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Non-invasive Ultra-early in Utero Detection and Precision CRISPR-mediated Correction of Monogenic Embryonic Mutations: A Critical Appraisal of a Hypothetical Therapeutic Framework

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Abstract

Advances in circulating placental DNA analysis and in programmable genome editing have developed largely in parallel, yet their conjunction has generated an increasingly discussed proposition: that a pathogenic single-gene variant might be identified non-invasively at the earliest stage of pregnancy and corrected in situ before irreversible pathology develops. This review examines whether that proposition is presently coherent as a therapeutic framework, rather than merely attractive as an idea. The analysis synthesises evidence on the provenance and kinetics of cell-free placental DNA, the analytical performance of relative mutation dosage, relative haplotype dosage, targeted haplotyping and cell-based prenatal diagnosis, and the preclinical record of

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nuclease-dependent editing, base editing and prime editing delivered to the fetal compartment by viral and lipid-nanoparticle carriers. Evidence quality was appraised with attention to study design, model relevance, endpoint validity, replication and the distance between mechanistic demonstration and clinical benefit. Three findings dominate. First, the detection half of the framework is constrained less by sequencing chemistry than by biology: circulating fetal-derived DNA is placental in origin, is present at low fractional abundance in the earliest weeks, and is an imperfect proxy for the fetal genotype. Second, the therapeutic half rests almost entirely on rodent studies in which editing efficiencies, delivery routes and endpoints do not correspond to the requirements of a human first-trimester intervention, and the only in utero therapies tested in human pregnancies have been protein and cell based rather than gene editing. Third, the interval implied by ultra-early diagnosis is precisely the interval in which delivery, dosing and germ-cell exposure are least characterised. The framework is therefore best regarded as a research programme with identifiable and testable intermediate objectives, not as an imminent clinical pathway. Priorities include gestational-age-resolved fetal fraction studies, editing outcome measurement at single-cell resolution, large-animal dosimetry, and governance work addressing the somatic and germline boundary in prenatal intervention.

Keywords: Cell-free fetal DNA; non-invasive prenatal diagnosis; in utero gene editing; base editing; prime editing; lipid nanoparticles; fetal therapy; research governance.

1. Introduction

Disorders caused by variation at a single locus remain a substantial and unevenly distributed contributor to perinatal and childhood morbidity. Modelling based on national and regional registries estimates that congenital disorders attributable to single-gene variation affect several per thousand live births worldwide, with the highest burdens in populations where consanguineous union is customary and where carrier screening and specialist services are least available (Blencowe *et al.*, 2018). Haemoglobin disorders alone account for a large share of that burden, and service-planning indicators derived from global epidemiological modelling have long indicated a mismatch between the geographical distribution of affected births and the distribution of diagnostic and therapeutic capacity (Modell & Darlison, 2008). The clinical problem is therefore not only that these conditions are severe, but that the interventions currently available to families are concentrated in high-income settings and are, for the most part, offered after the biological process they are intended to alter has already begun.

Two technological trajectories have altered what can plausibly be offered. The first began with the demonstration that fetal-derived DNA circulates in maternal plasma (Lo *et al.*, 1997), a finding that supported massively parallel sequencing approaches to aneuploidy detection (Chiu *et al.*, 2008) and, subsequently, reconstruction of substantial portions of the fetal genome from maternal plasma (Kitzman *et al.*, 2012; Lo *et al.*, 2010). Applied to monogenic conditions, the same substrate now supports accredited diagnostic services for selected autosomal dominant, X-linked and recessive conditions (Hanson *et al.*, 2024; Young *et al.*, 2020). The second trajectory began with nuclease-based editing and has moved through base editing (Komor *et al.*, 2016) and prime editing (Anzalone *et al.*, 2019) to approved autologous cell products (Frangoul *et al.*, 2021) and, most strikingly, to a bespoke in vivo base-editing agent designed, manufactured and administered to a single infant within months of diagnosis (Musunuru *et al.*, 2025).

Recent clinical literature illustrates both the expansion and the present boundary of this diagnostic trajectory: prospective comprehensive cell-free DNA screening has incorporated selected monogenic variants in high-risk pregnancies, while contemporary reviews continue to distinguish such screening from definitive diagnosis and to emphasize limitations relevant to clinical interpretation (Zhang *et al.*, 2024; Goodhue *et al.*, 2024).

The juxtaposition of these trajectories invites a specific proposition. If the causal variant can be identified from maternal plasma in the first weeks of pregnancy, and if a correcting agent can be delivered to the fetal compartment, then the pathological sequence might be interrupted before organ systems are irreversibly committed. Preclinical work has given the proposition partial empirical content. Nuclease and base-editing reagents delivered to fetal mice have altered metabolic and pulmonary phenotypes (Alapati *et al.*, 2019; Bose *et al.*, 2021; Rossidis *et al.*, 2018), and peptide nucleic acid nanoparticles have achieved site-specific correction of a globin variant and, more recently, of a cystic fibrosis transmembrane conductance regulator variant after systemic administration (Ricciardi *et al.*, 2018, 2025). Ionisable lipid nanoparticles have extended in utero editing to haematopoietic stem cells and to the developing brain (Gao *et al.*, 2024; Palanki *et al.*, 2024).

Existing reviews have treated the two halves of this proposition separately. Reviews of fetal gene therapy describe vector biology, candidate indications and preclinical progress without interrogating whether a diagnosis capable of triggering such therapy can be obtained early enough to matter (Jeanne & Chung, 2025; Katz *et al.*, 2026; Waddington *et al.*, 2024). Position statements on non-invasive prenatal testing and on prenatal genome-wide sequencing concentrate on screening performance, counselling and confirmatory testing, and do not consider the analytical requirements imposed by a downstream therapeutic decision (Hui *et al.*, 2023; Van den Veyver *et al.*, 2022). A recent scoping review of in utero gene therapy for sickle cell disease is closer to the intersection but restricts itself to one condition and does not evaluate the diagnostic pathway that would identify candidates (Cudjoe *et al.*, 2026). The result is a literature in which each half is optimistic about the other, and in which the assumptions each makes about the other are rarely stated, let alone tested.

Recent syntheses of embryo and fetal genome editing and of in-utero therapeutic study design similarly emphasize that clinical translation depends on resolving delivery, safety, maternal-fetal risk and evidentiary questions rather than on editing chemistry alone (Mattar *et al.*, 2024; Gough *et al.*, 2025).

That gap matters because the framework is temporally coupled in a way that most therapeutic proposals are not. The value of ultra-early detection depends entirely on whether an intervention exists that benefits from being applied ultra-early; the value of in utero correction depends on whether a diagnosis can be secured while the developmental advantage is still available. A critical appraisal must therefore evaluate the two halves against each other, and against the biology of the maternal-fetal interface that constrains both.

1.1 Scope, Research Gap and Objectives

This review examines the conjunction of two research programmes: non-invasive detection of pathogenic single-gene variants in ongoing pregnancies at the earliest gestational ages at which circulating placental DNA is analytically accessible, and programmable correction of such variants within the fetal compartment. The scope is deliberately restricted to monogenic conditions with a defined causal variant, to detection from maternal peripheral blood or from fetal-derived cells recovered from maternal blood, and to editing modalities that alter the nuclear genome of somatic cells after implantation. Chromosomal aneuploidy screening, preimplantation genetic testing, mitochondrial replacement, epigenetic modulation without sequence change, and postnatal gene therapy are outside the scope except where they provide comparative evidence. Editing of zygotes or preimplantation embryos is discussed only as a source of mechanistic evidence about editing behaviour in early human development and about the governance boundary that prenatal somatic intervention approaches.

The research gap addressed here is the absence of an integrated critical evaluation of whether the diagnostic and therapeutic halves of this framework are compatible in time, in analytical resolution and in biological substrate. Reviews of each half exist; an appraisal of the coupling does not.

Four objectives follow. The first is to establish, from the available evidence, what determines the earliest gestational age at which a monogenic diagnosis of therapeutic quality can be obtained non-invasively, and how far that limit is biological rather than technical. The second is to assess whether current editing chemistries and delivery systems can plausibly achieve the cellular coverage and precision that correction of a constitutional variant would require. The third is to identify where the two halves make incompatible assumptions about each other, and to distinguish problems that are engineering questions from those that are questions of principle. The fourth is to set out research priorities that would resolve the most consequential uncertainties, and to state which claims the present evidence cannot support. Cost-effectiveness modelling, jurisdiction-specific legislative analysis and detailed counselling protocols are excluded, although governance is addressed where it bears directly on evidentiary standards.

