

Assessing genetics providers' perceptions of epigenetic risk scores for prenatal exposures

by

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ABSTRACT

Background: DNA methylation (DNAm), a well-established epigenetic mechanism, has been associated with the long-term health effects of prenatal environmental exposures and has emerged as a potential biomarker linking those exposures to neurodevelopmental risk. Building on this research, epigenetic risk scores (ERS), which aggregate DNAm values across specific CpG sites, are increasingly being explored as tools to predict both prenatal exposure history and neurodevelopmental outcomes. While genetics providers already counsel patients on potential outcomes relating from environmental exposures, their perspectives on applying ERS in the prenatal setting remain unexplored. **Methods:** This study used a four-phase design to explore the clinical readiness of ERS by comparing researcher and provider perspectives. Phase 1 comprised a systematized literature review to identify ERS developed for prenatal exposures and neurodevelopmental outcomes. Phase 2 consisted of virtual focus groups with North American prenatal genetics providers to explore hypothetical clinical applications of ERS for prenatal genetic counselling identified in phase 1. Phase 3 applied deductive content analysis of discussion sections of the reviewed literature to extract researchers' perspectives on ERS utility. Phase 4 integrated findings from Phases 2 and 3 to identify areas of convergence and divergence. **Results:** The literature review identified 13 eligible ERS papers. Comparison with the perspectives of 17 genetic counsellors (GCs) revealed that, while both groups supported strengthening the ERS evidence base, they differed in what they prioritized. Researchers focused primarily on analytic validity and predictive performance, whereas GCs emphasized clinical validity, clinical utility, and ethical, legal, and social implications, including concerns related to eugenics, insurance, access, and stigmatization. GCs also highlighted a mismatch between current ERS technical capabilities and clinical actionability, indicating recommended

considerations for how ERS results could inform patient care and decision-making.

Significance: This study reveals a gap in the translational research pipeline, where technical development of ERS is outpacing progress toward clinical readiness. To move ERS beyond a promising research tool and support its responsible implementation, collaboration among clinicians, researchers, regulatory organizations, and end-users is needed to refine the evidence, evaluation frameworks, and implementation strategies required for clinical integration.

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LIST OF ABBREVIATIONS

ACCE	Analytic validity, clinical validity, clinical utility, and associated ethical, legal, and social implications
ACGC	Accreditation Council for Genetic Counseling
ACMG	American College of Medical Geneticists
AUC	Area under the curve
AV canal	Atrioventricular canal
BMI	Body mass index
CAGC	Canadian Association of Genetic Counsellors
CBGC	Canadian Board of Genetic Counselling
CCMG	Canadian College of Medical Geneticists
CMA	Chromosomal microarray
CMS	Centers for Medicare & Medicaid Services
CPS	Child Protective Services
CRP	C-reactive protein
CVS	Chorionic villus sampling
DNAm	DNA methylation
DNMTs	DNA methyltransferases
DOHaD	Developmental Origins of Health and Disease
DTC	Direct-to-consumer
EGAPP	Evaluation of Genomic Applications in Practice and Prevention
EI	Early intervention
ERS	Epigenetic Risk Scores

EWAS	Epigenome-wide association study
FAS	Fetal alcohol spectrum
FASD	Fetal alcohol spectrum disorder
FDA	Food And Drug Administration
GCs	Genetic counsellors
GETT	Genetic Testing Evidence Tracking Tool
HNSCC	Squamous cell carcinoma
HPA	Hypothalamic-pituitary-adrenal
IUGR	Intrauterine growth restriction
MFM	Maternal fetal medicine
MGs	Medical Geneticists
MRS	Methylation risk score
MSS	Maternal serum screening
NDD	Neurodevelopmental disorder
NDDs	Neurodevelopmental disorders
NIPS	Non-invasive prenatal screening
NIPT	Non-invasive prenatal testing
NPV	Negative predictive value
NSGC	National Society of Genetic Counselors
OB	Obstetrician
OB/GYN	Obstetrician-Gynecologist
PPV	Positive predictive value
PRS	Polygenic risk scores

PTE	Prenatal tobacco exposure
REDCap	Research Electronic Data Capture
RTA	Reflexive Thematic Analysis
U.S.	United States
UMGF	Univeristy of Manitoba Graduate Fellowship

