancy between related Golgi enzymes can mask disease mechanisms until carefully tested in appropriate cellular models [26].

3.1.2 | DDOST-CDG Has Also Moved From Isolated Patient Descriptions Toward a More Defined Ultra-Rare OST-Complex Disorder

DDOST encodes a non-catalytic subunit of the OST complex. The most recent report described a female patient with developmental disability, hypotonia, and dysmorphic features carrying compound heterozygous *DDOST* variants, including the first reported structural variant: a maternally inherited 413-kb deletion encompassing exons 3–11, together with a paternally inherited in-frame deletion p.Lys435del. Metabolic testing showed a type 1 transferrin isoform pattern. Hypotonia and motor delay seem to be consistent features, whereas strabismus, feeding difficulties, and hepatic dysfunction are variable [27, 28].

Finally, transporter-related and trafficking-related CDG continue to broaden the CDG spectrum. This group reinforces a central lesson of recent CDG discovery: classification increasingly depends on integrating genomic data with biochemical, glycomic, cellular, and pathway-level evidence rather than relying on transferrin analysis or gene nomenclature alone [29–33].

3.2 | Novel Biochemical and Pathophysiological Insights

Recent studies have expanded the biochemical and pathophysiological spectrum of CDG, particularly at the interfaces among precursor synthesis, intracellular trafficking, and glycoprotein quality control. Dolichol synthesis and utilization have become a particularly important biochemical link among glycosylation pathways. Dolichol phosphate is required as a lipid carrier for the assembly of lipid-linked oligosaccharides in N-glycosylation and for several other pathways, including O- and C-mannosylation and GPI-anchor biosynthesis. The 2025 review by Pieters, Jaeken, and Wilson emphasized that defects of dolichol synthesis, phosphorylation, and utilization should be considered a

connected biochemical group [12]. Within this group, DHRSX-CDG is especially instructive (see Section 3.1) [13].

Transporter defects constitute another expanding biochemical group. CAMLG-CDG is a useful example: impaired membrane trafficking can disturb Golgi organization, glycosylation-enzyme localization or substrate access [29]. Transporter-related CDG further extends this concept: defects affecting nucleotide sugars, activated sugars, PAPS or ions in the endoplasmic reticulum, Golgi apparatus or plasma membrane may alter glycoprotein, glycolipid or glycosaminoglycan synthesis [33]. Figure 1 summarizes the cellular localization and principal mechanisms of selected novel or recently refined CDG discussed in this review.

Established CDG are also being reinterpreted from a broader biochemical and pathophysiological perspective. PMM2-CDG is no longer viewed only through systemic glycoprotein hypoglycosylation; in vitro neural models, mouse models, and metabolomic studies point to neural and metabolic dysregulation as contributors to brain pathology [34–38]. Multiomics analysis in COG6-CDG showed deeper insights into the molecular mechanisms and the function of the *COG6* gene [39], whereas SRD5A3 deficiency was found to be associated with extensive hypoglycosylation of serum N-glycoproteins [40].

A related development is the rapid growth of tissue-specific disease models. Patient-derived fibroblasts and lymphoblasts remain important for confirming glycosylation defects, but induced pluripotent stem cell-derived neural models, mouse models, and organoid-like systems are increasingly used to ask why selected CDG predominantly affect the brain, muscle, liver, immune system, or skeleton [34–38].

3.3 | Advances in Diagnostics

The diagnostic approach to CDG has changed from a predominantly transferrin-centered pathway to a multi-layered strategy combining biochemical screening, pathway-specific biomarkers, glycomics or glycoproteomics, genomic testing, and functional validation [41–43].