2. Methods for Literature Selection

2.1 Review Design and Rationale

A critical narrative review was selected because the question posed here is integrative rather than comparative in the sense required by systematic review methodology. The evidence base spans human observational diagnostic studies, rodent and large-animal interventional work, single-patient therapeutic reports, and normative analysis, with no common intervention, comparator or outcome that would permit pooled estimation. A systematic review would either impose an artificial uniformity on these literatures or exclude most of them. Narrative synthesis is appropriate when the aim is to interrogate assumptions across bodies of work rather than to estimate an effect (Greenhalgh *et al.*, 2018; Sukhera, 2022). Narrative methodology does not remove the obligation of transparency, and the reporting of search sources, selection reasoning and appraisal criteria in this review follows the domains specified for narrative review quality assessment (Baethge *et al.*, 2019).

2.2 Information Sources

Literature was identified through Europe PMC, Crossref and the Directory of Open Access Journals. Bibliographic metadata for every cited item, including author order, journal title, volume, issue, pagination or article number and digital object identifier, were confirmed against Crossref records and, where available, against the corresponding Europe PMC record. Institutional material was retrieved directly from the websites of the World Health Organization and of the National Academies of Sciences, Engineering, and Medicine. Database searching was supplemented by backward citation searching of retrieved reviews and primary studies, by forward and related-article searching within the indexes named above, and by targeted verification searches for corrections and errata attached to individual records. Subscription-only bibliographic databases were not accessible during preparation and no search of such databases is claimed.

2.3 Search Strategy and Search Period

Search concepts were constructed from four domains: the analyte and its biology, the diagnostic method, the therapeutic modality, and the fetal or prenatal context. Representative strings combined controlled and free-text terms, for example (“cell-free fetal DNA” OR “circulating placental DNA” OR “fetal fraction”) AND (“non-invasive prenatal diagnosis” OR “relative haplotype dosage” OR “relative mutation dosage” OR “targeted haplotyping”) AND (monogenic OR “single gene”); (“in utero” OR fetal OR prenatal) AND (“gene editing” OR “genome editing” OR CRISPR OR “base editing” OR “prime editing”) AND (delivery OR “lipid nanoparticle” OR “adeno-associated virus”); and (“germ line” OR “germ cell” OR heritable) AND (“in utero” OR prenatal) AND (“gene transfer” OR “genome editing”). Additional strings addressed confined placental mosaicism, on-target genomic consequences of nuclease cleavage, pre-existing immunity to editing nucleases and vectors, and the ethical and regulatory literature on prenatal intervention and heritable genome editing.

The search period began in 1997, the year in which fetal-derived DNA was first demonstrated in maternal plasma, since no part of the detection framework is intelligible before that observation and the editing literature postdates it entirely. Foundational earlier work was eligible where it was necessary to explain developmental biology, established diagnostic practice or historical context. The final search date was 15 June 2026.

2.4 Eligibility Criteria

Eligible material comprised peer-reviewed original research, systematic and narrative reviews, professional society position statements, and reports of intergovernmental or national scientific bodies, published in English. Human diagnostic studies were eligible when they reported analytical or clinical performance for single-gene conditions or characterised the biology of circulating fetal-derived nucleic acids. Interventional studies were eligible when they administered an editing or gene-transfer agent to a fetus or to a pregnant animal, or when they characterised editing outcomes relevant to fetal application. Normative and governance sources were eligible when they addressed prenatal intervention, fetal therapy or heritable genome modification directly.

Excluded were conference abstracts without full reports, commercial and promotional material, patents cited as evidence of effectiveness, non-scholarly commentary, and any record whose bibliographic identity could not be confirmed. Preprints were excluded because peer-reviewed evidence was available for every theme addressed. Retracted material was not used. Studies of in utero electroporation and similar experimental manipulations were excluded when they served only as neuroscience research tools with no therapeutic delivery relevance.

2.5 Screening, Duplicate Handling and Study Selection

Records retrieved by each search string were screened by title and abstract against the eligibility criteria, and candidate records were then assessed in full text where accessible or, where full text was restricted, against the abstract together with the verified bibliographic record and any accessible author manuscript. Duplicates arising from overlapping index coverage were identified by digital object identifier and, where absent, by matching of title and first author, and were resolved to the version of record; where a preprint and a peer-reviewed article described the same work, only the peer-reviewed version was retained and cited. Records for which the version of record could not be located, or for which metadata conflicted irreconcilably across sources, were not used. Because selection was purposive rather than exhaustive, no screening counts are reported and no flow diagram is presented; reporting such figures would imply a systematic selection process that was not undertaken.

2.6 Critical Appraisal and Evidence Synthesis

Sources were appraised against criteria appropriate to their design. Human diagnostic studies were assessed for cohort size and composition, gestational age range, reference standard, handling of failed or uninformative results, and whether reported performance derived from prospective clinical testing or from retrospective reanalysis of selected samples. Animal interventional studies were assessed for species and model fidelity, route and timing of administration, whether editing efficiency was measured in the tissue responsible for the phenotype, duration of follow-up, and whether functional rather than molecular endpoints were reported. Single-patient reports were treated as demonstrations of feasibility rather than as evidence of efficacy. Normative sources were assessed for the transparency of their reasoning and the standing of the issuing body. Formal risk-of-bias instruments were not applied, because the heterogeneity of designs precluded consistent use of any single validated tool and because several key sources are not study reports at all.

Themes were developed inductively from recurring points of tension rather than imposed in advance, and were organised around the causal chain that the framework presupposes: what can be detected, when, with what fidelity to the fetal genotype; what can be delivered, where, and to what proportion of cells; and what follows from the answers for safety, governance and research design. Where studies disagreed, the disagreement was traced to its methodological source before any interpretive weight was placed on either result. Where a claim rested on a single study or a single laboratory, this is stated in the text.

3. Biological Constraints on Ultra-Early Non-Invasive Detection

Discussion of ultra-early prenatal diagnosis often proceeds as though the limiting factor were sequencing depth. The evidence indicates otherwise. Three biological properties of the analyte, its provenance, its fractional abundance and its fidelity to the fetal genome, set boundaries that additional sequencing does not remove.

3.1 Provenance and Kinetics of Circulating Placental DNA

The DNA that permits non-invasive prenatal analysis is released predominantly from apoptotic trophoblast rather than from fetal tissue proper. This provenance explains several observed behaviours of the analyte, including its rapid clearance after delivery and its characteristic fragment-length distribution, which is shorter than that of maternal DNA and reflects differences in nucleosomal packaging and processing (Chan *et al.*, 2004; Lo *et al.*, 2021). Fragment length has been exploited both to enrich the fetal-derived population and to infer tissue of origin, and the broader fragmentomic properties of circulating DNA are now understood as a structured signal rather than as degradation noise (Lo *et al.*, 2021).

Detection of fetal-derived sequences early in the first trimester has been reported since the earliest phase of the field. Fetal DNA has been detected in maternal plasma from around the fifth week of gestation, although in that report detection was inconsistent between individuals and quantities were low (Illanes *et al.*, 2007). The practical consequence is that presence and analytical sufficiency are

different properties. A sequence that can be shown to exist by a sensitive targeted assay is not thereby available at the depth and allelic balance required to genotype a locus with diagnostic confidence.

3.2 Fetal Fraction as the Rate-Limiting Quantity

Fetal fraction, the proportion of circulating DNA derived from the placenta, is the single variable that most strongly determines whether a monogenic analysis will succeed. It rises with gestational age, falls with increasing maternal body mass, and varies considerably between individuals at any given gestational age. Analyses of large testing cohorts have shown that the relationship with gestational age is not a simple monotonic increase across the first trimester, and that fetal sex and other factors modulate it in ways that complicate the use of gestational age alone as a proxy for analytical adequacy (Forgacova *et al.*, 2022). Comparison of early and late first-trimester samples in the same pregnancies confirms that the earliest weeks are systematically less favourable (Miltoft *et al.*, 2020).

The response to this constraint has been enrichment rather than deeper sequencing. Size-based enrichment has been reported to permit informative prenatal cell-free DNA analysis from eight weeks of gestation, a gestational age at which unenriched analysis frequently fails (Daryabari *et al.*, 2026). That report is important because it identifies enrichment, rather than sequencing capacity, as the operative lever; it is also a single study, addressed to screening rather than to diagnostic genotyping of a specified locus, and its performance characteristics have not been independently replicated at the time of writing. Quality-control approaches based on fetal fraction signatures have been proposed specifically for monogenic non-invasive diagnosis, on the reasoning that a low or anomalous fetal fraction is not merely a cause of test failure but a source of misclassification if unrecognised (Blouin *et al.*, 2026). The distinction matters for the framework under review: a screening test that fails is a nuisance, whereas a diagnostic test that fails silently and precipitates an irreversible intervention is a hazard.