CHAPTER ONE: INTRODUCTION

1.1 The Emergence and Evolution of Epigenetics

The field of epigenetics came about as our understanding of the influences of genetics and the environment on development expanded. Initially, Conrad Waddington, who coined the term “epigenetics”, wanted to acknowledge the important role of genetics in embryology, essentially how a genotype becomes a phenotype during development (Waddington, 2012). His model remained largely conceptual until Watson and Crick's 1953 description of DNA's double helix structure (Watson & Crick, 1953). With the discovery that all cells possess the same DNA, a question emerged: if heritable information is encoded in a single, stable sequence, how does that sequence give rise to such different tissue and cell types? Following Waddington, David Nanney was the next researcher who was able to connect that this postulation extended not only to tissue and cell types, but also to gene expression in a broader sense (Nanney, 1958; Ospelt, 2022). Slowly, this concept came to be defined as changes in gene expression that do not change the DNA sequence itself and can be stable through many cell divisions, and thus, heritable (Berger et al., 2009; Deans and Maggert, 2015). This definition leaves open which molecular mechanisms produce these changes in chromosome state. Three exist: histone modification, the regulatory activity of noncoding RNAs, and DNA methylation, which is the focus of this study (Al Aboud et al., 2026).

1.2 DNA Methylation (DNAm)

The most well-researched epigenetic mechanism is DNA methylation. This was the first mechanism to be discovered (Hotchkiss, 1948; Ospelt, 2022). It involves adding a methyl group to cytosine bases (Illingworth & Bird, 2009). Recognizing the need for a stable, heritable molecular switch that could silence genes without altering the underlying code, researchers such as Holliday and Riggs proposed that DNA methylation played a role in cell differentiation and

gene expression localized to certain cells or tissues. They hypothesized that these chemical tags could physically alter DNA-protein interactions and, crucially, be maintained across cell divisions (Holliday & Pugh, 1975; Shen et al., 2008).

DNAm occurs in specific regions of the genome. In mammals, methyl groups are added to cytosine bases that are immediately followed by a guanine, known as CpG dinucleotides (CpG sites), which are commonly grouped together in what are called “CpG islands” (Barnes, 2025; Ilingworth and Bird, 2009). CpG islands are usually located near gene promoters, serving as genomic markers and playing a role in regulation of expression of these genes (Bird, 1987; Deaton and Bird, 2011; Gillespie et al., 2025);

The process of DNAm is carried out by DNA methyltransferases (DNMTs), which either establish new patterns or maintain them across cell divisions (Bestor & Verdine, 1994). These methyl groups physically block transcription machinery and recruit binding proteins that condense the DNA into tightly packed heterochromatin, effectively silencing gene expression (Goll & Bestor, 2005). By altering chromosomal structure, DNAm influences the broader 3D arrangement of the genome and dictates how the genetic code interacts with proteins (Gillespie et al., 2025).

Today, the most well-characterized functions of DNA methylation include facilitating cellular differentiation, with applications ranging from estimating biological age to quantifying the impact of environmental exposures on gene expression, with the latter being the most relevant to this study (Christofidou & Bell, 2025).

1.3 The Role of DNAm in Development

In the early embryo, the DNA is a “blank slate” or totipotent (Condic, 2014). As development progresses, precise epigenetic programming must be incorporated into this slate to enable cellular specialization. This makes DNAm essential for several fundamental biological processes during embryogenesis, including selective silencing of genes (depending on the parent of origin), the suppression of transposable elements, and influencing X-chromosome inactivation, and the cellular changes associated with aging (Bird, 2002; Breton-Larrivée et al., 2019; Smith & Meissner, 2013). When a gene becomes methylated in the embryo, it is not transcribed (i.e. silenced); and the specific genetic segment crucial for expression is no longer accessible to the transcriptional machinery (Gillespie et al., 2025). For instance, once a cell differentiates into a neuron, DNAm silences genes associated with other organs such as muscle or liver. This ensures mitotic heritability.

