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REVIEW

Advancing precision care in pregnancy through a treatable fetal findings list

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Summary

The use of genomic sequencing (GS) for prenatal diagnosis of fetuses with sonographic abnormalities has grown tremendously over the past decade. Fetal GS also offers an opportunity to identify incidental genomic variants that are unrelated to the fetal phenotype but may be relevant to fetal and newborn health. There are currently no guidelines for reporting incidental findings from fetal GS. In the United States, GS for adults and children is recommended to include a list of "secondary findings" genes (ACMG SF v.3.2) that are associated with disorders for which surveillance or treatment can reduce morbidity and mortality. The genes on ACMG SF v.3.2 predominantly cause adult-onset disorders. Importantly, many genetic disorders with fetal and infantile onset are treatable as well. A proposed solution is to create a "treatable fetal findings list," which can be offered to pregnant individuals undergoing fetal GS or, eventually, as a standalone cell-free fetal DNA screening test. In this integrative review, we propose criteria for a treatable fetal findings list, then identify genetic disorders with clinically available or emerging fetal interventions and those for which clinical detection and intervention in the first week of life might lead to improved outcomes. Finally, we synthesize the potential benefits, limitations, and risks of a treatable fetal findings list.

Introduction

The clinical use of genomic sequencing (GS) for prenatal diagnosis of fetuses with sonographic abnormalities has grown tremendously in recent years. The International Society of Prenatal Diagnosis (ISPD) recommends offering fetal GS to individuals with pregnancies affected by a major single anomaly, multiple anomalies, or with a history of an undiagnosed fetus or child with a congenital anomaly,[1] likely affecting up to 2%–3% of pregnancies.[2] The diagnostic yield of GS varies by indication, ranging from 2% for isolated increased nuchal translucency to 53% for skeletal abnormalities.[3]

In the United States, indication-based genome sequencing for children and adults includes the optional analysis of a list of "secondary findings" genes recommended by the American College of Medical Genetics (ACMG) (ACMG SF v.3.2).[4] These genes are predominantly associated with adult-onset cardiac, cancer, and inherited metabolic disorders (IMDs). Secondary findings have been identified in at least 1%–3% of adults.[5–8] Once detected, these disorders can often be managed with medication, dietary changes, or long-term surveillance aimed at improving morbidity and mortality in affected individuals.[9] The ACMG secondary findings list is recommended both for adults and children undergoing GS. However, professional organizations differ in their recommendations on reporting secondary findings for adult-onset conditions in children. While the recommendations of organizations such as Genomics England[10] generally align with ACMG, the European Society of Human Genetics and others argue that it is premature to screen for later-onset conditions in children.[11]

The ACMG SF v.3.2 recommendations do not apply to fetuses, and guidance regarding the reporting of incidental findings from fetal GS remains unclear.[12] An ACMG Points

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Table 1. Selection criteria for genes associated with fetal, delivery, or neonatal interventions

Topic	Selection criteria
Age of treatment initiation	intervention administered *in utero* or in the first week of life is expected to prevent morbidity, mortality, or irreversible organ damage to the infant
Safety and efficacy of intervention	intervention is safe and plausibly effective
Clinical severity	gene is associated with critical illness or chronic disease
Gene-disease validity	genes with limited, disputed, or refuted ClinGen validity scores have been excluded

to Consider document states that "prenatal exome sequencing analysis could be limited to the reporting of variants in genes associated with the ultrasound findings," while also recommending that "highly penetrant pathogenic variants detected in genes unrelated to the fetal phenotype, but known to cause moderate to severe childhood onset disorders, are recommended to be reported."[13] The ISPD suggests that secondary findings analyzed in fetal GS might include "moderate to severe childhood conditions" but does not provide specific guidance on which genes to include.[1] Reporting practices vary across clinical labs, and pregnant individuals are not routinely offered a choice regarding the type of genomic findings they receive.

Of note, many pregnancies affected by actionable monogenic conditions show no sonographic abnormalities, or the abnormalities are too subtle to detect with current imaging technology.[14,15] Recent studies have demonstrated that 0.6%–2.7% of sonographically normal fetuses harbor pathogenic or likely pathogenic variants (PLPVs) expected to cause genetic disease,[16–19] and 1.85%–9.4% of infants have PLPVs associated with a monogenic childhood-onset disorder,[20,21] including IMDs, cardiomyopathies, and syndromic intellectual disability disorders.

Over 700 genetic disorders are now treatable with dietary changes, medication, hematopoietic stem cell transplantation, solid organ transplantation, or gene therapies.[22] The number of *in utero* interventions for genetic disorders is rapidly expanding,[23] supported by clinical trials, case reports, and animal model studies. Many of these disorders do not present with ultrasound findings, meaning that the benefits of prenatal interventions can only be realized by individuals with known family history or carrier status.[24] However, most countries lack a uniform approach to carrier screening,[25] and the genes included in these panels vary widely, with none addressing *de novo* disorders in the fetus.[26,27]

Shortly after birth, newborn screening (NBS) identifies many severe, treatable genetic disorders in infants. However, many of the disorders included in NBS programs can cause morbidity or mortality shortly after birth before the receipt of results at 5–7 days of life (see web resources for NBS process). Prenatal diagnosis of these disorders may allow for improved care during the perinatal period, including appropriate labor and delivery planning, mobilization of relevant medical teams, and the acquisition of specialized medical formulas, medications, or other therapeutics needed for immediate intervention.

A prior commentary by Gold et al. suggested offering pregnant individuals who are undergoing fetal GS the optional analysis of a "treatable fetal findings list."[28] This list is not intended to replace NBS or diagnostic GS for infants but would enhance reproductive options and management capabilities of conditions not typically identified during pregnancy or the immediate perinatal period.

We used an integrative review approach to propose criteria for a treatable fetal findings list, then identified genetic disorders with clinically available or emerging fetal interventions and those for which clinical detection and intervention in the first week of life might lead to improved outcomes. Finally, we synthesized the potential benefits, limitations, and risks of a treatable fetal findings list.

Criteria for and identification of genetic disorders with interventions *in utero* or treatments during the first week of life

Integrative review criteria

The integrative review includes five stages: problem identification, literature search, data evaluation, data analysis, and presentation.[29,30] This approach allows for the use of several study designs, with the aim of generating new frameworks or ideas.[29,30]

The search strategies for genetic disorders that have *in utero* interventions and genetic disorders that are treatable in the first week of life are described in the supplemental methods and Table S1.