3.3 Placental Provenance and the Genotype Concordance Problem

Because the analyte is placental, discordance between the placental and fetal genotypes propagates directly into the test result. Confined placental mosaicism is the best-characterised form of this discordance, and cohort data on pregnancies with confirmed confined placental mosaicism show both that it is a recognised cause of discordant cell-free DNA results and that it carries its own obstetric associations (Grati *et al.*, 2020). The literature on this phenomenon is dominated by chromosomal analysis, for the straightforward reason that aneuploidy screening generates the case volume; the corresponding evidence base for single-nucleotide and small insertion or deletion variants is comparatively thin.

Table 1. Biological properties of circulating placental DNA and their consequences for diagnosis intended to trigger prenatal intervention

Property	What the evidence shows	Consequence for a therapeutic pathway	Supporting references
Tissue of origin	The circulating fetal-derived fraction is released predominantly from trophoblast; fragment-length and fragmentomic properties differ systematically from maternal DNA.	The measurement is of placental, not fetal, genotype; fidelity must be demonstrated rather than assumed.	Chan *et al.* (2004); Lo *et al.* (2021)
Earliest detectability	Fetal-derived sequences are detectable in maternal plasma from approximately the fifth week of gestation, inconsistently between individuals.	Detectability of a sequence does not establish sufficiency for diagnostic genotyping at a defined locus.	Illanes *et al.* (2007)
Fetal fraction trajectory	Fetal fraction rises with gestational age but not monotonically across the first trimester, and is modified by maternal body mass and fetal sex.	Gestational age alone is an unreliable predictor of analytical adequacy in the earliest weeks.	Forgacova *et al.* (2022); Miltoft *et al.* (2020)
Enrichment as a lever	Size-based enrichment has enabled informative cell-free DNA analysis from eight weeks of gestation in a single reported cohort.	Enrichment, not sequencing depth, is the operative variable; independent replication for locus-specific diagnosis is absent.	Daryabari *et al.* (2026)
Failure mode	Low or atypical fetal fraction can produce misclassification rather than overt test failure in monogenic analysis; signature-based quality control has been proposed.	Silent misclassification is tolerable in screening but not when it would precipitate an irreversible intervention.	Blouin *et al.* (2026)
Placental-fetal discordance	Confined placental mosaicism is an established cause of discordant cell-free DNA results, characterised mainly for chromosomal rather than single-nucleotide variation.	The discordance rate for the variant classes relevant to monogenic correction is not established.	Grati *et al.* (2020); Hui *et al.* (2023)

Note. All entries derive from the sources cited in the final column; the table summarises properties reported in those sources and does not present new data

For the framework considered here, that thinness is consequential in an asymmetric way. In screening, a discordant result leads to invasive confirmation, and the cost of discordance is anxiety and an additional procedure. In a therapeutic pathway, the same

discordance would determine whether a fetus receives an editing agent directed at a variant it may not carry, or fails to receive one for a variant it does. Professional guidance on non-invasive testing has consistently emphasised that confirmatory invasive testing remains necessary before irreversible decisions (Hui *et al.*, 2023), and nothing in the current evidence base for monogenic non-invasive diagnosis displaces that requirement. Any framework that proposes to act on a non-invasive result without confirmation is therefore proposing a change in evidentiary standard, not merely a change in timing.

Table 1 assembles the principal biological constraints, the evidence from which each is inferred, and the specific consequence each has for a diagnosis intended to trigger intervention rather than to inform counselling. The pattern that emerges is that no single constraint is absolute, but that they compound: the gestational window in which fetal fraction is lowest is also the window in which enrichment is least validated and in which placental-fetal discordance is least characterised for the variant classes of interest.

4. Analytical Strategies for Monogenic Diagnosis in the First Trimester

Given those constraints, the analytical question is what can be extracted from a low and placentally derived signal. Four strategies dominate the literature, and they differ not only in performance but in what they presuppose about the family being tested.

4.1 Relative Mutation Dosage and Relative Haplotype Dosage

The founding insight was that a maternally inherited variant cannot be detected by presence or absence, because the maternal genome contributes the same allele to the plasma pool, but can be detected as a departure from the expected allelic balance. Digital size selection combined with relative mutation dosage demonstrated this for haemoglobin variants and established the statistical logic on which the field still rests (Lun *et al.*, 2008). Extension from single loci to haplotype blocks produced relative haplotype dosage, which improves precision by aggregating information across many linked polymorphisms and has been applied to spinal muscular atrophy and other conditions (Parks *et al.*, 2017).

The strongest evidence for clinical utility comes from accredited service delivery rather than from proof-of-concept studies. A national laboratory service reported outcomes for non-invasive prenatal diagnosis by relative haplotype dosage across a range of single-gene disorders, describing referral patterns, informativeness and the practical determinants of success (Young *et al.*, 2020). Subsequent methodological work extended the approach to consanguineous families, in whom extended homozygosity reduces the density of informative markers and had previously excluded many families from the service (Hanson *et al.*, 2024). Enhanced analytical pipelines have also been reported to improve the robustness of relative haplotype dosage for diagnostic implementation (Pacault *et al.*, 2023). This is a mature and honestly reported literature; its principal limitation for the present framework is structural rather than technical.

Relative haplotype dosage requires phase. Phase is obtained from a proband, from parental and grandparental genotypes, or from direct molecular haplotyping. In the ultra-early setting, an affected proband may not exist, and family structures capable of supporting phasing may not be available. The method is therefore best suited to couples already known to be at risk through a previous affected pregnancy, which is precisely the population least likely to require ultra-early detection as a novel capability, since their risk is already recognised and other reproductive options are already in view.

4.2 Direct Haplotyping, Targeted Enrichment and Long-Read Approaches

Targeted locus amplification and related proximity-ligation methods construct haplotypes directly from a parental sample, removing the requirement for an affected proband and allowing sensitive analysis at defined loci (Vermeulen *et al.*, 2017). Targeted nanopore sequencing has been combined with relative haplotype dosage in a feasibility study for beta-thalassaemia, exploiting long reads to establish phase and to interrogate the locus in a single workflow (Jiang *et al.*, 2021). More recently, an approach described as universal non-invasive prenatal diagnosis for monogenic disorders has been reported, seeking to remove the dependence on family-specific design (Zhang *et al.*, 2026).

These developments address the phasing bottleneck rather than the fetal fraction bottleneck, and the two should not be conflated. A method that removes the need for a proband still requires sufficient placental DNA to resolve allelic imbalance. Reported feasibility studies have generally been conducted at gestational ages beyond the ultra-early window, in modest cohorts, and with reference standards derived from invasive sampling or postnatal testing. The evidence supports the conclusion that phasing is a solvable problem; it does not yet support the conclusion that the resulting assays perform adequately before ten weeks of gestation.

4.3 De Novo and Paternally Inherited Variants

Conditions arising from de novo variation are, in one sense, the natural target of a framework based on ultra-early detection, because these are the pregnancies in which no prior risk is recognised and in which reproductive alternatives have not been considered. They are also the case the technology handles least well. A systematic review of the feasibility of screening maternal plasma for fetal de novo or paternally inherited pathogenic single-nucleotide variants concluded that the evidence remains preliminary and that performance is materially limited by fetal fraction and by the statistical burden of distinguishing a genuine low-abundance variant from sequencing error (Valovičová *et al.*, 2025). Direct evaluation of non-invasive prenatal exome sequencing reached a similar conclusion, attributing limited diagnostic utility specifically to the interaction between sequencing depth and fetal fraction (Filer *et al.*, 2022).

Clinical implementations have nevertheless moved forward for selected autosomal dominant conditions. Routine prenatal cell-free DNA screening panels for dominant single-gene conditions have been evaluated in unselected and indication-based populations, and expanded panels have been assessed for proof of concept and performance (Adams *et al.*, 2025; Chen *et al.*, 2025). These reports describe screening, with positive results requiring confirmation, and their positive predictive values depend heavily on the prior probability conferred by ultrasound findings or paternal age. Ultrasound findings, however, are generally unavailable in the ultra-early window, which removes the very factor that makes these panels perform acceptably later in pregnancy. The framework thus encounters a circularity: the pregnancies most in need of ultra-early detection are those in which the detection method has the weakest prior information and the lowest analyte abundance.

4.4 Cell-Based Non-Invasive Prenatal Diagnosis

Recovering intact fetal-derived cells from maternal blood offers a route around the fractional abundance problem, because a single trophoblast provides a complete diploid genome uncontaminated by maternal sequence. Validation studies of single circulating trophoblast testing have demonstrated genome-wide analysis from recovered cells and comparison with invasive reference standards (Vossaert *et al.*, 2019). The limiting factor is cell yield, which is low, variable and influenced by maternal body mass index and gestational age in ways that have been quantified directly (Panchalee *et al.*, 2020).