1.4 Environmental Influences on Fetal Development

David Barker's hypothesis of "fetal programming," introduced in the 1980s, states that the in-utero environment induces developmental adaptations in the fetus, which can significantly influence the individual's physiology and metabolic function (Barker & Osmond, 1986; Barker, 1990; Godfrey & Barker, 2001; Kwon & Kim, 2017). This was supported by studies of the Dutch Famine of the mid 1940's (Lumey and Van Poppel, 1994); Ospelt, 2022). Researchers identified specific fetal survival adaptations to maternal starvation. They discovered infants born to starved pregnant individuals had smaller livers and a resistance to insulin as adults (de Rooij et al., 2006; Ravelli et al., 1998; Roseboom et al., 2001). Physiologically, to preserve neural development, blood flow is shunted away from peripheral organs, resulting in reduced liver mass and diminished pancreatic beta-cell proliferation (Barker & Osmond, 1986; Belkacemi et al.,

2010; Hales & Barker, 1992). Simultaneously, exposure to elevated maternal stress hormones alters metabolism to maximize energy conservation (Hales & Barker, 1992). While these permanent structural and endocrine adjustments optimize in-utero survival, they create a severe metabolic defect in adulthood if nutrition becomes abundant, driving insulin resistance, obesity, and cardiovascular disease later in life (Barker, 1990; Barker & Osmond, 1986; de Rooij et al., 2006); Ravelli et al., 1998; Roseboom et al., 2001; Roseboom et al., 2006; Schulz, 2010).

The evidence depicting the influence of environmental factors on fetal development was central to forming the concept known as the Developmental Origins of Health and Disease (DOHaD). The DOHaD framework postulates that the in-utero environment can impact an individual's development and lead to adverse health outcomes through lasting changes to bodily organs and systems (Dieckmann & Czamara, 2024; Wadha et al., 2009).

1.5 Environmental Influences on DNAm

One of the ways in which in-utero environmental exposures are thought to leave these lasting marks on a cellular level is by altering DNAm (Breton-Larrivee et al., 2019). Though DNAm is heritable through mitosis, it is also remarkably dynamic. Because the process of DNAm is being actively programmed during embryogenesis, the embryo is incredibly vulnerable to external signals (Seisenberger et al., 2013). These signals can influence the efficiency of enzymes implicated in DNAm, potentially resulting in lasting impacts on the epigenome and altering the individual's phenotype after development is complete. For example, disruptions to essential enzymes like DNMT1 can permanently wipe out genomic imprints that the embryo cannot later restore. Since these imprinted genes control critical growth processes, losing their strict regulation can trigger developmental issues, including lethal consequences or sex-specific defects in placental function and X-chromosome inactivation (Breton-Larrivee et al., 2019).

1.5.1 Internal Exposures

Indeed, studies have shown that internal and external exposures can impact gene expression through modulating the function and activity of DNAm. Internal exposures can include hormonal fluctuations such as cortisol caused by maternal stress. Recently, in a large, diverse cohort, researchers found that higher maternal perceived stress during pregnancy is directly associated with altered newborn DNA methylation within key stress-response genes, specifically *FKBP5* (Jones et al., 2025).

Another study investigating a cohort of Brazilian mother-infant pairs demonstrated that prenatal psychological distress and elevated maternal cortisol levels correlate with distinct epigenetic changes in the offspring's stress-response and oxytocin receptor genes (*NR3C1*, *FKBP5*, and *OXTR*). Notably, maternal anxiety was linked to reduced infant *OXTR* methylation, suggesting a molecular pathway for the fetal programming of hypothalamic-pituitary-adrenal (HPA)-axis function (Wiley et al., 2023).

1.5.2 External Exposures

External exposures, such as infections or air pollution in-utero have also been linked to altered fetal DNAm. A large-scale epigenome-wide meta-analysis revealed that prenatal exposure to particulate air pollution alters DNAm patterns in newborns. These chemical exposures specifically modified genes critical to embryonic growth and respiratory development, such as *FAM13A* and *NOTCH4*, with some of these epigenetic signatures persisting well into childhood (Gruzieva et al., 2019).

1.5.3 Link to Health Outcomes

Whether driven by internal psychological distress or external chemical pollutants, the clinical significance of *in-utero* DNAm alterations lies in their capacity to predict health outcomes at or after birth. An epigenome-wide association study (EWAS) using 1,200 archived newborn blood spots, investigated this immediate postnatal window (Hannon et al., 2019). Hannon and colleagues demonstrated that prenatal and obstetric factors, specifically maternal smoking, gestational age, and birth weight, leave detectable DNA methylation signatures at birth. Their team was able to show that smoke-induced DNAm variation at specific loci may result in lower infant birth weights, highlighting how in-utero environmental exposures can directly alter early-life gene regulation to influence long-term health outcomes.