Selection criteria for genes associated with fetal, delivery, or neonatal interventions

We established inclusion and exclusion selection criteria (Table 1) and created gene lists as follows: the first main category includes genetic disorders with *in utero* interventions that have variable degrees of clinical evidence including clinical trials (Table 2), case reports or case series (Table S2), and preclinical animal model studies (Table S3), which may be future candidates for a more expansive treatable fetal findings list. The second main category includes genetic disorders for which prenatal diagnosis could

Table 2. Genes associated with disorders with *in utero* fetal interventions in clinical trials ($n = 11$)

Phenotype	OMIM	Gene	Inheritance	ClinGen gene-disease validity	Fetal intervention	Clinical area	References
Clinical trials							
Osteogenesis imperfecta type III or severe type IV	259420	*COL1A1*	AD	definitive	prenatal administration of allogeneic expanded fetal mesenchymal stem cells (NCT03706482)	endocrine disorder	Sagar et al.[31]; Lang and Semon[32]
	166220						
	259420	*COL1A2*	AD	definitive			
	166220						
Infantile-onset Pompe disease	232300	*GAA*	AR	definitive	prenatal ERT (NCT04532047)	inherited metabolic disorder	Borges et al.[33]; Cohen et al.[34]
Lysosomal acid lipase deficiency	620151	*LIPA*	AR	definitive	prenatal ERT (NCT04532047)	inherited metabolic disorder	Borges et al.[33]; Cohen et al.[34]
Hurler syndrome	607014	*IDUA*	AR	definitive	prenatal ERT (NCT04532047)	inherited metabolic disorder	Borges et al.[33]; Cohen et al.[34]
Mucopolysaccharidosis 2 (Hunter)	309900	*IDS*	XL	definitive	prenatal ERT (NCT04532047)	inherited metabolic disorder	Borges et al.[33]; Cohen et al.[34]
Mucopolysaccharidosis 4a (Morquio)	253000	*GALNS*	AR	definitive	prenatal ERT (NCT04532047)	inherited metabolic disorder	Borges et al.[33]; Cohen et al.[34]
Mucopolysaccharidosis 6 (Maroteaux-Lamy)	253200	*ARSB*	AR	definitive	prenatal ERT (NCT04532047)	inherited metabolic disorder	Borges et al.[33]; Cohen et al.[34]
Mucopolysaccharidosis 7 (Sly)	253220	*GUSB*	AR	definitive	prenatal ERT (NCT04532047)	inherited metabolic disorder	Borges et al.[33]; Cohen et al.[34]
Neuronopathic Gaucher disease	231000	*GBA*	AR	definitive	prenatal ERT (NCT04532047)	inherited metabolic disorder	Borges et al.[33]; Cohen et al.[34]
Ectodermal dysplasia, hypohidrotic, X-linked	305100	*EDA*	XL	no VS	protein administered via intra-amniotic injection (NCT04980638)	multi-system disorder	Schneider et al.[35]; Schneider et al.[36]

The table is formatted so that for each phenotype, the columns for "OMIM," "Gene," "Inheritance," and "ClinGen gene-disease validity" are aligned horizontally within the same row to designate their association. The columns for "Fetal intervention," "Clinical area," and "References" are associated with the overall phenotype but not tied to specific genes within that phenotype unless otherwise indicated.
AD, autosomal dominant; AR, autosomal recessive; ERT, enzyme replacement therapy; VS, validity score; XL, X-linked.
A full list of genes associated with disorders that have *in utero* fetal interventions at varying levels of human evidence are included in Table S2 ($n = 54$).

Table 3. Illustrative examples of the 267 genes associated with disorders with clinically available therapies that could be applied in the first week of life ($n = 22$)

Phenotype	OMIM	Gene	Inheritance	ClinGen gene-disease validity	Treatment	Reason for early detection	References
Endocrine disorders							
AVP resistance (formerly nephrogenic diabetes insipidus)	304800	*AVPR2*	XL	no VS	low-solute diet, thiazide diuretics, DDAVP, and NSAIDs	can present with hypovolemic shock in the first days of life	Wesche et al.[37]; Monnens et al.[38]; Libber et al.[39]
	125800	*AQP2*	AD; AR	no VS			
Gastrointestinal disorders							
Congenital sucrase-isomaltase deficiency	222900	*SI*	AR	no VS	avoidance of sucrose and isomaltose	getting sucrose in the first days of life (e.g., from a sweetened medication) could cause serious diarrhea, dehydration, or electrolyte abnormalities	Smith et al.[40]; Esposito et al.[41]; Danialifar et al.[42]
Hematologic disorders							
Coagulation factor deficiencies	613679	*F2*	AR	definitive	plasma product therapy, replacement of appropriate factor	diagnosis may lead to prompt and appropriate treatment of intracranial hemorrhage or cephalohematoma	Leebeek et al.[43]
	227400	*F5*	AR	definitive			
	227500	*F7*	AR	definitive			
	306700	*F8*	XL	definitive			
	306900	*F9*	XL	definitive			
	227600	*F10*	AR	definitive			
	612416	*F11*	AD; ARAR	definitive			
	234000	*F12*	AR	definitive			
	613225	*F13A1*	AR	definitive			
	613235	*F13B*	AR	definitive			
	202400	*FGG*	AR	definitive			
	202400	*FGB*	AR	definitive			
	202400	*FGA*	AR	definitive			
Protoporphyria, erythropoietic	177000	*FECH*	AR	definitive	avoidance of phototherapy, blood transfusion, splenectomy	jaundice and hepatosplenomegaly can develop in the first days of life; phototherapy causes severe blistering	Nordmann et al.[44]
	263700	*UROS*	AR	no VS			
Inherited metabolic disorders							
Biotin-thiamine responsive basal ganglia disease	607483	*SLC19A3*	AR	definitive	oral biotin and thiamine	treatment is benign and may prevent basal ganglia stroke; although neonatal presentation is rare, it can occur	Tabarki et al.[45]; Değerliyurt et al.[46]

(*Continued on next page*)

Table 3. ***Continued***

Phenotype	OMIM	Gene	Inheritance	ClinGen gene-disease validity	Treatment	Reason for early detection	References
Hereditary fructose intolerance	229600	*ALDOB*	AR	no VS	strict avoidance of fructose	infant formulas that contain fructo-oligosaccharides, as well as common medications in the neonatal period that contain sucrose (e.g., Sweet-ease) can cause life-threatening hepatic failure in the first week of life	Civit et al.[47]
Neurologic disorders							
Deafness, aminoglycoside-induced	580000	*MT-RNR1*	mtDNA	no VS	avoidance of aminoglycoside antibiotics	aminoglycosides are commonly used to prevent neonatal sepsis, but individuals with this variant are at risk for associated hearing loss	Göpel et al.[48]; Rahman et al.[49]
STXBP1-related neonatal epilepsy	612164	*STXBP1*	AD; AR	definitive	levetiracetam	complete seizure control and EEG normalization reported with levetiracetam (not a first-line neonatal ASM)	Dilena et al.[50]