Cell-based testing does not escape the placental provenance problem, since circulating trophoblasts are placental cells, and it introduces a new one: a genotype derived from one or a few cells is vulnerable to allele dropout and to the possibility that the sampled cells are not representative. The approach remains promising, and it is the only strategy that in principle delivers a complete fetal-derived genome rather than a statistical inference about one, but the published evidence is confined to a small number of centres and cohorts.

Table 2 compares these four strategies against the requirements that a therapeutic pathway would impose. The comparison shows that no current strategy satisfies all requirements simultaneously, and that the strategies with the strongest clinical evidence are those with the most restrictive family prerequisites. This is the first of several places in which the framework's two halves make incompatible demands: the therapeutic half is most attractive for unanticipated de novo disease, while the diagnostic half performs best for anticipated inherited disease.

Table 2. Comparison of non-invasive strategies for first-trimester monogenic diagnosis against the requirements of a prenatal therapeutic pathway

Strategy	Family prerequisites	Principal analytical limitation	Evidence maturity	Fit to ultra-early therapeutic use	Supporting references
Relative mutation dosage	Known parental variants; single-locus design	Requires allelic imbalance to exceed measurement noise at low fetal fraction	Foundational proof of concept, extended by later work	Limited; designed for known at-risk couples	Lun *et al.* (2008)
Relative haplotype dosage	Phase from proband or extended family	Informativeness falls with homozygosity; phase may be unobtainable	Accredited clinical service with reported outcomes	Restricted to pregnancies with recognised prior risk	Hanson *et al.* (2024); Pacault *et al.* (2023); Parks *et al.* (2017); Young *et al.* (2020)
Direct and long-read haplotyping	Parental sample only; proband not required	Addresses phasing but not fetal fraction; early-gestation performance unreported	Feasibility and single-centre studies	Promising but unvalidated before ten weeks	Jiang *et al.* (2021); Vermeulen *et al.* (2017); Zhang *et al.* (2026)
Genome-wide and panel screening for de novo or paternal variants	None	Depth-by-fetal-fraction interaction; dependence on ultrasound-derived prior probability	Screening implementations with confirmatory testing required	Weakest precisely where the therapeutic rationale is strongest	Adams *et al.* (2025); Chen *et al.* (2025); Filer *et al.* (2022); Valovičová *et al.* (2025)
Cell-based testing (single circulating trophoblast)	None	Low and variable cell yield; allele dropout from few-cell input; placental origin retained	Validation studies from a small number of centres	Conceptually best suited but least mature	Panchalee *et al.* (2020); Vossaert *et al.* (2019)

Note. Evidence maturity reflects the strongest design reported for each strategy in the cited sources. The table is not an exhaustive inventory of published methods

5. Editing Chemistries and Their Fitness for the Fetal Compartment

If a diagnosis of therapeutic quality could be secured, the next question is what would be administered. The three principal editing chemistries differ in the DNA lesion they create, in the repair biology they depend upon, and consequently in the risks they carry when applied to a rapidly proliferating embryo or fetus. These differences are not incremental refinements of a single technology, and treating them as interchangeable has been a persistent weakness in discussion of prenatal application.

5.1 Nuclease-Dependent Editing and On-Target Genomic Consequences

Nuclease-dependent editing creates a double-strand break and relies on endogenous repair to produce the intended outcome. The efficiency of this approach in haematopoietic stem cells has been sufficient to support approved autologous cell products, and the clinical experience with these products in sickle cell disease and transfusion-dependent beta-thalassaemia is the strongest evidence that editing can deliver durable clinical benefit (Frangoul *et al.*, 2021). That experience, however, was obtained ex vivo, in a setting where edited cells can be characterised, selected and released before administration.

Applied in vivo, and particularly in dividing cells, double-strand break repair generates a spectrum of outcomes wider than the small insertions and deletions usually reported. Repair at nuclease-induced breaks produces large deletions and complex rearrangements extending many kilobases from the cut site, which conventional amplicon-based genotyping systematically fails to detect (Kosicki *et al.*, 2018). More severely, nuclease cleavage can initiate chromothripsis, a catastrophic rearrangement of the affected chromosome, as an on-target rather than off-target consequence (Leibowitz *et al.*, 2021). Evidence from human preimplantation embryos points in the same direction: editing at a targeted locus has been associated with frequent loss of heterozygosity across large genomic intervals (Alanis-Lobato *et al.*, 2021), and with removal of the entire targeted chromosome in an allele-specific manner (Zuccaro *et al.*, 2020). Earlier embryo studies had already documented mosaic and off-target outcomes and had been interpreted cautiously by their own authors (Liang *et al.*, 2015), and the claim that gene conversion from the maternal allele mediates efficient correction in human zygotes (Ma *et al.*, 2017) has been contested precisely because the alternative explanation is allelic dropout arising from large deletions.

The relevance to prenatal somatic editing is direct rather than analogical. The embryo and early fetus contain populations of rapidly dividing progenitor cells whose descendants will constitute entire organ systems. A rearrangement or chromosome loss arising in one such cell is not diluted in the way an equivalent event in a mature tissue would be; it is clonally amplified. The available evidence does not quantify this risk in the fetal setting, and no study identified in this review has measured large-scale on-target genomic consequences after in utero editing at a resolution capable of detecting them.

5.2 Base Editing

Base editors couple a catalytically impaired Cas protein to a deaminase, converting one base pair to another without a double-strand break (Komor *et al.*, 2016). Because they avoid the break, they avoid the class of large rearrangements described above, and they achieve high efficiencies at permissive positions. This combination has made base editing the modality of choice in most in utero preclinical work. Adenine base editing delivered to fetal mice corrected multi-organ pathology in a lethal lysosomal storage disease model (Bose *et al.*, 2021), and earlier work established the feasibility of in utero editing of metabolic genes (Rossidis *et al.*, 2018).
The most consequential human evidence is a single-patient report in which a base-editing agent was designed against a private variant in carbamoyl phosphate synthetase 1 deficiency, manufactured, and administered to an infant, with clinical stabilisation reported over the subsequent months (Musunuru *et al.*, 2025). The report is properly described as a demonstration of feasibility and of regulatory tractability rather than as evidence of efficacy; it involves one patient, an uncontrolled design, and a follow-up period far shorter than the timescale on which durability and delayed adverse events would become apparent. Its significance for the present framework lies in what it establishes about process rather than outcome: that a bespoke editing agent can be designed and delivered within a clinically meaningful interval. Whether that interval can be compressed to fit a first-trimester therapeutic window is a separate question, and the reported timeline does not answer it.

Base editing carries its own liabilities. Bystander editing of adjacent bases within the editing window is intrinsic to the mechanism, and deaminase activity produces sequence-independent off-target events at DNA and RNA that are not predicted by guide-sequence homology. These are engineering problems with active solutions, but they are not solved, and their consequences in a developing organism have not been characterised.

5.3 Prime Editing

Prime editing writes a specified sequence directly, using a reverse transcriptase fused to a nickase and a guide that encodes the intended edit (Anzalone *et al.*, 2019). It is the only modality capable in principle of correcting the full range of pathogenic variation, including insertions, deletions and transversions inaccessible to current base editors, and it does so without a double-strand break. In vivo demonstration has followed in liver-directed applications: prime editing corrected a metabolic liver disease phenotype in mice (Böck *et al.*, 2022), and lipid nanoparticle delivery of prime editing components corrected disease phenotypes in a citrullinaemia type I model (Tálas *et al.*, 2026). Regulatory analysis of a personalised in vivo prime editing platform has begun to address how such agents might be evaluated when each is, by construction, unique (Feierman *et al.*, 2026).

Prime editing efficiencies in vivo remain substantially lower than base editing efficiencies at comparable targets, and the reagent is larger and more complex, which constrains packaging and formulation. For the framework under review, its theoretical universality is the relevant property: a framework predicated on correcting whichever variant the diagnosis reveals cannot rely on a modality restricted to transition mutations. That the most versatile modality is also the least efficient in vivo is an unresolved tension rather than a transient inconvenience.

5.4 What Precision Means at the Level of a Whole Fetus

Reported editing efficiencies are almost always allele frequencies measured in bulk tissue. A tissue in which thirty per cent of alleles are edited may consist of uniformly heterozygous corrected cells or of a minority of fully corrected cells among uncorrected ones, and these two states have different functional consequences depending on whether the gene product acts cell-autonomously,

whether corrected cells enjoy a selective advantage, and whether cross-correction occurs. For secreted enzymes and for conditions with strong selective pressure favouring corrected cells, low bulk efficiency may suffice; for structural proteins acting within the cell that produces them, it will not.