Serum transferrin isoelectric focusing, capillary electrophoresis or mass spectrometry remains the first-line biochemical test when an N-glycosylation defect is suspected. A type 1 serum transferrin isoelectrofocusing pattern reflects impaired assembly or transfer of lipid-linked oligosaccharides, whereas a type 2 pattern reflects abnormal processing of protein-bound glycans. However, a normal transferrin profile does not exclude CDG, particularly when the defect is tissue-restricted, variant-specific or poorly reflected in circulating transferrin. Among N-glycosylation CDG that might otherwise be expected to show a type 1 or type 2 pattern, normal transferrin profiles have been reported in ALG13-CDG and PGM3-CDG, whereas normal, near-normal or only mildly abnormal profiles may occur in selected patients with PMM2-CDG, especially in milder or older patients. Other examples include selected SLC35A2-CDG and DHDDS-CDG patients. GNE myopathy and several disorders primarily affecting O-glycosylation, GPI-anchor biosynthesis,

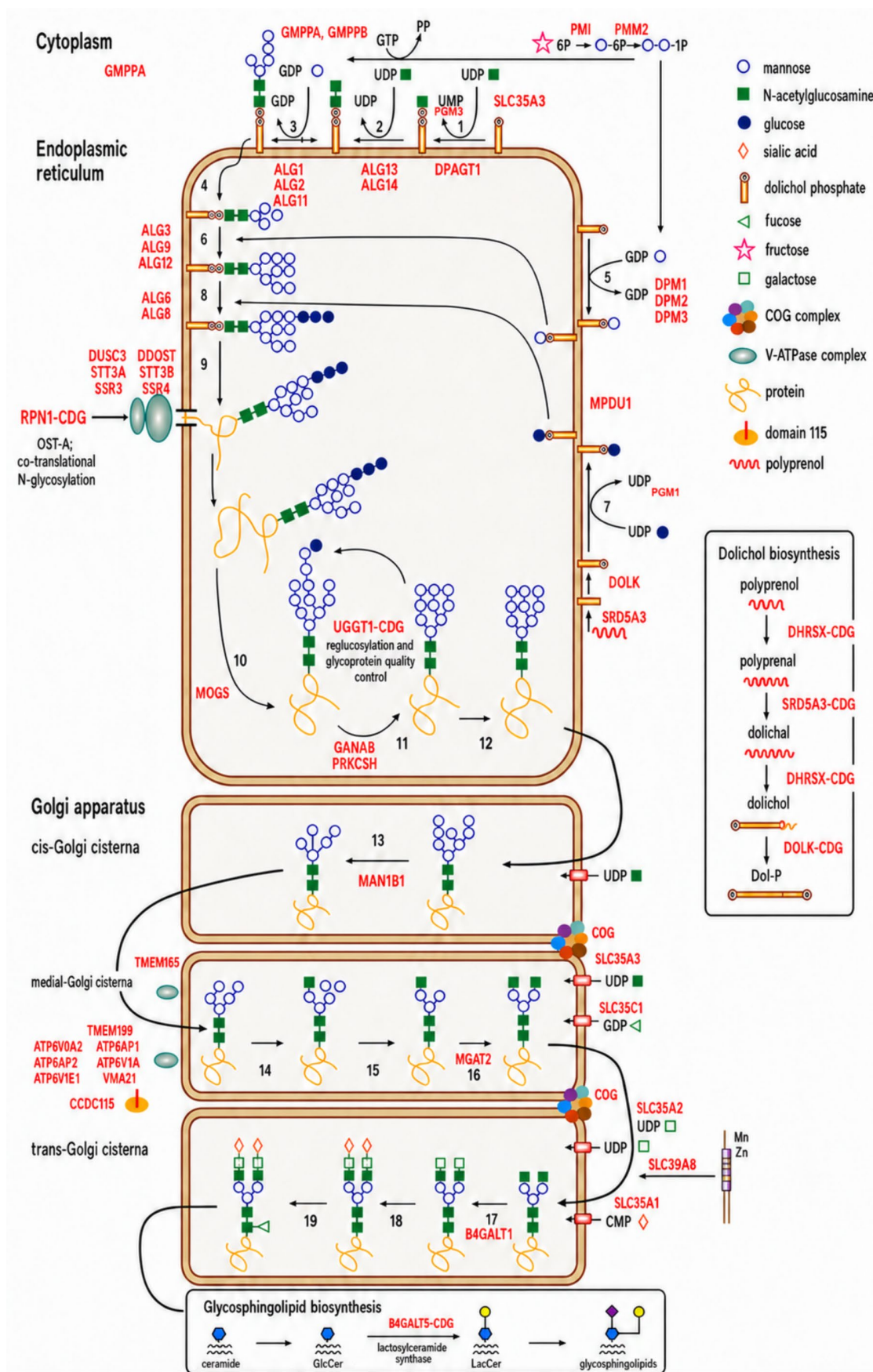


FIGURE 1 | Legend on next page.

FIGURE 1 | Cellular localization and principal mechanisms of selected novel or recently refined congenital disorders of glycosylation. The figure highlights defects affecting co-translational N-glycosylation and the oligosaccharyltransferase complex, ER glycoprotein quality control, dolichol biosynthesis, Golgi processing, nucleotide-sugar transport, Golgi homeostasis and glycosphingolipid biosynthesis. The revised figure also includes PGM1-CDG and PGM3-CDG as representative cytosolic precursor-related disorders.

glycosaminoglycan or glycolipid metabolism show evidently a normal pattern [3, 41–43].

Additional biochemical markers are useful when transferin tests are normal, borderline, or insufficiently informative. Serum apolipoprotein C-III isoelectrofocusing helps assess mucin-type O-glycosylation, whereas other markers such as bikunin, selected serum glycoproteins, coagulation factors, immunoglobulins, glycosaminoglycans, glycolipids, enzyme activities, and flow-cytometric cell-surface glycans may point to more specific pathways [3, 41–43]. Albumin has recently been proposed as a biomarker in CDG [44].