1.6 Using DNAm as a Biomarker

Given the influence of the environment on DNAm of the newborn genome, researchers are increasingly investigating how DNAm patterns can be used as clinical biomarkers for identifying and diagnosing a range of diseases, including those affecting the brain and nervous system (Levenson, 2010). A DNAm biomarker is an umbrella term that is defined as a measurable epigenetic mark which aims to either provide a diagnosis, prognosis, prediction, or response to treatment (Califf, 2018; García-Giménez et al., 2017).

In addition to DNAm's stability in biological samples and dynamic responsiveness to environmental influences, it also exhibits significant inter- and intra-individual variability, shaped by factors like exposure history, age, cell type, and genetic background (Bulla et al., 2016; García-Giménez et al., 2017; Nabais et al., 2023; Wisman et al., 2024). Due to their plasticity and reflection of environmental interactions, DNAm markers have been proposed as more informative than static genetic biomarkers in certain contexts, earning the term

“bioarchives” as they can carry imprints of past exposures across time (García-Giménez et al., 2017; Relton et al., 2015).

As a result of these characteristics, researchers believe that differences in DNA methylation at specific sites can aid in disease detection and diagnosis, including a patient's likely response to treatment and the likely patient outcome (Levenson et al., 2010).

As such, DNAm-based biomarkers have been developed for a range of clinical applications. For example, a diagnostic biomarker was developed as an objective method for central nervous system tumor classification using DNA methylation profiling. The researchers believed that this biomarker reduces inter-observer variability compared to traditional histology. By matching tumors to distinct DNA methylation classes, this technique standardized diagnostics, identified rare or previously unrecognized tumor entities, and assisted in clinical subclassification (Capper et al., 2018).

More recently, a prognostic biomarker was developed in the field of oncology. In head and neck squamous cell carcinoma (HNSCC), synchronous promoter hypermethylation of the somatostatin (*SST*) and somatostatin receptor type 1 (*SSTR1*) genes served as a prognostic biomarker by linking to disease recurrence and decreased disease-free survival following surgical resection. The aim is to help clinicians identify high-risk patients who require adjuvant therapy and intensive monitoring (Misawa et al., 2015; Liouta et al., 2023).

Prognostically and predictively, variations in methylation levels can signal tumour progression or dictate therapeutic efficacy. For instance, in patients with newly diagnosed glioblastoma, methylation of the *MGMT* gene promoter silences a key DNA repair mechanism, making the tumor highly sensitive to alkylating chemotherapy. Consequently, evaluating *MGMT*

methylation status serves as a critical predictive biomarker to identify patients who will derive a significant survival benefit from temozolomide treatment versus those who require alternative therapeutic strategies (Hegi et al., 2005).

Collectively, these examples demonstrate the expanding application of DNAm-based biomarkers and their increasing use in informing disease diagnosis, prognosis, and treatment decision-making across diverse clinical contexts.

1.7 Technological and Analytical Advances

The development of epigenome-wide association studies (EWAS) has been instrumental in enabling investigation of DNA methylation across the genome. This allowed researchers to link specific DNA methylation sites to environmental exposures and health outcomes (Ladd-Acosta, 2015). Advances in high-throughput array platforms and next generation sequencing have all made it possible to measure hundreds of thousands of CpG sites with great precision (Moran et al., 2016). The application of machine learning technology has further enhanced the predictive capacity of methylation data (Gagliardi et al., 2024). These advancements have laid the foundation for translating DNAm signatures into tools that can predict exposures and outcomes, including the generation of epigenetic risk scores (ERS).

1.8 Emerging DNAm Diagnostics

It has been proposed that integrating DNAm biomarkers could complement and potentially enhance risk prediction models that rely on traditional clinical indicators, such as medical history, or genetic risk profiles like polygenic risk scores (PRS). By incorporating epigenetic data, these models can offer a more comprehensive and personalized assessment of disease risk, as demonstrated in cardiovascular research (Christofidou & Bell, 2025). Currently, several

diagnostic tools already leverage these methylation signatures. For instance, specific non-invasive prenatal screening (NIPS) methods utilize distinct methylation patterns to differentiate fetal cell-free DNA from maternal background DNA, enabling the detection of fetal chromosomal abnormalities such as trisomies 21, 18, and 13 (Lim et al., 2013; Lee et al., 2013). Additionally, the Food And Drug Administration (FDA)-approved colorectal cancer screening test, “Epi proColon”, detects methylated SEPT9 DNA in peripheral blood, identifying individuals who require follow-up diagnostic colonoscopies (Lamb & Dhillon, 2017; Tóth et al., 2012). As technological capabilities improve and our understanding of the methylome matures, the landscape of available DNAm-based diagnostic and prognostic tools is expected to expand.