The table is formatted so that for each phenotype, the columns for "OMIM," "Gene," "Inheritance," and "ClinGen gene-disease validity" are aligned horizontally within the same row to designate their association. The columns for "Treatment," "Reason for early detection," and "References" are associated with the overall phenotype but not tied to specific genes within that phenotype unless otherwise indicated.
AD, autosomal dominant; AR, autosomal recessive; ASM, anti-seizure medication; DDAVP, desmopressin; HSCT, hematopoietic stem cell transplantation; 5-HTP, 5-hydroxytryptophan; MAO-B, monoamine oxidase B; NSAIDs, nonsteroidal anti-inflammatory drugs; r-hIL-18BP, recombinant human interleukin-18 binding protein; SSRI, selective serotonin reuptake inhibitors; VS, validity score; XL, X-linked.
A full list of genes that could benefit from treatment in the first week of life are included in Table S4 ($n = 267$).

plausibly improve outcomes in the first week of life (Tables 3 and S4). For these conditions, all treatments discussed are clinically accepted (approved and standard of care) and can potentially improve outcomes if implemented at an earlier time in an individual's life. The disorders that may receive intervention *in utero* are organized by their level of clinical evidence along a continuum toward clinical approval. The disorders that may benefit from earlier implementation of approved treatments in the first week of life are organized alphabetically by the primary organ system affected.

Inclusion criteria

Risk-benefit ratio considered to be acceptable for fetus and pregnant person

With any fetal intervention, two individuals are implicated: the pregnant person and the fetus.[51] Because of this, the risk-benefit ratio of a fetal intervention must be tolerable, and there must also be potential efficacy without inflicting undue risk to either the pregnant person or fetus. For example, certain procedural fetal interventions carry a risk of preterm delivery, premature rupture of membranes, and oligohydramnios,[52] while the risks of medication administration to the pregnant individual may vary.[53] We defined a safe *in utero* intervention as one that did not result in fetal demise, did not lead to adverse side effects in the neonate or child, and did not cause unexpected adverse events in the mother.

In the case of *in utero* enzyme replacement therapy or other prenatal interventions administered directly to the fetus, there is limited concern for the drug to harm the mother, although these safety aspects are monitored in the pregnant individual through an active phase 1 clinical trial.[33,34,54] The reason for this is the relatively small medication dose compared to the pregnant individual's weight and the low risk of the pregnant individual (an obligate heterozygote in the majority of cases) recognizing the drug as a foreign antigen.

In the case of oral medications that have tolerable safety profiles in adults but may have a risk of embryotoxicity due to the potential impact on organogenesis based on animal studies (everolimus [Afinitor; see web resources] and sirolimus [Rapamune; see web resources]), it is important to note that the majority of medications discussed in Table 2 and S2 would not be implemented until after diagnosis is confirmed on amniocentesis, which is a procedure that occurs after organogenesis is complete. On the other hand, some medications are deemed extremely safe in pregnancy. An illustrative example is oral levothyroxine, which has not been shown to increase birth defects, miscarriages, or other adverse maternal or fetal outcomes.[55,56] Vitamins such as biotin, folic acid, vitamin B12, and pyridoxine are deemed safe in pregnancy as well.[57] Dietary supplements such as L-carnitine (levocarnitine [Carnitor; see web resources]), L-serine, and sialic acid are considered generally safe but may have more limited data in human pregnancy.[58]

Pregnancy registry data on antiepileptics have not reported risk with levetiracetam,[59] but instead indicate that dose adjustments may be required during pregnancy due to a decrease in plasma concentrations later in pregnancy (levetiracetam [Keppra; see web resources]). Mammalian target of rapamycin (mTOR) inhibitors, such as sirolimus and everolimus, have warnings surrounding potential risk to the fetus.[60] In cases such as these, systematic clinical trials are needed to further understand risk, given the competing risk posed by the fetal genetic disease. Many animal studies for various cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapies have not shown adverse events, but it is important to note that the human data from clinical trials is too incomplete to fully inform drug-associated risk in pregnant individuals.[61]

For disorders with treatments that may improve clinical outcomes in the first week of life, the available treatments are broadly considered safe for affected infants.

Plausibly efficacious treatment

Treatment efficacy was defined as improved neonatal outcomes when compared to the natural history of the disease.[34,62–64] We selected only disorders with treatments that are considered to be potentially effective in human case series or clinical trials. Although some disease-targeted interventions have been successful, others have led to adverse events and therefore were not included. For instance, intrauterine dexamethasone treatment for adrenal hyperplasia, congenital (MIM: 201910, 201810, 201710, 613743; clinicaltrials.gov: NCT02795871, NCT00617292) has extensive literature dating back to the 1980s and 1990s, but more recently was discovered to lead to cognitive impairment in children and was therefore deemed to be potentially harmful.[65–71] Additionally, reports of significant maternal side effects from dexamethasone administration present another concern.[72]

In some instances, the benefit of an intervention was incomplete or inconsistent. For example, in a case report of maternal biotin administration to a fetus with holocarboxylase synthetase deficiency (MIM: 253270), the authors concluded that although it may have improved fetal growth, the prenatally administered dose was insufficient to prevent the neonatal acidotic crisis this particular individual experienced.[73] We included this particular gene and disease because it suggests that the treatment was safe for the mother and fetus and that a higher dose of maternal biotin may have the potential to improve neonatal outcomes.

For disorders with treatments that may improve clinical outcomes in the first week of life, the available treatments are broadly considered effective but may not necessarily have reported use in newborns. In many cases, a confirmatory non-molecular test, such as a biochemical laboratory test or flow cytometry, can be completed shortly after birth to determine if signs of disease are present. Such tests ensure that the appropriate treatment is applied

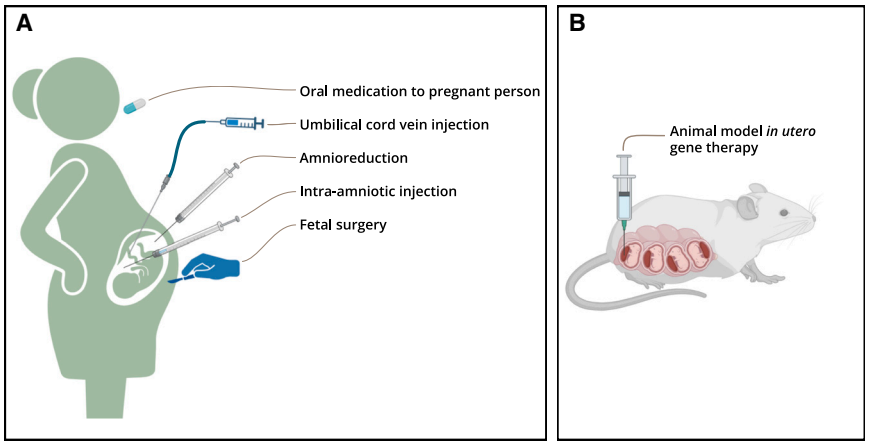

Figure 1. Methods of delivering fetal intervention in humans and animal models

(A) An increasing number of genetic disorders can now be intervened upon in the fetal period through various methods, including oral medication, umbilical cord vein injection, amnioreduction, intra-amniotic injection, and fetal surgery.