Mass-spectrometry-based glycomics and glycoproteomics are becoming central diagnostic tools. Serum or plasma N-glycan profiling can define glycan signatures, distinguish primary CDG from secondary glycosylation abnormalities, and guide targeted gene interpretation. Glycoproteomics adds protein-level context by identifying affected circulating glycoproteins. Combined plasma glycan profiling and targeted molecular analysis have established diagnoses in unresolved patients with CDG-I [41, 43, 45].

Genomic testing has made CDG diagnosis bidirectional. Exome or genome sequencing may identify candidate variants before biochemical testing is performed; targeted biochemical and functional studies can then establish the defect and support variant interpretation [41–43].

The diagnostic odyssey remains substantial. Community-based investigations continue to show delayed diagnosis, incomplete access to expert centers and uneven availability of glycosylation testing [46]. For clinicians, the practical message is that CDG should remain in the differential diagnosis not only in infants with multisystem disease, but also in patients with unexplained neurological involvement, liver disease, coagulopathy, endocrine abnormalities, skeletal dysplasia, immune dysfunction, recurrent infections, congenital malformations and selected adult phenotypes. Natural history and cohort studies have contributed recently to diagnostic recognition by providing more reliable phenotype anchors for PMM2-CDG, ALG13-CDG, ALG8-CDG, GMPPA-CDG, PGAP3-CDG, TRAPPC11-CDG and MOGS-CDG [7, 8, 15, 16, 19–25, 47–50].

3.4 | Advances in Treatment

Disease-specific treatment remains available for only a small minority of CDG, and no FDA/EMA-approved disease-modifying therapy is currently available for any CDG. Current strategies include substrate supplementation, dietary manipulation, organ transplantation in selected patients, repurposed drugs, and emerging pathway- or gene-directed approaches [51]. Mannose for MPI-CDG remains the clearest example of bypassing a

metabolic block when the substrate reaches the affected tissues and downstream pathway capacity is preserved [51, 52].