The term precision, as used in discussion of this framework, therefore conflates two distinct properties: fidelity at the sequence level, and completeness at the cellular level. Current in utero studies report the former and rarely the latter. Table 3 sets out the comparison across modalities, including the distinction between demonstrated capability and demonstrated suitability for prenatal use. The table makes visible a pattern that the narrative literature tends to obscure: the modality with the most in utero preclinical evidence is not the modality with the broadest variant coverage, and the modality with the broadest coverage has never been administered to a fetus in any species reported here.

Table 3. Editing modalities assessed against the requirements of prenatal somatic correction

Modality	Lesion and repair dependence	Variant coverage	Documented in utero use	Principal unresolved liability	Supporting references
Nuclease-dependent (Cas9)	Double-strand break; endogenous repair	Disruption and, with donor template, replacement	Rodent studies of metabolic and pulmonary targets	Large deletions, complex rearrangements and chromothripsis clonally amplified in progenitor populations	Alapati *et al.* (2019); Kosicki *et al.* (2018); Leibowitz *et al.* (2021); Rossidis *et al.* (2018)
Base editing	Nick only; deaminase chemistry	Transitions at permissive positions	Rodent multi-organ correction; one postnatal human single-patient report	Bystander and sequence-independent off-target deamination; no developmental characterisation	Bose *et al.* (2021); Komor *et al.* (2016); Musunuru *et al.* (2025)
Prime editing	Nick and reverse transcription from an encoded template	In principle all substitution, small insertion and deletion classes	None identified in fetal administration	Low in vivo efficiency and large reagent size; regulatory pathway for bespoke agents still forming	Anzalone *et al.* (2019); Böck *et al.* (2022); Feierman *et al.* (2026); Tálas *et al.* (2026)
Peptide nucleic acid triplex-forming correction	No nuclease; recruits endogenous repair	Site-specific correction at defined targets	Systemic in utero correction of globin and cystic fibrosis transmembrane conductance regulator variants in mice	Modest editing frequencies; limited replication beyond the originating group	Ricciardi *et al.* (2018, 2025)

Note. Documented in utero use refers to administration to a fetus in any species as reported in the cited sources. Absence of an entry indicates that no such report was identified in this review, not that such use is impossible

6. Delivery into the Gravid Uterus

Editing chemistry determines what happens once the reagent reaches a nucleus. Delivery determines which nuclei it reaches, in what proportion, and at what cost to the pregnant person. In the fetal setting, delivery is the dominant constraint, and it is the aspect of the framework least addressed in speculative accounts of it.

6.1 Viral Vectors

Adeno-associated viral vectors have carried most fetal gene-transfer work. In utero administration of an adeno-associated viral vector encoding factor IX produced long-term expression in a cynomolgus macaque model, providing the most substantial non-human primate evidence for fetal gene transfer durability (Mattar *et al.*, 2017). Fetal administration in a neuronopathic lysosomal disease model produced marked phenotypic rescue where postnatal administration did not, and this comparison remains one of the strongest arguments that the timing of intervention matters biologically rather than merely logistically (Massaro *et al.*, 2018). Minimally invasive ultrasound-guided delivery has been demonstrated in fetal pigs, addressing the procedural feasibility question in a species with relevant anatomy (Di Donfrancesco *et al.*, 2025).

Two features of viral delivery are difficult to reconcile with prenatal editing. The first is persistence: an editing nuclease delivered by a vector that continues to express it accumulates off-target activity for as long as expression continues, whereas the intended edit is complete within days. The second is maternal immunity. Pre-existing maternal immunity to adeno-associated virus, but not to Cas9, impaired in utero gene editing in mice, and the mechanism implicates transfer of maternal antibody across the placenta (Riley *et al.*, 2024). Since seroprevalence of adeno-associated virus in adult populations is substantial, this observation places a population-level ceiling on the proportion of pregnancies in which viral in utero delivery could be effective, independent of any other consideration.

6.2 Lipid Nanoparticles and Non-Viral Carriers

Ionisable lipid nanoparticles carrying messenger RNA offer transient expression, which aligns the duration of nuclease activity with the duration of the intended edit, and they avoid the anti-vector immunity problem. Targeted ionisable lipid nanoparticles delivered

in utero achieved in vivo editing of haematopoietic stem cells in mice (Palanki *et al.*, 2024), and acid-degradable formulations produced widespread editing in the fetal brain after in utero delivery (Gao *et al.*, 2024). Peptide nucleic acid nanoparticles have achieved site-specific correction after systemic administration in utero (Ricciardi *et al.*, 2018, 2025).

Formulation strongly determines biodistribution in pregnancy. Lipid nanoparticle structure and route of administration during pregnancy determine messenger RNA potency, immunogenicity and both maternal and fetal outcomes, and these variables cannot be optimised independently (Chaudhary *et al.*, 2024). Placenta-tropic formulations have been developed for maternal indications and demonstrate that tropism within the gravid uterus can be engineered (Swingle *et al.*, 2023); the same work also demonstrates that reaching the placenta and reaching the fetus are distinct achievements, and that the former does not entail the latter.

6.3 Route, Dose and the Maternal Compartment

Preclinical in utero editing studies have used direct fetal injection, whether intravenous, intrahepatic, intra-amniotic or intracranial, under direct visualisation in animals whose gestational anatomy permits it. Human first-trimester application would require either a percutaneous procedure at a gestational age at which fetal vascular access is not feasible, or maternal systemic administration with transplacental transfer. The first is not available in the ultra-early window; the second requires that a therapeutic dose reach the fetus while exposing the pregnant person to a systemic dose of an immunogenic nucleic acid formulation for no direct benefit to herself.

The maternal exposure question is under-treated in the literature. Reports of in utero delivery in animals characterise fetal outcomes in detail and maternal outcomes cursorily, and the maternal immunological consequences of systemic lipid nanoparticle administration in pregnancy have been examined in only a small number of studies (Chaudhary *et al.*, 2024). Any human protocol would have to specify a maternal risk profile that current evidence does not support. This is a substantive obstacle rather than a documentation gap, because the pregnant person is a patient in her own right and bears procedural and pharmacological risk that cannot be justified by fetal benefit alone under the frameworks that govern maternal-fetal intervention (Chervenak & McCullough, 2017).

7. Preclinical Evidence for In Utero Correction and the Limits of Extrapolation

The preclinical record is often summarised as showing that in utero editing works. A closer reading shows something more specific and more limited: that in defined mouse models, delivered by direct fetal injection at a late gestational stage, editing reagents can alter measurable phenotypes.

7.1 Rodent Proof of Concept

The rodent studies are consistent and reasonably well conducted within their own terms. In utero CRISPR-mediated editing of metabolic genes altered target gene function and, in a hereditary tyrosinaemia model, improved survival (Rossidis *et al.*, 2018). In utero editing directed at surfactant protein deficiency improved survival in a monogenic lung disease model (Alapati *et al.*, 2019). In utero adenine base editing corrected multi-organ pathology in a lysosomal storage disease model, and reported functional as well as molecular endpoints (Bose *et al.*, 2021). Nanoparticle-delivered peptide nucleic acid correction improved haematological parameters in a thalassaemia model and, more recently, corrected a cystic fibrosis transmembrane conductance regulator defect after systemic in utero administration (Ricciardi *et al.*, 2018, 2025).

Several features recur across these studies and constrain what they establish. Editing frequencies in the target tissue are typically modest, and benefit in each case depends on the specific relationship between the corrected fraction and the disease mechanism rather than on the correction being complete. Follow-up periods correspond to a small part of the murine lifespan. Delivery is by direct fetal injection at a gestational stage that, scaled to human development, lies well beyond the first trimester. And in most cases the work originates from a small number of collaborating groups, so independent replication is limited.

7.2 Large-Animal and Non-Human Primate Evidence

Large-animal work is sparse and concerns gene transfer rather than editing. The macaque factor IX study demonstrates durable transgene expression after in utero vector administration (Mattar *et al.*, 2017); the fetal pig work demonstrates procedural feasibility of ultrasound-guided delivery (Di Donfrancesco *et al.*, 2025). Neither reports genome editing. The absence of large-animal editing data is the single largest evidentiary gap in the therapeutic half of the framework, because it is in large animals that the questions most relevant to human translation, namely dose scaling, biodistribution across a fetus of comparable size, procedural risk and germ-cell exposure, can be addressed.

7.3 What Human in Utero Therapy Has Actually Achieved

It is worth stating plainly what has been done in human pregnancies, because the preclinical literature is sometimes read as though it had already been translated. In utero enzyme-replacement therapy has been administered for infantile-onset Pompe disease with reported clinical benefit (Cohen *et al.*, 2022). In utero haematopoietic cell transplantation has completed a phase 1 trial in fetuses with alpha-thalassaemia major (MacKenzie *et al.*, 2026). Both are landmark demonstrations that the fetal compartment can be reached and treated, and both establish the procedural and regulatory precedent on which any editing protocol would build. Neither involves genome modification. No in utero genome-editing intervention in a human pregnancy has been reported in the literature identified for this review.