1.9 Epigenetic Risk Scores

With advancements in epigenetic technology and improved understanding of epigenetic biomarkers, there has been growing interest in developing epigenetic risk scores (ERS). Often referred to as epigenetic predictors, methylation risk scores (MRS), (poly)epigenetic scores, methylation scores, or methylation profile scores, these scores have been proposed to serve four principal functions (Nabais et al., 2023). First, they are used to impute missing or incorrect phenotypic data, such as determining smoking exposure. Second, ERS provide an objective method for monitoring and measuring treatment adherence. Third, they offer valuable applications in forensic investigations by predicting demographic traits like age from biological samples. Last, ERS act as biomarkers for assessing disease risk and progression, even before clinical signs (Wisman et al., 2024; Nabais et al., 2023).

1.9.1 How are ERS Constructed?

The development of an ERS typically involves three distinct phases: discovery, validation, and application (Nabais et al., 2023) (Figure 1).

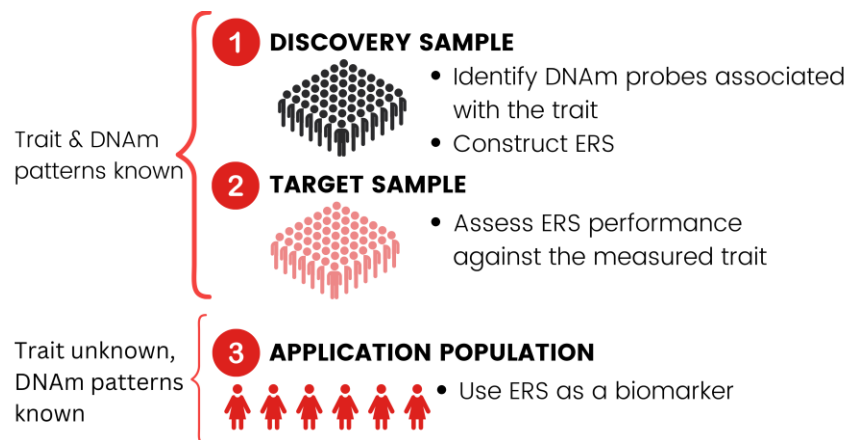


Figure 1: Overview of Epigenetic Risk Score Construction. The discovery phase involves score development, the validation phase assesses predictive performance, and the application phase uses the score to measure exposures or predict outcomes in a population of interest

1.9.1.1 Discovery

In the discovery phase, researchers use EWAS data from a representative "discovery sample" to analyze DNAm levels across individuals with differing disease statuses or exposure histories. By comparing these groups, specific CpG sites demonstrating consistent differential methylation are identified. Each selected site is then assigned a statistical weight, based on its effect size or strength of association with the phenotype. Finally, an individual's weighted methylation values across all selected loci are aggregated into a single cumulative score, which is compared against a reference population to establish the ERS.

1.9.1.2 Validation

In the validation phase, the predictive accuracy of the newly constructed ERS is evaluated in an independent "target sample." To ensure clinical and statistical validity, this target cohort must not overlap with the discovery sample, yet it must closely match the demographic and

environmental characteristics of the population for which the ERS is intended. Because both the discovery and validation phases require prior knowledge of both the DNAm patterns and the true phenotype (e.g., confirmed prenatal exposure to maternal smoking), this step is critical to quantifying the sensitivity, specificity, and overall performance of the score.

1.9.1.3 Application

Once validated, the ERS can serve as a functional proxy or biomarker in a novel "application population." This final cohort consists of individuals for whom genome-wide methylation data is available, but whose specific exposure history or disease status is unknown. By using the ERS in this group, researchers and clinicians can infer missing phenotypic data, such as determining whether an individual was historically exposed to maternal smoking in utero, purely from their ERS.