D-galactose treatment of PGM1-CDG has improved hypoglycemia, coagulopathy, hepatopathy, myopathy, exercise intolerance, and endocrine abnormalities. International guidelines support early diagnosis, standardized monitoring, and individualized dosing; longer-term patient-series data and a treatment-monitoring index link exposure to biochemical and clinical response [53–55]. Hypoglycemia may additionally require frequent complex carbohydrate feeds, uncooked cornstarch, and, when hyperinsulinemic, diazoxide [53]. Galactose has also been studied in SLC35A2-CDG: an 18-week study showed improvement in the Nijmegen Pediatric CDG Rating Scale and glycomic abnormalities, and subsequent work demonstrated partial restoration of glycosphingolipid synthesis [56, 57].

In SLC39A8-CDG, manganese supplementation corrected glycosylation and several manganese-dependent enzyme abnormalities and was associated with clinical improvement in two patients. Because excessive manganese is neurotoxic, treatment requires biochemical monitoring [58]. In disorders of fucosylation, L-fucose has produced biochemical and clinical improvement in GFUS-CDG and selected SLC35C1-related phenotypes, whereas D-mannose improved fucosylation and clinical manifestations in a single patient with FCSK-CDG [59–61]. Ribitol supplementation for CRPPA-CDG is still experimental: patient-derived fibroblast studies showed partial restoration of alpha-dystroglycan glycosylation in selected genotypes, but clinical efficacy and optimal dosing have not been established [62].

In PMM2-CDG, acetazolamide improved motor manifestations of cerebellar dysfunction in the AZATAX trial [63], although a recent study found no improvement in objective ataxia scores [21]. GLM101, an investigational mannose-1-phosphate replacement approach, is currently being evaluated in clinical trials [64, 65]. Biotin supplementation has been explored in PMM2-CDG because secondary biotinidase deficiency may occur in this disorder; however, in a 2026 study, 12 months of supplementation did not produce measurable improvement in objective clinical outcomes [66]. Oral sialic acid supplementation in NANS-CDG is another preliminary example of a pathway-informed or secondary-metabolite intervention [67].

GNE myopathy illustrates the difficulty of translating pathway rationale into proven clinical benefit. Extended-release sialic acid, also known as aceneuramic acid, has been evaluated in clinical trials: an international phase 3 study did not demonstrate superiority over placebo on prespecified functional outcomes, whereas a Japanese phase II/III study suggested possible benefit in upper-limb function [68, 69].

Organ transplantation may be considered for severe organ-dominant disease. Successful heart transplantation has been

reported in PGM1-CDG, and liver transplantation has been discussed for severe hepatic involvement in PMM2-CDG [70, 71]. Decisions require careful assessment of neurological disease, extrahepatic burden, and the likelihood that organ replacement will alter meaningful outcomes.

Multi-omics, cellular models and artificial-intelligence-assisted drug repositioning are increasingly used to identify shared therapeutic targets across CDG [72, 73]. These approaches may shorten early development but do not replace dose finding, controlled evaluation, validated endpoints or toxicity monitoring. Delivery to the central nervous system remains a major obstacle.

4 | Discussion

This review shows that progress in the CDG field from 2023 to 2026 was characterized less by a simple increase in the number of recognized disorders than by closer integration of clinical phenotyping, genomic analysis, glycomics, glycoproteomics, and functional studies. Newly described disorders extend CDG beyond classical defects of glycan assembly to include impaired glycoprotein quality control, lipid-carrier metabolism, glycosphingolipid synthesis, and intracellular trafficking. At the same time, larger cohorts and longitudinal studies have converted isolated observations in established CDG into more clinically useful phenotypic patterns, particularly for neurological, growth, endocrine, hepatic, immunological, and hematological involvement. In this context, disease-specific growth charts and improved estimates of the incidence and prevalence of PMM2-CDG represent important advances [6–8, 15, 16, 19–25].

As to classification, the eight-category nosology proposed by Ng et al. provides a broad clinical and biochemical framework [9], with the restriction that congenital disorders of deglycosylation such as NGLY1 deficiency and the lysosomal disorders do not belong to the CDG that by definition are anabolic or synthetic disorders. Dolichol-related disorders illustrate the limitations of rigid categories because dolichol metabolism supports N-glycosylation, O- and C-mannosylation, and GPI-anchor biosynthesis [12, 13].