The distinction matters because protein and cell therapies are reversible in a sense that editing is not. An enzyme infusion that proves misdirected ceases to act; a transplanted cell population can, in principle, be lost or replaced. A sequence change is permanent in every descendant of the edited cell. The precedent established by the trials above therefore supports the feasibility of fetal access, not the acceptability of fetal genome modification.

Table 4 summarises the in utero interventional evidence, separating gene editing from gene transfer and from protein and cell therapy, and stating for each the species, the delivery route and the strongest endpoint reported. The table is not exhaustive of the preclinical literature; it includes the studies that carry the greatest weight in current argument. Reading down the final columns makes clear that the studies with human subjects are those without editing, and the studies with editing are those without large-animal or human subjects.

Table 4. Principal in utero interventional studies by modality, species and strongest reported endpoint

Study focus	Modality	Species	Route	Strongest reported endpoint	Supporting references
Metabolic gene targets	Nuclease and base editing	Mouse	Direct fetal injection	Improved survival in a hereditary tyrosinaemia model	Rossidis *et al.* (2018)
Surfactant protein deficiency	Nuclease editing	Mouse	Intra-amniotic	Improved survival in a monogenic lung disease model	Alapati *et al.* (2019)
Lysosomal storage disease	Adenine base editing	Mouse	Direct fetal injection	Correction of multi-organ pathology with functional endpoints	Bose *et al.* (2021)
Beta-globin and cystic fibrosis loci	Peptide nucleic acid nanoparticle correction	Mouse	Intravenous and systemic	Haematological improvement; correction of a cystic fibrosis transmembrane conductance regulator defect	Ricciardi *et al.* (2018, 2025)
Haematopoietic stem cells and fetal brain	Lipid nanoparticle delivered editing	Mouse	Direct fetal injection	In vivo editing of haematopoietic stem cells; widespread editing in the developing brain	Gao *et al.* (2024); Palanki *et al.* (2024)
Neuronopathic lysosomal disease	Gene transfer (adeno-associated virus)	Mouse	Intracranial and intravenous	Phenotypic rescue exceeding that achieved postnatally	Massaro *et al.* (2018)
Haemophilia B	Gene transfer (adeno-associated virus)	Cynomolgus macaque	In utero vector administration	Long-term factor IX expression	Mattar *et al.* (2017)
Vector delivery feasibility	Gene transfer (adeno-associated virus)	Pig	Ultrasound-guided transabdominal	Demonstrated minimally invasive fetal delivery	Di Donfrancesco *et al.* (2025)
Infantile-onset Pompe disease	Enzyme replacement	Human	Umbilical vein	Reported clinical benefit in treated pregnancies	Cohen *et al.* (2022)
Alpha-thalassaemia major	Haematopoietic cell transplantation	Human	In utero transplantation	Completed phase 1 trial	MacKenzie *et al.* (2026)

Note. The table includes the studies carrying the greatest weight in current argument and is not an exhaustive inventory of the preclinical literature

8. Germ-Cell Exposure, Insertional Risk and Immunology

Three safety questions distinguish prenatal editing from postnatal editing rather than merely intensifying it. Each has an evidence base, and in each case the evidence is thinner than the confidence with which the framework is often described.

8.1 Inadvertent Modification of the Germ Line

The primordial germ cells that will give rise to gametes migrate and proliferate during early gestation. An agent distributed systemically in a first-trimester fetus encounters this population at the point of its greatest mitotic activity and its least anatomical sequestration. The relevant empirical work predates the editing era and concerns retroviral gene transfer in sheep, where direct-injection in utero gene transfer placed male germ-line cells at risk of transduction (Porada *et al.*, 2005), and where the factors determining that risk, including vector dose, route and gestational timing, were subsequently characterised (Park *et al.*, 2009). The general finding is that germ-cell exposure is a function of when and how the agent is delivered, and that earlier and more systemic delivery increases it.

No study identified in this review has quantified germ-cell editing after in utero delivery of a base editor, prime editor or nuclease, in any species, at a gestational stage corresponding to the human first trimester. This is the most consequential single gap in the safety evidence, because a heritable edit arising as an unintended consequence of somatic therapy would place the intervention within the scope of governance frameworks that presently regard heritable modification as impermissible in clinical practice (National Academy of Medicine *et al.*, 2020; World Health Organization, 2021). By contrast, in utero haematopoietic cell

transplantation has been shown not to alter the germ line, which illustrates that the question is empirically tractable and that a negative answer for a given modality can be established (Grant & Vrecenak, 2021).

8.2 Insertional and Oncogenic Risk

Vector-associated insertional risk is not hypothetical. Adeno-associated viral vector integration sites were identified in murine hepatocellular carcinoma, establishing that a vector regarded as predominantly episomal integrates at appreciable frequency (Donsante *et al.*, 2007). More recently, a neuroepithelial tumour containing an integrated adeno-associated viral vector has been reported following intracisterna magna vector administration in a human recipient (Ahrens-Nicklas *et al.*, 2026). That report concerns a postnatal recipient and a single case, and causal attribution from one case is necessarily limited; its importance for the present framework lies in the demonstration that vector integration in human central nervous tissue can be identified in a clinically consequential lesion.

Applied prenatally, the risk profile changes in two directions at once. The number of dividing target cells is greater, increasing the number of integration opportunities and the clonal amplification of any consequence; and the period over which a malignancy could emerge is the whole of a human lifespan, rather than the remaining life expectancy of an adult recipient. Non-viral delivery removes vector integration as a mechanism but does not remove the on-target genomic risks associated with nuclease cleavage described earlier (Kosicki *et al.*, 2018; Leibowitz *et al.*, 2021).

8.3 Immunology of the Maternal-Fetal Dyad

The immunological situation is unusual because two immune systems are exposed and only one is mature. Pre-existing maternal immunity to adeno-associated virus impaired in utero editing in mice, whereas pre-existing immunity to Cas9 did not, indicating that the transferred maternal antibody acted against the vector rather than the nuclease (Riley *et al.*, 2024). Pre-existing adaptive immunity to Cas9 proteins is common in human populations, having been identified against nucleases derived from bacteria to which most adults have been exposed (Charlesworth *et al.*, 2019). The fetal immune environment is comparatively tolerogenic, which is the basis for the durable engraftment sought in in utero cell transplantation, but the maternal compartment is not, and any agent administered systemically to the pregnant person is presented first to a fully competent adult immune system.

The practical consequence is that immunological screening of the pregnant person would be a prerequisite for viral approaches, that a substantial proportion of pregnancies would be ineligible on that basis, and that non-viral delivery is favoured for reasons of immunology as well as of expression kinetics. None of this has been examined in a human pregnancy.

9. Ethical, Regulatory and Equity Dimensions

The normative questions raised by this framework are not downstream of the science; they determine which experiments would be permissible and what evidence would be required before any first-in-human application could be contemplated.

9.1 Two Patients, One Body

Prenatal intervention operates on a fetus through a pregnant person who is herself a patient. The established framework treats the fetus as a patient when it is presented for care and when interventions of demonstrated benefit exist, while holding that beneficence-based obligations to the fetus never override the pregnant person's autonomy (Chervenak & McCullough, 2017). Applied to prenatal editing, this framework yields a demanding standard: an intervention that carries maternal procedural and pharmacological risk, that is irreversible, and whose benefit rests on animal data, would be difficult to justify as anything other than research.

Professional guidance has taken this position explicitly. A special statement on in utero fetal gene therapy set out the conditions under which such research might responsibly proceed, emphasising the strength of preclinical evidence required and the primacy of maternal consent (Shanahan *et al.*, 2021). Analyses of the ethical, legal and social implications of fetal gene therapy have identified the same pressure points, including the difficulty of obtaining consent in the compressed interval that follows an unexpected first-trimester diagnosis (Brown & Koenig, 2021). Reviews of in utero fetal therapy more broadly reach compatible conclusions about the evidentiary threshold (Shear & Massa, 2021). Empirical work on the views of those most directly affected is limited but not absent: patients with haemophilia and their relatives held differentiated views about gene therapy and in utero gene editing, distinguishing between the modalities rather than treating them as a single proposition (Vasquez-Loarte *et al.*, 2020).