1.9.2 Emerging Evidence of ERS Utility

ERS has demonstrated clinical utility in oncology. For example, a 2021 study developed and validated a prognostic ERS based on over 1,200 samples to predict overall survival and therapeutic response in breast cancer patients. The resulting score successfully categorized individuals into distinct risk categories and demonstrated that higher scores correlate with immune-inhibited tumour microenvironments and lower sensitivity to both chemotherapy and immunotherapy (Zhang et al., 2021).

ERS have also been developed linking environmental stressors to psychiatric symptoms. Recently, Segura and colleagues constructed an ERS as a surrogate marker to quantify the cumulative biological impact of prenatal, birth, and childhood stressors. The results demonstrate a dose-response relationship, where higher epigenetic loads from these environmental exposures

significantly correlate with an increased risk of relapse in patients with their first episode of schizophrenia (Segura et al., 2025). Furthermore, ERS efforts have been expanded to capture infectious exposures; for example, an ERS for cytomegalovirus was shown to successfully predict post-transplant viral replication and clinical complications in organ recipients by quantifying host immune epigenetic responses (Hsu et al., 2024).

1.9.3 Application of ERS in the Prenatal Period

The same capacity to decode environmental exposures from DNA methylation patterns being used in oncology, psychiatry, and immunology, among other disciplines, is now being applied to map the impacts of early life environments on embryological development. Given the established link between the *in-utero* environment and fetal development discussed previously, researchers are working to generate ERS to 1) detect prenatal exposures and to 2) predict individualized disease outcomes.

To date, ERS have been created for several prenatal exposures and outcomes. For instance, a neonatal ERS has been generated to assess an infant's epigenetic association with weight gain by six months, while longitudinal blood-based methylation scores have been constructed to evaluate whether DNAm variation functions as a causal predictor of future body mass index (BMI) or as a downstream biomarker of existing weight and cardiometabolic traits (Lariviere et al., 2024; Reed et al., 2020). Furthermore, ERS have been created to study environmental and psychosocial stressors. Recent studies have used birth-tissue methylation scores to examine the relationship between prenatal socioeconomic position and childhood language development at 36 months, as well as composite adversity scores to link maternal stress and depression to altered infant methylomes (Abrishamcar et al., 2022 ; Rajaprakash et al., 2024).

Despite these expanding applications, it is not well described how clinicians could apply these tools into patient care. Specifically, the perspectives of providers in the prenatal setting, where maternal exposures such as stress or substance use are linked to long-term neurodevelopmental outcomes, remain unexplored.

1.9.4 ERS in Prenatal Genetic Counselling

Genetics providers, including medical geneticists (MGs) and genetic counsellors (GCs), are specialized healthcare professionals who support patients and families in understanding the clinical characteristics, heritability, and personal and familial ramifications of genetic conditions. While medical geneticists primarily focus on clinical diagnosis, medical management, and metabolic or physical evaluations, GCs integrate expertise in medical genetics and psychosocial counselling to facilitate informed decision-making and psychological adaptation (ACGC, 2023; Korf et al., 2011). In the prenatal setting, these genetics providers play a unique role helping patients navigate rapidly evolving genomic technologies, personal factors and values, and reproductive decision-making. This positioning makes them critical stakeholders in discussions surrounding the clinical application of novel predictive tools, such as ERS.

The rapid expansion of prenatal genomic technologies, from simple screens like alpha-fetoprotein screening in the late 1970s to comprehensive options like chromosomal microarrays and whole exome sequencing, has fundamentally transformed the landscape of prenatal care, increasing both test complexity and volume (Schaa & Biesecker, 2024). As the scope of available testing expands, the sheer volume of choices can overwhelm patients and severely strain the time limits of a prenatal consultation (Ravitsky, 2017). These systemic pressures risk the “routinization of testing”, a phenomenon where offering multiple, highly technical options can inadvertently pressure patients into accepting all available screens without fully grasping

their clinical implications, thereby undermining truly informed consent and compromising equitable care (Ravitsky, 2017; Ravitsky et al., 2021; Schaa & Biesecker, 2024).

1.9.5 Rationale and Research Question:

Despite growing academic interest, ERS have not yet been integrated into routine prenatal risk assessment for environmental exposures and neurodevelopmental outcomes. A clear understanding of how these scores are constructed, validated, and interpreted is necessary to evaluate their potential clinical relevance in prenatal genetic counselling. As ERS emerge as a novel class of prenatal biomarkers, it is critical to investigate the perspectives of the genetics providers who will be tasked with their clinical translation. As medical geneticists and GCs are uniquely positioned to interpret these tools and support patients through complex reproductive decision making, understanding their views on the utility and applicability of ERS is crucial. This can ensure that this new technology, if ever integrated into clinical care, is done so in a way that supports informed choice and high-quality, patient-centered care.