(B) Ongoing preclinical research in fetal gene therapy explores different delivery routes and vectors across mouse, rat, and canine models.

Drawings created with BioRender.

only to infants who are symptomatic or have orthogonal evidence of disease, which is of particular importance for disorders with incomplete penetrance or variable expressivity.

Clinically severe disorders

We selected only disorders that were associated with critical or chronic childhood illness. We excluded disorders such as adrenal hyperplasia, congenital, due to 21-hydroxylase deficiency (MIM: 201910), which more commonly presents in late childhood, adolescence, or adulthood, with symptoms that are not medically harmful, such as hirsutism and acne.

Potential as a fetal secondary findings list

Of note, the most common reason for ordering fetal GS is the presence of fetal structural anomalies.[74,75] However, many genes on this list are not associated with structural anomalies detectable by sonography. As such, these genes are unlikely to be considered diagnostic for the specific sonographic abnormalities that prompted an individual obtaining GS and may be better suited for separate interrogation as part of a secondary fetal findings gene list.

Exclusion criteria

Limited gene-disease validity

Gene-disease validity refers to the strength of evidence supporting or refuting a claim that variation in a particular gene causes a corresponding monogenic disorder.[76] All tables predominantly include genes with definitive, strong, or moderate gene-disease validity as annotated in ClinGen.[76] Some genes have not yet been curated by ClinGen. Genes with limited, disputed, or refuted ClinGen validity scores have been excluded.

Genetic disorders with evidence for fetal diagnosis and fetal intervention

An increasing number of genetic disorders can receive interventions in the fetal period through a range of therapeutic methods (Figure 1A). Fetal intervention and treatments for humans with various genetic disorders are in preclinical research stages, have advanced to clinical trials, or have been reported in single case reports.[77–80]

Interventions in preclinical research stages

Ongoing preclinical research in the field of fetal gene therapy explores various delivery routes and vectors across mouse, rat, and canine models (Figure 1B).[77–80] These delivery routes include injections that are intrahepatic, intracerebroventricular, intraplacental, intraperitoneal, intravenous, and into the yolk sac.[77] While the field of *in utero* gene therapy and gene editing continues to hold great promise for a range of disorders, some approaches have met with limited success, such as hematopoietic stem cell gene therapy in a canine model of Hurler syndrome (MIM: 607014), which was unable to reduce disease burden.[81]

Interventions in clinical trials

Systemically administered enzyme replacement therapy delivered through the umbilical cord vein (Figure 1A) has advanced to human clinical trials. This route of administration, also used for transfusions in fetal anemia,[82,83] delivers therapy directly to the fetus and has an acceptable safety profile. Another human clinical trial involves intra-amniotic injection (Figure 1A) of the protein that is absent in ectodermal dysplasia 1, hypohidrotic, X-linked (MIM: 305100).[35]

Additionally, administering low-toxicity medications to a pregnant individual, either orally or through injections or infusions, can treat fetal genetic disorders by crossing the placenta (Figure 1A). For instance, certain IMDs can be treated with a nutritional supplement or medication provided to the mother, which then crosses the placenta and improves enzyme activity or prevents toxic substrate accumulation in the fetus.[84–87] Furthermore, promising outcomes have also been observed in more prevalent diseases such as cystic fibrosis (MIM: 219700), in which modulator therapy administered to

pregnant individuals can improve outcomes of affected fetuses.[62–64] The ongoing exploration of therapeutic delivery to the pregnant individual or direct delivery to the fetus remains a viable path forward.

Interventions published in case reports

Cardiac disorders

In a recent example, a case of fetal bradycardia with positive maternal autoimmune antibodies was found to be unresponsive to maternal dexamethasone treatment, and genetic testing later revealed a *KCNH2* (MIM: 152427) variant-induced long QT syndrome 2 (MIM: 613688), demonstrating how molecular diagnosis can guide management by alerting the team that conventional prenatal treatment for a common problem may not be sufficient.[88] Relatedly, pathogenic variants in *SCN5A* (MIM: 600163), which can cause long QT syndrome 3 (MIM: 603830), can be treated with targeted medications.[88,89] Additionally, there are times that a genetic diagnosis can lead to management changes such as avoiding the otherwise accepted prenatal therapy; for example, fetal chylothorax in fetuses with *PTPN11* (MIM: 176876)-related Noonan syndrome 1 (MIM: 163950) responded poorly to *in utero* pleurodesis by OK-432.[90]

Hematologic disorders

Disorders that require disease-specific obstetric management should also be considered for inclusion in a treatable fetal findings list. For instance, for fetuses affected by hemophilia or another factor deficiency (MIM: 202400, 613679, 227400, 227500, 306700, 306900, 227600, 612416, 234000, 613225, 613235), cesarean section could be considered, and the use of vacuum-assisted delivery or forceps should be avoided to prevent intracranial hemorrhage.[91]

Inherited metabolic disorders

Case reports for disorders such as liver failure, infantile, transient (MIM: 613070) and methylmalonic aciduria and homocystinuria, cblC type (MIM: 277400), in which a safe postnatal medication is trialed prenatally via administration to the pregnant person, provide early evidence from which larger prospective clinical trials can be launched.[84–87] For these cases, the risk-benefit profile is favorable due to the low potential for maternal medication side effects. Among the case reports of oral administration of medication to a mother carrying an affected fetus, it is evident that the underlying molecular cause of a symptomatic presentation may help guide specific intervention.

Disorders for which prenatal genomic diagnosis may improve outcomes by administering treatment in the first week of life

Although NBS has prevented morbidity and mortality in infants with a range of IMD and other genetic disorders, several disorders included on the Recommended Uniform Screening Panel (RUSP) can cause critical illness in the first week of life before NBS results are typically returned. Additionally, there are a range of other disorders not yet included in public health NBS programs that also present with symptoms or have clinical therapies that could be initiated promptly after birth. These treatments are approved and represent the standard of care following the diagnosis of affected infants. None are preclinical treatments or currently in clinical trials. Here, we suggest beginning intervention immediately after birth.

Examples of treatment in the first week of life

Cardiac disorders

The genes that most commonly account for long QT syndrome (MIM: 613688, 192500, 603830) can cause fatal arrhythmias in fetuses or infants and have even been implicated in some cases of infant and childhood sudden death.[92,93] Medical management with beta-blockers or the implantation of a cardioverter-defibrillator may be lifesaving. Additional genes associated with long QT syndrome account for a very small proportion (<1%) of diagnoses (see web resources for long QT syndrome overview).