9.2 The Somatic and Germline Boundary in the Prenatal Setting

Governance of genome editing rests on a distinction between somatic modification, which is regulated as therapy, and heritable modification, which is not currently permissible in clinical practice in any jurisdiction that has addressed it. The international expert reports that structure this consensus were framed around editing of embryos and gametes (National Academy of Medicine *et al.*, 2020; World Health Organization, 2021). Prenatal somatic editing sits awkwardly against that framing, because it is somatic in intent but occurs at a developmental stage where germ-cell exposure is plausible and unquantified. Legal and ethical analysis has begun to examine how correction, selection and treatment are distinguished in heritable editing debates (Scott, 2024), and the same analytical distinctions apply with modification to the prenatal case.

The framework under review therefore does not merely raise safety questions within an existing regulatory category; it tests whether that category is stable. If germ-cell editing were shown to occur at non-negligible frequency after first-trimester administration, the

intervention would be, in effect, heritable modification undertaken without the deliberation that heritable modification is held to require. Resolving this is a matter of measurement, and the measurement has not been made.

9.3 Reproductive Choice, Disability and Access

Expansion of prenatal detection is not normatively neutral. Empirical work with people living with disability documents sustained objections to the expressive implications of prenatal screening and testing, and shows that these objections are held alongside, rather than instead of, support for reproductive choice (Boardman & Thomas, 2023). A framework that offers correction rather than termination is sometimes presented as an answer to these objections. It is at best a partial one, because the offer of correction presupposes the judgement that the condition warrants correction, and because in the ultra-early window the realistic alternative to an unproven intervention is not a different treatment but a different reproductive decision.

Access is the other dimension. The burden of severe monogenic disease is concentrated in settings where the diagnostic infrastructure required by any version of this framework, including haplotype phasing, high-depth sequencing and specialist fetal medicine, is least available (Blencowe *et al.*, 2018; Modell & Darlison, 2008). Governance frameworks for genome editing identify equitable access as a central rather than incidental concern (World Health Organization, 2021). A technology whose feasibility depends on early gestational-age dating, rapid variant confirmation and bespoke reagent manufacture is, on its face, one that would widen rather than narrow existing disparities unless deliberately designed otherwise.

10. Integrated Appraisal: Does the Framework Cohere?

Bringing the two halves together produces four specific incompatibilities, each of which is more informative than a general judgement that the framework is premature.

The first is a population mismatch. The diagnostic methods with the strongest clinical evidence, relative haplotype dosage and its extensions, require phase derived from an affected proband or an informative family structure, and therefore serve couples whose risk is already recognised (Hanson *et al.*, 2024; Parks *et al.*, 2017; Young *et al.*, 2020). The therapeutic rationale for ultra-early correction is strongest for unanticipated de novo disease, where no prior risk exists and no reproductive alternative has been considered. For that population, the available detection methods are screening tests whose performance depends on prior probability that the ultra-early window does not supply (Adams *et al.*, 2025; Chen *et al.*, 2025; Valovičová *et al.*, 2025).

Table 5. Research priorities, current evidentiary basis and what resolution would establish

Priority	Current evidence and its limitation	Study design required	What resolution would establish	Supporting references
Gestational-age-resolved analytical performance for locus-specific diagnosis	Fetal fraction trajectories and enrichment feasibility reported for screening, largely in single cohorts	Prospective cohorts sampled weekly from six to twelve weeks with invasive or postnatal reference standards	The earliest gestational age at which monogenic genotyping meets a diagnostic rather than screening standard	Blouin *et al.* (2026); Daryabari *et al.* (2026); Forgacova *et al.* (2022); Miltoft *et al.* (2020)
Placental-fetal concordance for single-nucleotide and small insertion or deletion variants	Discordance characterised chiefly for chromosomal abnormality	Paired placental and fetal genotyping in prospectively collected pregnancies across variant classes	Whether a non-invasive result could ever justify intervention without invasive confirmation	Grati *et al.* (2020); Hui *et al.* (2023)
Germ-cell editing frequency after in utero administration	Characterised only for retroviral gene transfer in sheep; no data for any editing modality	Dose- and timing-stratified large-animal studies with direct assay of germ-cell genotype	Whether prenatal somatic editing falls within or outside heritable-modification governance	Park *et al.* (2009); Porada *et al.* (2005); World Health Organization (2021)
Editing outcome measurement beyond bulk allele frequency	In utero studies report tissue-level allele frequencies; cellular completeness rarely reported	Single-cell and long-read genotyping of edited fetal tissues, including assays capable of detecting large on-target events	Whether reported efficiencies correspond to functionally corrected cell populations	Alanis-Lobato *et al.* (2021); Kosicki *et al.* (2018); Leibowitz *et al.* (2021); Zuccaro *et al.* (2020)
Large-animal editing dosimetry and biodistribution	Large-animal work concerns gene transfer, not editing	Non-human primate or porcine studies with editing reagents, staged by gestational age and route	Whether doses achieving therapeutic editing scale to a fetus of human size and anatomy	Di Donfrancesco *et al.* (2025); Mattar *et al.* (2017)
Maternal risk characterisation for systemic administration	Maternal outcomes reported cursorily in preclinical delivery studies	Formal maternal toxicology and immunogenicity endpoints in pregnant large animals	Whether a maternal risk profile compatible with ethical review can be defined	Chaudhary *et al.* (2024); Chervenak & McCullough (2017); Shanahan *et al.* (2021)

Note. Priorities are ordered by the extent to which resolution would alter what may legitimately be attempted rather than by ease of execution

The second is a temporal mismatch. The developmental advantage claimed for prenatal intervention derives from acting before irreversible pathology, and the strongest evidence for such an advantage is a comparison of fetal with postnatal administration in a neurodegenerative model (Massaro *et al.*, 2018). Yet the interval in which fetal fraction is lowest, enrichment least validated and placental-fetal discordance least characterised is the same interval in which the advantage is greatest. Moving the intervention later improves the diagnosis and erodes the rationale.

The third is a modality mismatch. A framework that corrects whichever variant the diagnosis reveals requires a modality with broad variant coverage. The modality with broad coverage, prime editing, has the lowest in vivo efficiency and no reported fetal administration; the modality with the most in utero evidence, base editing, covers a restricted class of substitutions (Anzalone *et al.*, 2019; Bose *et al.*, 2021; Tálas *et al.*, 2026).

The fourth is an evidentiary mismatch. Human in utero therapy has been achieved with reversible modalities (Cohen *et al.*, 2022; MacKenzie *et al.*, 2026), and human genome editing has been achieved postnatally with an irreversible one (Musunuru *et al.*, 2025). The framework requires the irreversible modality in the prenatal setting, which is the combination for which no human evidence exists and for which the germ-cell question remains unmeasured (Park *et al.*, 2009; Porada *et al.*, 2005).

None of these is a demonstration that the framework is impossible. Each identifies a determinate question whose answer would move the framework closer to or further from feasibility. Table 5 states these questions in the form of research priorities, distinguishing those that could be addressed with existing methods from those requiring new capability, and identifying the evidence that currently defines each gap. The organising judgement is that the framework should be evaluated as a research programme with sequenced intermediate objectives, and that progress on the detection half and the therapeutic half is not interchangeable: resolving the germ-cell question would alter what is permissible, whereas improving fetal fraction recovery would only alter what is measurable.

11. Future Directions

The priorities below are ordered by the extent to which resolving them would change what may legitimately be attempted, rather than by ease of execution. Two are immediate in the sense that existing methods suffice; the remainder require capability that does not yet exist in the relevant form.

The first immediate priority is direct measurement of germ-cell editing after in utero administration of contemporary editing reagents. The problem is that the only relevant data concern retroviral gene transfer in a single species and predate every editing modality now proposed (Park *et al.*, 2009; Porada *et al.*, 2005), while the demonstration that in utero cell transplantation leaves the germ line unaltered shows that the question can be answered definitively for a given modality (Grant & Vrecenak, 2021). The appropriate design is a large-animal study stratified by gestational age at administration, by route and by dose, with direct genotyping of isolated germ cells rather than of gonadal tissue in bulk, since bulk gonadal assay cannot distinguish germ-cell from somatic editing. Outcome measures should include the frequency of the intended edit in germ cells and the frequency of unintended events at and around the target. This work would determine whether prenatal somatic editing can be pursued within somatic-therapy governance or whether it engages the frameworks that presently exclude heritable modification from clinical practice (National Academy of Medicine *et al.*, 2020; World Health Organization, 2021). No other single result would alter the permissible research agenda so substantially.