While prior literature has examined DNA methylation in relation to childhood behavioural traits (Ware et al., 2025), there is currently no published review synthesizing epigenetic risk scores developed for prenatal exposures associated with neurodevelopmental disorders, to the author's knowledge. This gap raises crucial questions about how ERS might fit into prenatal risk assessment, patient counselling, and reproductive decision-making. Therefore, my thesis aims to address the question: "How do genetics providers perceive the feasibility and clinical utility of epigenetic risk scores for prenatal exposures for neurodevelopmental disorders, and how do these views compare to published literature?"

To explore this question, this study utilizes a qualitative approach, conducting and analyzing focus groups with practicing genetics providers across Canada and the United States to capture their insights on the feasibility of prenatal ERS in clinical practice. This research also analyzes the published literature on ERS for prenatal exposures linked to neurodevelopmental outcomes, extracting researchers' perspectives on the utility and feasibility of their constructed scores. By comparing and contrasting these clinical and research viewpoints, this study aims to provide a preliminary understanding of the gaps that must be addressed before ERS can be responsibly integrated into prenatal genetic counselling.

CHAPTER TWO: METHODS

2.1 Study Design and Overview

This study utilized an integrative qualitative design, chosen to allow each phase of the research to systematically build upon the next (Figure 2). The study comprised four distinct, interconnected phases: 1) a systematized literature review, 2) participant focus groups, 3) a deductive content analysis of the discussion sections of the reviewed papers, and 4) integration of both datasets from phase 2 and 4. This study received approval from the University of Manitoba's Bannatyne Campus Research Ethics Board (approval number HS26949, H2025:159).