Serum transferrin analysis remains valuable, but the expanding number of disorders with normal or atypical transferrin profiles confirms its limitations. Diagnosis is increasingly bidirectional: biochemical abnormalities may guide molecular testing, while genomic findings may prompt targeted glycomic, glycoproteomic, or cellular validation. This is particularly important for variants of uncertain significance and candidate disease genes, for which pathway-level evidence is needed to distinguish causality from incidental findings [40–45]. Access to these methods remains uneven, as reflected in the diagnostic odyssey reported by many families [46].

As usual in metabolic disorders, therapeutic development remains less advanced than disease discovery. Mannose in MPI-CDG and galactose in PGM1-CDG provide proof that pathway-directed supplementation can be effective when the biochemical block is amenable to substrate bypass [51–55]. Other interventions, including manganese, fucose, mannose for FCSK-CDG, sialic acid, biotin, GLM101, and organ transplantation, are supported by

evidence of variable quality and should not be considered equivalent to treatments backed by guidelines or replicated clinical experience [56–71]. Future trials will require disease-relevant outcome measures, validated pharmacodynamic biomarkers, prospective natural-history data, and explicit assessment of neurological as well as systemic benefit. Correction of a circulating glycosylation marker alone cannot be assumed to represent meaningful clinical improvement.

This narrative review has limitations. Although the search strategy was structured, the literature was selected for clinical and conceptual relevance rather than by formal systematic-review methods, and selection bias cannot be excluded. The evidence base is also uneven: many recent advances come from single families, case reports, small series, or in vitro studies, whereas prospective natural-history cohorts, randomized trials, and validated outcome measures remain scarce. This imbalance is especially important for treatment sections, where biochemical correction, parent-reported improvement, or short follow-up should not be equated with durable clinical benefit.

Regional disparities remain a major barrier to CDG diagnosis and care. Access to transferrin mass spectrometry, glycomics, glycoproteomics, and functional validation differs substantially between countries and even between centers. International registries, harmonized phenotyping, shared variant databases, standardized biochemical pipelines, and agreed outcome measures are therefore essential. The diagnostic odyssey also has a patient-facing dimension that remains underrepresented in the literature: patient-reported outcomes, quality-of-life measures, caregiver burden, and family experience should be incorporated into future natural-history studies and therapeutic trials [46].

Newborn screening remains an emerging and unsettled issue. Incorporating selected CDG into newborn screening could shorten the diagnostic odyssey, particularly for disorders in which early treatment may change clinical outcomes. However, population-based screening for CDG is not yet ready for broad implementation. Candidate disorders require reliable dried-blood-spot assays, acceptable false-positive rates, rapid confirmatory pathways, evidence that presymptomatic diagnosis improves management, and defined treatment or surveillance protocols. MPI-CDG and CAD-CDG may warrant evaluation as candidate conditions because disease-specific treatment with oral mannose and uridine monophosphate, respectively, is available [51, 74].

In conclusion, the principal advance from 2023 to 2026 is the transition toward a more integrated, pathway-based view of CDG. Novel disorders such as RPN1-CDG, UGGT1-CDG, and DHRSX-CDG broaden the biological boundaries of the field, while refined phenotyping, multi-omic diagnostics, and functional validation improve interpretation of established and emerging entities. Further progress will depend on international registries, prospective natural-history studies, standardized biomarkers, and clinical trials designed to demonstrate meaningful clinical outcomes.

Author Contributions

P.L. conceptualized the review, performed the literature search, selected and interpreted the literature, drafted the manuscript and approved the

final version. He accepts full responsibility for the work, has access to the source literature and controlled the decision to submit the manuscript. J.J. contributed to conceptualization, interpretation of the literature, critical revision of the manuscript and approved the final version.

Funding

The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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