The second immediate priority is measurement of editing outcomes at cellular rather than tissue resolution, together with assays capable of detecting large on-target rearrangement. Current in utero studies report allele frequencies in bulk tissue, which cannot distinguish a uniformly heterozygous population from a corrected minority, and short-amplicon genotyping systematically misses the deletions, rearrangements and chromosome-scale events documented after nuclease cleavage (Kosicki *et al.*, 2018; Leibowitz *et al.*, 2021) and in edited human embryos (Alanis-Lobato *et al.*, 2021; Zuccaro *et al.*, 2020). Single-cell and long-read genotyping of edited fetal tissue, applied to the existing rodent models rather than to new ones, would establish whether reported efficiencies correspond to functionally corrected cell populations and whether clonally amplified genomic damage occurs. This is achievable with current technology and would materially change the interpretation of the existing preclinical record.

A third priority requires new cohorts rather than new methods. Analytical performance for locus-specific monogenic diagnosis has not been characterised as a function of gestational age in the six to twelve week interval. Prospective cohorts sampled serially across that interval, with paired invasive or postnatal reference genotyping and with explicit reporting of uninformative and failed results, would establish the earliest gestational age at which a diagnostic rather than screening standard is met, and would test whether enrichment approaches reported for screening extend to locus-specific genotyping (Blouin *et al.*, 2026; Daryabari *et al.*, 2026). The same cohorts should generate the paired placental and fetal genotype data needed to estimate discordance for single-nucleotide and small insertion or deletion variants, which is currently characterised principally for chromosomal abnormality (Grati *et al.*, 2020). Adequately powered estimation of discordance requires cohorts substantially larger than those in the current literature, and is therefore best pursued through multicentre collaboration within existing prenatal diagnostic networks.

A fourth priority is large-animal editing dosimetry. Every large-animal in utero study identified here concerns gene transfer rather than editing (Di Donfrancesco *et al.*, 2025; Mattar *et al.*, 2017), so no data exist on how editing doses scale to a fetus of human size, how reagent distributes across a fetal circulation of relevant volume, or what proportion of a target organ can be reached by a route that would be feasible percutaneously. Studies in non-human primates or in pigs, staged by gestational age and comparing systemic maternal administration with direct fetal delivery, would address these questions and would simultaneously supply the maternal toxicology and immunogenicity endpoints that preclinical delivery studies have reported only cursorily (Chaudhary *et al.*, 2024).

Without such data no first-in-human protocol could specify a maternal risk profile capable of satisfying the standards articulated for fetal gene therapy research (Shanahan *et al.*, 2021).

A fifth, longer-term priority concerns modality development directed specifically at the fetal setting. A framework that corrects whichever variant is identified requires broad variant coverage, which at present implies prime editing, yet in vivo prime editing efficiencies remain well below those of base editing and no fetal administration has been reported (Anzalone *et al.*, 2019; Böck *et al.*, 2022; Tálas *et al.*, 2026). Development work should prioritise transient, non-integrating formulations, since expression duration and off-target accumulation are coupled, and should evaluate efficiency in proliferating fetal progenitor populations rather than in quiescent adult hepatocytes, which are the tissue in which most in vivo editing has been optimised. The regulatory pathway for agents that are unique to each patient is being defined in parallel, and prenatal application would inherit both the flexibility and the evidentiary burden of that pathway (Feierman *et al.*, 2026; Musunuru *et al.*, 2025).

A final priority is normative and empirical work on consent and on the framing of choice in the ultra-early window. An unexpected first-trimester diagnosis followed by an offer of unproven irreversible intervention compresses deliberation into an interval that existing counselling models were not designed for, and the alternatives against which such an offer would be weighed are reproductive rather than therapeutic (Brown & Koenig, 2021). Empirical study of how affected communities and prospective parents evaluate this trade-off, extending the small existing evidence base (Boardman & Thomas, 2023; Vasquez-Loarte *et al.*, 2020), should precede rather than follow protocol development, since it bears directly on whether a first-in-human study could be designed with a defensible consent process.

12. Conclusions

The framework examined in this review couples two capabilities that have each advanced substantially but that have not been evaluated against one another. The review set out to determine what limits the earliest gestational age at which a monogenic diagnosis of therapeutic quality can be obtained non-invasively, whether current editing and delivery systems could plausibly achieve the coverage and precision that correction would demand, where the two halves make incompatible assumptions, and what research would resolve the most consequential uncertainties.

On the first question, the limiting factors are biological rather than computational. The circulating analyte is placental in origin, is present at low and variably rising fractional abundance in the earliest weeks, and is an imperfect proxy for the fetal genotype. Enrichment rather than sequencing depth is the operative lever, and the single report extending informative analysis to eight weeks of gestation concerns screening rather than locus-specific diagnosis and has not been independently replicated. The methods with the strongest clinical evidence require haplotype phase from an affected proband or informative family, which restricts them to pregnancies where risk is already recognised. This conclusion is well supported.

On the second question, the evidence permits a narrower conclusion than is often drawn. Editing reagents delivered directly to fetal mice at a late gestational stage can alter measurable phenotypes, and this has been shown across several models and two delivery chemistries. It has not been shown in any large animal, at any gestational stage corresponding to the human first trimester, or by any route feasible in early human pregnancy. Human in utero therapy has been achieved only with reversible protein and cell modalities, and human genome editing only after birth. The distinction between these achievements and the framework's requirement is one of kind rather than degree.

On the third question, four incompatibilities are specific enough to be actionable. The population best served by ultra-early detection is the one the detection methods serve worst; the gestational interval offering the greatest developmental advantage is the one in which diagnosis is least secure; the editing modality with the broadest variant coverage is the one with no fetal evidence; and the combination the framework requires, namely irreversible modification applied prenatally, is the one for which no human data exist. These are conclusions about coherence rather than about feasibility, and they hold regardless of how rapidly individual components improve.

On the fourth question, the germ-cell exposure question is the pivot. It is unmeasured for every editing modality now proposed, it is empirically tractable, and its answer determines whether prenatal somatic editing sits within somatic-therapy governance or engages the frameworks that exclude heritable modification from clinical practice. Measuring editing outcomes at cellular resolution and generating gestational-age-resolved diagnostic performance data are the other two priorities that would most change interpretation of the existing record.

The broader significance of this synthesis is that the framework is best understood as a research programme with sequenced intermediate objectives rather than as a clinical pathway awaiting incremental refinement. Progress on its two halves is not interchangeable, and improvements in detection would not by themselves bring intervention closer. The most defensible position the current evidence supports is that the framework is a legitimate object of preclinical and normative inquiry, that several of its central premises remain untested rather than disproved, and that claims of imminent clinical application are not warranted by the evidence assembled here.

13. Limitations

This review is a narrative synthesis, and its selection of sources was purposive rather than exhaustive. Although search concepts, information sources and eligibility criteria were specified in advance and reported transparently, purposive selection admits both selection bias and interpretive bias. A different reviewer working from the same literature could reasonably weight the preclinical

record more favourably, or could organise the synthesis around disease categories rather than around the causal chain adopted here. No formal risk-of-bias instrument was applied, because the heterogeneity of designs precluded consistent use of any single validated tool, and appraisal therefore rested on judgement guided by stated criteria rather than on scored assessment.

Access to subscription-only bibliographic databases was unavailable, and searching was confined to freely accessible indexes together with institutional sources and citation-based supplementary searching. Literature indexed only in subscription databases, and literature published in languages other than English, may therefore be under-represented, with the likely direction of bias being under-representation of regionally published work from the settings where the burden of monogenic disease is greatest. Grey literature, conference proceedings and preprints were excluded, which may have omitted recent findings not yet peer reviewed in a field that is developing quickly.

The evidence base itself imposes further constraints. Study designs are heterogeneous to a degree that precludes any quantitative synthesis, and no meaningful pooled estimate of diagnostic performance or editing efficiency could be produced. Much of the therapeutic evidence derives from a small number of collaborating laboratories, so apparent consistency across studies may reflect shared methods and assumptions rather than independent replication. Geographical representation is uneven in both halves of the literature, with diagnostic service evaluations concentrated in a small number of high-income health systems. Long-term evidence is scarce throughout: follow-up in the preclinical studies corresponds to a fraction of the relevant lifespan, and the human in utero and editing interventions cited were reported within a few years of administration. Publication bias favouring positive preclinical results is plausible and cannot be assessed from the available material.

Finally, the subject of this review is in part a proposition rather than an established practice, and appraising a proposition requires inference about how components not yet combined would behave together. Those inferences are constrained by the evidence cited but are not themselves empirically tested, and they should be read as structured argument rather than as findings.

Consent

It is not applicable.

Ethical Approval

It is not applicable.

Declaration of AI Use

This manuscript was prepared through the intellectual contributions of the author(s) to the study design, data analysis, interpretation of results, and scholarly content. Grammarly and ChatGPT were used solely to assist with grammatical refinement and reference formatting during manuscript revision. The author(s) accept full responsibility for the accuracy, integrity, and final content of the manuscript.

Competing Interests

Authors have declared that no competing interests exist.

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