Endocrine disorders

Many neonatal-onset endocrine disorders can cause electrolyte disturbances, hypoglycemia, or salt-wasting crises in the first days of life, which lead to neurologic sequelae and even death.[94,95] While these symptoms can be partially managed without knowledge of the specific genotype, prenatal detection of these disorders may allow for more proactive clinical care and thereby prevent acute manifestations.[96] Additionally, in the example of congenital hyperinsulinism (MIM: 601820, 256450, 602485, 606762, 125850, 600496), knowledge of the underlying genotype allows for the appropriate treatment to be expedited, as diazoxide may not be effective in certain genetic subtypes.[97] Relatedly, the more common forms of diabetes mellitus, permanent neonatal (MIM: 618856, 618857) caused by pathogenic variants in *KCNJ11* (MIM: 600937) and *ABCC8* (MIM: 600509) typically present after the first week of life but can be improved by targeted treatment with sulfonylureas.[98]

Gastrointestinal disorders

There are several gastrointestinal disorders for which early identification could improve outcomes in infants. A variety of congenital diarrheas and enteropathies manifest immediately after birth and can be treated with disease-specific fluid and electrolyte therapies in the first few days of life (see web resources for Glucose galactose malabsorption).[99] Importantly, limitation of enteral feeding can lead to life-threatening acid-base instability.[100] Additionally, accurate identification of these disorders may prevent potentially unnecessary evaluations or surgeries for conditions such as pseudo-obstruction, which show imaging

findings similar to those of certain genetic conditions.[101] Autosomal recessive hyperlipoproteinemia, type 1D (MIM: 615947) can present with chylomicronemia shortly after birth, and early intervention can reduce morbidity.[102]

Hematologic disorders

A wide variety of genetic disorders of hematopoiesis as well as plasma proteins, particularly those involved in hemostasis, are amenable to *in utero* or perinatal therapies or management strategies. Nearly all severe fetal anemias, for example, respond to *in utero* transfusion, which can bridge the gap to birth, after which chronic transfusion, hematopoietic stem cell transplantation, or, increasingly, gene therapy can be delivered.[103–110] The erythroid porphyrias, protoporphyria, erythropoietic, 1 (MIM: 177000) and porphyria, congenital erythropoietic (MIM: 263700), do not themselves cause severe anemia, but the overproduction of porphyrins results in extreme light sensitivity, warranting the avoidance of neonatal phototherapy.[44] Disorders of granulocyte or platelet numbers or function generally do not cause disease in prenatal or perinatal life, but early identification may lead to prophylactic therapies to avoid bleeding or infectious complications (see web resources for Chediak-Higashi syndrome).[111,112] Recognition of clotting factor deficiencies may be an indication for cesarean section, prompt initiation of factor replacement, or avoidance of common procedures such as circumcision (see web resources for hemophilia A).[91]

Inborn errors of immunity

NBS for severe combined immunodeficiencies (SCIDs [MIM: 102700, 267500, 615617, 615615, 610163, 615401, 602450, 300400, 608971, 600802, 619374, 606593, 300988, 611291, 615966, 619924, 601457, 243150, 617514, 618986]) has improved morbidity and mortality for infants with the most severe form of immunodeficiency. Nonetheless, neonates with SCIDs can acquire life-threatening infections, in particular cytomegalovirus (CMV) from breast milk, prior to detection by NBS and confirmatory flow-cytometry testing.[113,114] In addition, false-negative NBS results for SCIDs do occasionally occur.[113] Prenatal detection of fetuses at risk for SCIDs would allow for improved management both pre- and postnatally. Prenatally, families could be referred for initial bone marrow transplant evaluation, and HLA typing could be initiated. Families could be referred to specific tertiary centers with providers experienced in treating individuals with SCIDs. In the neonatal period, measures including isolation precautions, immune prophylaxis, and counseling against breastfeeding for mothers positive for CMV could further reduce morbidity and mortality as confirmatory testing is performed. Of note, we did not include genes recently associated with SCIDs, which have a limited or not yet curated gene-disease relationship based on the ClinGen SCID-CID expert panel, e.g., *MAN2B2* (MIM: 618899) and *BCL11B* (MIM: 606558), both of which are associated with congenital anomalies and could be ascertained by indication-based testing.[115]

Variable expressivity is a common feature of inborn errors of immunity (IEIs), including SCIDs and combined immunodeficiencies (CIDs [MIM: 606843, 308230, 209920, 243700, 616873, 300636, 620815, 620816, 620817, 250250, 147060, 301000, 269840, 615758, 615816]). Many genes are associated with both SCIDs and CIDs, often due to hypomorphic variants linked to the latter. Due to the critical importance of identifying individuals at risk for SCIDs, we included genes associated with CIDs that can present in the neonatal period with SCIDs.[116] Because of the heterogeneity of CIDs and marked variable expressivity, it is challenging to definitively distinguish which CIDs would benefit from diagnosis within the first week of life. Early detection of many IEIs including CIDs could decrease morbidity and mortality during infancy but is beyond the scope of this review.[117]

We included genes associated with agammaglobulinemia (MIM: 613502, 300755, 613501, 601495, 616941/619824, 619705), a category of disorders predominantly associated with antibody deficiencies. Although infants with agammaglobulinemia typically present at 3–6 months of age, earlier diagnosis and treatment would likely prevent morbidity and mortality.[114] Several countries are implementing B cell kappa-chain receptor excision circles (KRECs) screening in conjunction with SCID NBS. This screening can detect individuals at risk for agammaglobulinemia.[114] These programs will provide critical information regarding the utility of neonatal detection, which can help inform genes chosen for the treatable fetal findings list.

We also included genes associated with diseases of immune dysregulation, congenital defects of phagocyte number, function, or both, defects in intrinsic and innate immunity, and autoinflammatory disorders. We included IEIs that can present during the neonatal period and are treatable.[116,118] We did not include complement deficiencies, as the typical age of onset is usually in childhood, although one neonatal presentation has been reported.[116,118] This is an area of active investigation, in particular for diseases of immune dysregulation and autoinflammatory disorders.[118] We anticipate that the list of genes associated with fetal and perinatal presentation will rapidly increase as these disorders are further characterized with growing awareness of potential fetal presentation.

Variable expressivity and incomplete penetrance are common features of IEIs. In particular, for IEIs with genotype-phenotype associations, consideration of both gene and specific variant would be important to consider prior to inclusion in a treatable fetal findings list. Neonatal orthogonal testing for IEIs, particularly flow cytometry, is a powerful additional tool when penetrance is unknown.

Inherited metabolic disorders

Many IMDs lead to symptoms in the first days of life, prior to the receipt of NBS results. The detection of at-risk fetuses

would allow pregnant individuals to prepare for delivery in a clinical center where a specialized biochemical genetics team is present or allow advanced notice for the birth center to procure the necessary metabolic medications and formulas.

In a recent example, a female fetus with pyruvate dehydrogenase E1-alpha deficiency (MIM: 312170) was diagnosed via exome sequencing in the setting of structural brain malformations.[119] This prenatal diagnosis allowed for interdisciplinary delivery planning among the pregnant individual's obstetric providers and the institution's pediatrics teams, including biochemical genetics specialists, neonatologists, and dieticians with expertise in the ketogenic diet. The infant was placed on a ketogenic diet immediately after birth and, as a possible result, experienced no seizures or lactic acidosis in the neonatal period. This case illustrates the potential opportunity for infants with other IMDs requiring specialized diets or medications, such as organic acidemias or urea cycle disorders, to receive appropriate treatment beginning at birth. In some cases, prompt initiation of treatment may prevent the accumulation of toxic intermediates that lead to severe metabolic decompensations, characterized by lethargy, seizures, and even early death. Early treatment of IMDs therefore has the potential to improve lifelong health and quality of life for affected individuals.

Of note, one challenge that may arise across these disorders is that specific variants in some genes (such as those associated with carnitine palmitoyltransferase II deficiency, myopathic, stress-induced [MIM: 255110]) are strongly associated with attenuated or late-onset forms of disease, which do not meet the inclusion criteria for this review. If these genes were adapted for a treatable fetal findings list, further discussion will be needed regarding which PLPVs to analyze and report.

Neurologic disorders

The management of infants at risk for many monogenic disorders with neurologic symptoms could be improved by identification prior to birth. In particular, several syndromes causing neonatal seizures are optimally treated with specialized management that differs from the standard of care; prompt initiation of the appropriate anti-seizure medication is more likely to lead to complete seizure control.[120] Additionally, for disorders such as the congenital myasthenic syndromes (MIM: 614750, 610542, 615350, 614198, 618197, 616228, 617143, 616040, 601462, 616313, 616322, 608931, 616326, 254300, 616325, 613723, 603034, 616720, 615120, 254210, 617239, 616330, 618323, 616224), the effect of acetylcholinesterase therapy depends directly on the genotype, which in some cases can worsen symptoms and lead to critical illness (see web resources for congenital myasthenic syndromes overview).

One unique entity that meets criteria for inclusion is the mtDNA variant m.1555A>G in the *MT-RNR1* gene (MIM: 561000). This variant is a risk allele for deafness, aminoglycoside-induced (MIM: 580000). Although this variant is not expected to cause symptoms *a priori*, for infants who undergo preventive treatment of sepsis, commonly used aminoglycoside antibiotics may put them at risk for hearing loss. Instead, targeted pharmacologic treatment for these infants might lead to the use of a different antibiotic.[121]

Renal disorders

Infants at risk for two renal disorders, cystinosis (MIM: 219800) and hyperoxaluria, primary, type 1 (MIM: 259900), would particularly benefit from treatment in the first week of life to preserve renal function. Cystinosis leads to cystine accumulation in various tissues, including the kidney. Although clinical symptoms do not typically occur until approximately 6 months of age, glomerular damage accumulates from birth. Early treatment with cystine-depleting agents such as cysteamine immediately after birth can slow this damage.[122,123] Hyperoxaluria, primary, type 1, which presents in the first months of life in 10% of affected individuals, results in oxalate accumulation, causing nephrocalcinosis, nephrolithiasis, and progressive kidney damage (see web resources for primary hyperoxaluria type-1: an unprecendented presentation at birth).

Exploring the potential for a secondary findings panel specific to fetal sequencing

Fetal GS is poised to play an increasingly significant role in prenatal diagnosis. The ISPD recommends offering GS to all pregnant individuals whose fetuses have structural abnormalities,[1] which would encompass up to 2%–3% of pregnancies.[2] Additionally, several research studies have explored fetal GS in non-anomalous fetuses, finding that 0.06%–2.7% have variants associated with monogenic disease.[16–19] Currently, no established guidelines regarding which monogenic variants to report in fetal GS exist, and the role of secondary findings remains unclear. Analysis of a treatable fetal findings list could be optionally offered to pregnant individuals undergoing diagnostic fetal GS. Alternatively, this list might eventually serve as a panel for non-anomalous fetuses or couples with a family history of an undiagnosed disorder and could eventually be ascertained using cell-free fetal DNA.[124–127] Of note, however, the list in this review is not comprehensive or consensus based and will require updates as new research and interventions emerge.

Importantly, parents have demonstrated interest in using GS to diagnose disorders with available experimental *in utero* interventions. In surveys of parents with children affected by mucopolysaccharidoses (MIM: 607014, 309900, 253000, 253200, 253220), for example, the majority of parents had a favorable attitude toward phase 1 clinical trials for fetal therapy.[128] Similarly, survey results from families affected by spinal muscular atrophy (MIM: 253300) and sickle cell disease (MIM: 603903)

overwhelmingly supported prenatal diagnosis, and the majority expressed an interest in fetal therapy.[129,130] Identifying treatable monogenic disorders during the fetal period could therefore enhance individuals' care options and autonomy during pregnancy as well as improve the neonatal and lifelong health of affected infants.

In this integrative review, we compiled a list of 296 genes associated with disorders for which therapeutic intervention—either in the fetus (54 genes, Tables 2 and S2) or in the first week of life (267 genes, including 25 genes that appear on both lists, Tables 3 and S4)—could improve health outcomes. Tables 2 and S2 are organized by the highest level of evidence, and Table 2 focuses on those diseases for which a fetal clinical trial is currently available. Tables 3 and S4 describe standard-of-care early-life treatments, with Table 3 detailing illustrative examples of the complete gene list shared in Table S4. At present, we suggest that the disorders for which there have been successful treatments reported in individual human cases, disorders with fetal interventions that are currently in clinical trials, and disorders for which treatment in the first week of life may improve outcomes should be considered for a treatable fetal findings list, taking into account the selection criteria established in Table 1. If this list is implemented, the efficacy and safety of fetal interventions, based on information conveyed in the pregnancy and lactation labeling rule, should also be continuously monitored and updated. In practice, genomic variants related to this gene list will lead to the need for further clinical correlation, personalized discussions of the risks and benefits of each treatment, and shared decision-making with patients. Ultimately, additional systematic clinical trials will be needed in many cases. Yet, providing care teams and patients with this information has the potential to improve fetal outcomes and neonatal health.

Although GS allows for querying the entire genome, and any genomic finding could be considered actionable in the perinatal period, presenting the option to assess a list of treatable fetal disorders is an important step toward enhancing the autonomy of pregnant individuals. In the future, pregnant individuals could be offered the option for GS to focus on variants associated with sonographic findings or to also include additional treatable findings or analysis of the whole genome. If whole-genome analysis were pursued, these lists of disorders could also be used to guide discussions on potential treatment opportunities, which would provide people with a more comprehensive range of care options. Furthermore, reporting all PLPVs associated with childhood-onset disorders may be premature and pose challenges to counseling, as the penetrance and expressivity of many variants are not yet well understood.[131]

Although the treatable disorders listed in this review are all relatively well characterized in the medical literature, other challenges remain in establishing the clinical utility of a treatable fetal findings list. The penetrance of many of these disorders is unknown, and the paucity of diagnostic imaging signs or non-molecular confirmatory testing available in fetuses limits diagnostic certainty.[132,133] Fetal GS is complicated by incomplete phenotyping due to ultrasound limitations,[14] and many disorders may have no discernible prenatal phenotype to substantiate the diagnosis.[132,133] Efforts are underway to expand entries in the Human Phenotype Ontology related to prenatal presentations; however, this does not address incomplete phenotyping related to technological limitations.[133] While tests such as fetal enzyme activity using placental[134] or umbilical cord blood samples are possible, interpreting results is difficult without established fetal norms.[135] After birth, genetic diagnoses can be confirmed by non-genetic findings, but during the fetal period, treatment decisions may rely solely on genetic information.

Implementation of a treatable fetal findings list may also be complicated by barriers to care in resource-limited settings and by psychosocial ramifications. Access to fetal GS is inequitable,[136] and the additional analysis of treatable disease genes could potentially widen health disparities. Reporting only PLPVs, as has been recommended by the ACMG, may lead to inequities for reproductive couples of non-European ancestry in whom variants of uncertain significance are more common.[137] When a positive finding is identified, it may be infeasible for some individuals to receive care at a clinical center where the appropriate treatment is available.[138] Pregnant individuals offered GS in the setting of a fetal anomaly might face an overwhelming amount of information if offered multiple secondary or treatable findings lists, and it may be a new challenge for physicians and genetic counselors to consent individuals for the analysis of potential secondary findings.[139–142] We also acknowledge that a list of treatable disorders could be used as a justification to limit pregnant individuals' reproductive options. In addition to deciding whether to continue or terminate a pregnancy of a fetus with a genetic disorder, these lists of genes are meant only to provide another option of early treatment, which in some cases has the potential to change the natural history of a disease. However, many of these interventions are not yet proven and are not the standard of care, and therefore should not be viewed as a reason to curtail reproductive decision-making. As the clinical use of fetal GS expands, the clinical, ethical, legal, and social ramifications of this technology will continue to be a field of active research.

The use of trio GS as a tool to investigate conditions affecting the pregnant individual is also an important new direction for investigation. Given that fetal GS typically includes a sample from the pregnant individual and that the maternal genome is also assessed in cell-free DNA (cfDNA) sequencing, additional genetic disorders that affect fetal or maternal health, or lead to pregnancy complications, could also be considered for inclusion. For example, the pregnant individual's sample could reveal disorders that are teratogenic to the fetus, such as maternal phenylketonuria (MIM: 261600)[143] or thrombotic thrombocytopenic purpura, hereditary (MIM: 274150).[144] Additionally, analysis of this sample could identify a risk for

disorders that may present in the breastfeeding infant, such as zinc deficiency, transient neonatal (MIM: 608118) or acrodermatitis enteropathica, zinc-deficiency type (MIM: 201100),[145] which can be prevented by supplementation of the deficient nutrient. Furthermore, identifying genetic conditions that affect the health of the pregnant or postpartum individual, such as ornithine transcarbamylase deficiency (MIM: 311250), Ehlers-Danlos syndrome, vascular type (MIM: 130050), or cardiomyopathies, could prevent deadly complications such as hyperammonemia or uterine rupture.[146] Lastly, detecting fetal conditions such as fatty acid oxidation disorders may also inform prenatal care, as they can cause secondary effects in the pregnant individual.[147]

As access to fetal GS grows and the capabilities of cfDNA sequencing advance, the field of prenatal genetic diagnosis will continue to expand. The implementation of a treatable fetal findings list has the potential to enhance the autonomy of pregnant individuals and improve the health of infants with rare diseases. There is evidence to suggest that a large number of genes are associated with conditions that are intervenable *in utero* or during the immediate perinatal period. In time, our understanding of variant curation and prenatal phenotypes will grow, which will improve post-test counseling for pregnant individuals with PLPVs found on fetal GS. Although challenges remain regarding the equitable implementation of fetal GS, a treatable fetal findings list could currently be offered to individuals who are undergoing this test, and eventually may form the basis of a non-invasive screening tool performed on cfDNA that could be offered to all pregnant individuals.

Data and code availability

This study did not generate any datasets or code.

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Declaration of interests

J.L.C. has received compensation for advising at Bayer HealthCare Pharmaceuticals and served as an advisor on a Sanofi Advisory Board. M.D. has received a speaking honorarium from Illumina, Inc. M.F. has received compensation for advising the following companies: Vertex Pharmaceuticals, Affyimmune Pharmaceuticals, and Evolve Immune Pharmaceuticals. He also serves on scientific advisory boards for Disc Medicine and Minerva Biotechnologies. R.G. is a paid consultant for Nurture Genomics & Minovia Therapeutics. D.M.M. receives compensation for advising the following companies: Amolyt and Ascendis. W.T. serves as a paid consultant for Amgen Pharmaceuticals and participates on an Advisory Board for cystinosis. M.A.W. is an author on a pending patent application, US Provisional Patent Application 63/034,740 "Methods of Detecting Mitochondrial Diseases." R.C.G. has received compensation for advising the following companies: Allelica, Atria, Fabric, and Juniper Genomics; and is a co-founder of Genome Medical and Nurture Genomics. N.B.G. has received an honorarium from Ambry Genetics.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT in order to generate ideas about disorders with fetal interventions and clarify grammar and syntax of some sentences. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

Supplemental information

Supplemental information can be found online at https://doi.org/10.1016/j.ajhg.2025.03.011.

Web resources

Afinitor (everolimus), https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/203985s023,022334s051lbl.pdf
Carnitor (levocarnitine), https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/018948s028,019257s014lbl.pdf
Chediak-Higashi syndrome, https://www.ncbi.nlm.nih.gov/books/NBK5188/
ClinicalTrials.gov, https://clinicaltrials.gov/
Congenital myasthenic syndromes overview, https://www.ncbi.nlm.nih.gov/books/NBK1168/
Glucose galactose malabsorption, https://www.ncbi.nlm.nih.gov/books/NBK22210/
Hemophilia A, https://www.ncbi.nlm.nih.gov/books/NBK1404/
Keppra (levetiracetam), https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/021035s115,021505s053lbl.pdf
Long QT syndrome overview, https://www.ncbi.nlm.nih.gov/books/NBK1129/
Newborn Screening Process, https://newbornscreening.hrsa.gov/newborn-screening-process
OMIM, https://www.omim.org/
Primary hyperoxaluria type-1: an unprecedented presentation at birth, https://www.ncbi.nlm.nih.gov/pubmed/15767715
Rapamune (sirolimus), https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021083s069s070,021110s087s088lbl.pdf

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Supplemental information

Advancing precision care in pregnancy through a treatable fetal findings list

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Supplemental Material and Methods

Supplemental Methods

Search strategy for genetic disorders that have in utero interventions

A literature review was conducted to develop the list of disorders that can receive intervention *in utero*. The authors conducted a review of clinicaltrials.gov (search terms: “fetal therapy”, “genetic” returned 256 results, with 8 relevant studies), ChatGPT[1] and Microsoft CoPilot[2] queries for available prenatal therapies for genetic disease, and a medical librarian-led search in Embase using search terms: “fetal therapy,” “fetal treatment,” “*in utero* therapy,” “*in utero* treatment,” “prenatal therapy,” “prenatal treatment” and limited to randomized controlled trials, clinical trials, case studies, and case reports (Table S2) that yielded 593 titles and abstracts which were reviewed by two authors (J.L.C. and M.D.) for relevance. The searches were limited to English. These titles and abstracts were reviewed using Covidence.[3] Articles deemed relevant by one or both authors were added to the tables and manuscript text if they met inclusion criteria. Full text manuscripts were reviewed on an as-needed basis.

Development of a list of disorders that are treatable in the first week of life

To develop a list of disorders that are treatable in the first week of life, the authors reviewed the disorders on the Recommended Uniform Screening Panel (RUSP)[4] and a list of 651 genes associated with treatable genetic disorders,[5] aggregated from various online tools and published reports.[6–11] Using these previously compiled lists, the authors included disorders that could benefit from antenatal detection and early postnatal treatment to improve neonatal outcomes. Additionally, the authors incorporated several disorders based on new evidence since the publication of the prior lists or as deemed appropriate according to the selection criteria.

Authors with expertise in various disease areas constructed each clinical section of this list (cardiac disorders: A.R.; endocrine disorders: D.M.M.; gastrointestinal disorders: A.S., J.R.T.; hematologic disorders: M.D.F.; inborn errors of immunity: R.H.; inherited metabolic disorders: R.G., N.B.G.; neurologic disorders: M.A.W.; renal disorders: W.T.). The list of all genes and disorders were then reviewed by the senior author (N.B.G.) for consistency with the selection criteria.

Set #	Search Strategy	Results
1 *Fetal therapy*	'fetal therapy'/exp OR 'fetal therapy' OR 'fetal therapies' OR 'foetal therapy' OR 'foetal therapies' OR 'fetal treatment' OR 'fetal treatments' OR '*in utero* treatment' OR '*in utero* treatments' OR '*in utero* therapy' OR '*in utero* therapies' OR 'prenatal therapy' OR 'prenatal therapies' OR 'prenatal treatment' OR 'prenatal treatments'	5,610
2 *And study filters*	('fetal therapy'/exp OR 'fetal therapy' OR 'fetal therapies' OR 'foetal therapy' OR 'foetal therapies' OR 'fetal treatment' OR 'fetal treatments' OR '*in utero* treatment' OR '*in utero* treatments' OR '*in utero* therapy' OR '*in utero* therapies' OR 'prenatal therapy' OR 'prenatal therapies' OR 'prenatal treatment' OR 'prenatal treatments') AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim OR 'clinical trial' OR 'controlled trial' OR 'case report' OR 'case study')	1,041
3 *And article status and english*	('fetal therapy'/exp OR 'fetal therapy' OR 'fetal therapies' OR 'foetal therapy' OR 'foetal therapies' OR 'fetal treatment' OR 'fetal treatments' OR '*in utero* treatment' OR '*in utero* treatments' OR '*in utero* therapy' OR '*in utero* therapies' OR 'prenatal therapy' OR 'prenatal therapies' OR 'prenatal treatment' OR 'prenatal treatments') AND ([controlled clinical trial]/lim OR [randomized controlled trial]/lim OR 'clinical trial' OR 'controlled trial' OR 'case report' OR 'case study') AND ([article]/lim OR [article in press]/lim OR [data papers]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [short survey]/lim OR [preprint]/lim) AND [english]/lim	601

Table S1. Search strategies and results for titles and abstracts detailing genetic disorders with *in utero* interventions. Date: August 13, 2024. Database / Study Registry (including vendor/platform): Embase (Elsevier).

Table S2. Genes associated with disorders with *in utero* fetal interventions in clinical trials and case reports (n = 54). See supplemental excel file.

The table was formatted so that for each phenotype, the columns for "OMIM," "Gene," "Inheritance," and "ClinGen gene-disease validity" were aligned horizontally within the same row to designate their association. The columns for "Fetal intervention," "Clinical Area," and "Citations" were associated with the overall phenotype but not tied to specific genes within that phenotype unless otherwise indicated.

Abbreviations: AD: Autosomal dominant; AR: Autosomal recessive; ERT: Enzyme replacement therapy; hAFMSCs: Human amniotic fluid mesenchymal stromal cells; HSC: Hematopoietic stem cells; HSCT: Hematopoietic stem cell transplantation; LT4: Levothyroxine; LXR-agonist: Liver X receptor agonist; VS: Validity score; VT: Ventricular tachycardia; XL: X-linked

Table S3. Genes associated with disorders with experimental *in utero* fetal interventions in animal models (n = 19). See supplemental excel file.

Abbreviations: AAV: adeno-associated virus; AD: autosomal dominant; ASO: antisense oligonucleotide; AR: autosomal recessive; ERT: enzyme replacement therapy; HSC: hematopoietic stem cells; HSCT: hematopoietic stem cell transplantation; LXR-agonist: Liver X receptor agonist; SAMe: S-adenosylmethionine; VS: validity score; XL: X-linked

Table S4. Genes associated with disorders with clinically available therapies that could be applied in the first week of life (n = 267). See supplemental excel file.

The table was formatted so that for each phenotype, the columns for "OMIM," "Gene," "Inheritance," and "ClinGen gene-disease validity" were aligned horizontally within the same row to designate their association. The columns for "Treatment," "Reason for early detection," and "Citations" were associated with the overall phenotype but not tied to specific genes within that phenotype unless otherwise indicated.

Abbreviations: AChE: Acetylcholinesterase; AD: Autosomal dominant; AR: Autosomal recessive; ASM: Anti-seizure medication; BCAA: Branched chain amino acids; DDAVP: Desmopressin; G-CSF: Granulocyte colony stimulating factor; GM-CSF: Granulocyte-macrophage colony-stimulating factor; HSCT: Hematopoietic stem cell transplantation; GOF: Gain of function; 5-HTP: 5-hydroxytryptophan; LT4: Levothyroxine; LOF: Loss of function; MAO-B: Monoamine oxidase B; N/A: Not Applicable due to absent OMIM entry; NSAIDs: Nonsteroidal anti-inflammatory drugs; rhGH: Recombinant human growth hormone; r-hIL-18BP: Recombinant human interleukin-18 binding protein; SCID: Severe combined immunodeficiency; SSRI: Selective serotonin reuptake inhibitors; TSH: Thyroid-stimulating hormone; VS: Validity score; XL: X-linked

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