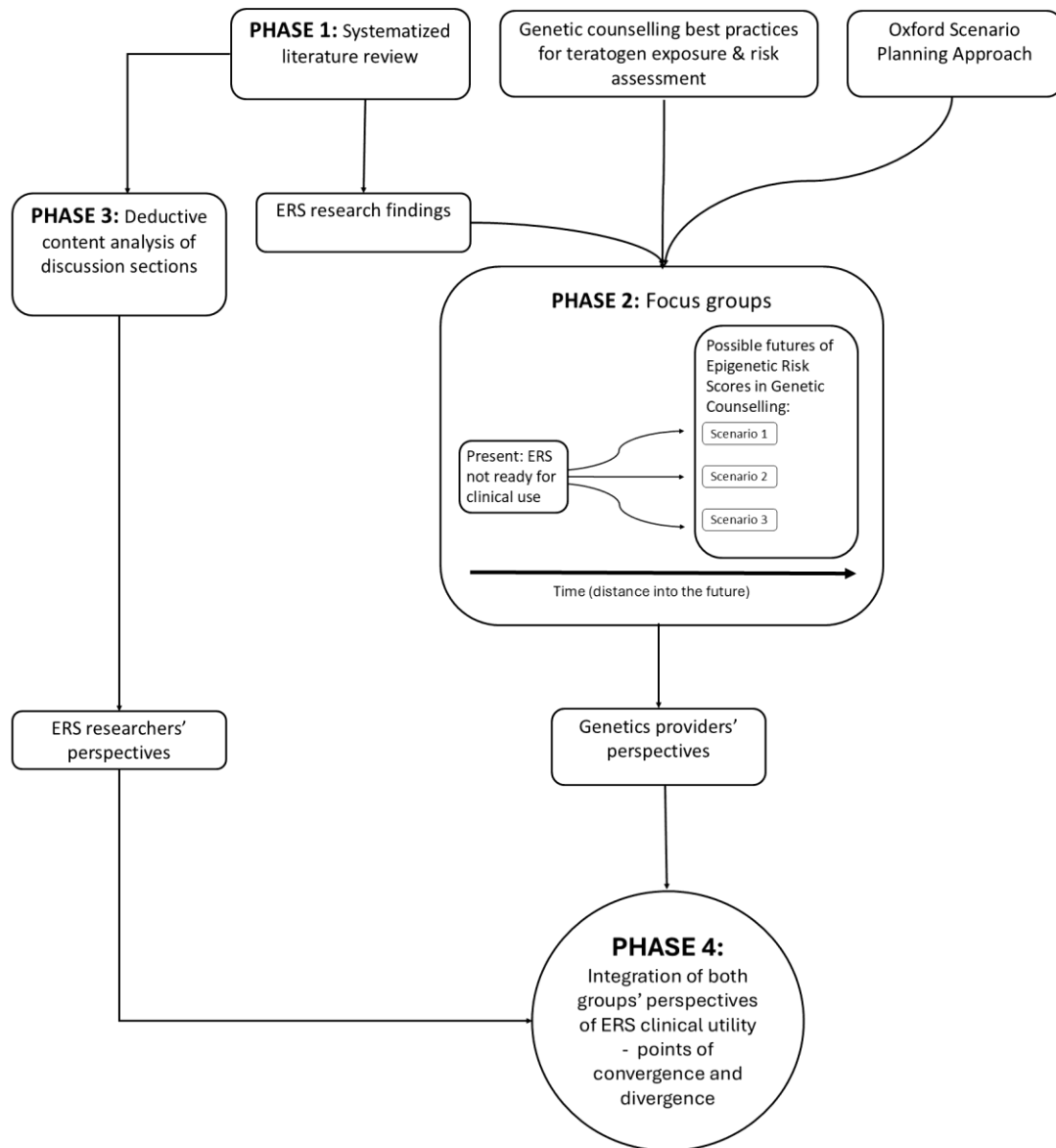


Figure 2: *Study Design Overview: A four-phase design involving a systematized literature review of prenatal ERS research, focus groups with genetics providers, deductive content analysis of discussion sections, and comparison of researcher and provider perspectives.*

2.2 PHASE ONE: Systematized Literature Review

2.2.1 Rationale and Methodological Approach

A systematized literature review was conducted to identify and synthesize published evidence on ERS, with a focus on their construction, validation, and interpretation. The findings informed the development of hypothetical case scenarios used in the subsequent focus groups.

This type of review was selected to balance methodological transparency with the practical feasibility and timeline of a Master's thesis project (Celeste, n.d.; Grant & Booth, 2009; Oliveira et al., 2021). The objective was not to produce an exhaustive, definitive meta-analysis of all available evidence, but rather to offer a structured, transparent, and reproducible overview of the literature directly informing the broader study's aims. By using a systematized design, the review maintains the rigour of systematic methods, such as a predefined search strategy and organized data extraction, while accommodating a single-reviewer scope by eliminating formal risk-of-bias appraisals.

2.2.2 Search Strategy and Information Sources

The search strategy was designed to ensure transparency and reproducibility. A preliminary scoping search was conducted to refine core concepts and variations in terminology. Following this, the primary search strategy was drafted by the student investigator, Z.N.M., using index terms from identified papers, and subsequently refined and finalized in consultation with an academic librarian, M.R.

The literature search was restricted to the Ovid MEDLINE and Scopus databases, which were executed on May 14, 2025, and May 3, 2025, respectively. These databases were selected to ensure both depth and biomedical specificity. Ovid MEDLINE provided comprehensive

indexing of medical, life sciences, and biomedical literature using Medical Subject Headings (MeSH), which supported precise and reproducible search terms. Given that ERS research frequently intersects genomics, epidemiology, environmental health, and data science, Scopus was included alongside MEDLINE to capture multidisciplinary publications that might not be fully indexed within standard biomedical repositories (Block, n.d.; Bramer et al., 2018; Cooke, 2026; Feenstra, 2026). Together, these databases provided a comprehensive, balanced coverage of the biomedical and interdisciplinary literature aligned with the objectives of the review.

The search strings were constructed combining controlled vocabulary and free-text keywords using Boolean operators (AND, OR) and wildcard truncation symbols. The search logic was structured around three core concepts: epigenetic or methylation risk scores, prenatal or early life exposures, and neurodevelopmental outcomes. To align with the project constraints and the niche nature of the topic, specific search limits were applied, including human studies and English language publications. The complete search strategies for both databases are detailed in Appendix A.1.

This search strategy was designed to ensure it was broad enough to capture all preliminary eligible papers without becoming overwhelmingly large. Because a standardized MeSH term for "epigenetic risk scores" does not exist, it was necessary to compile an extensive list of synonyms and related terms under this umbrella, including "methylation risk scores" and "epigenetic scores." Combining these variations with broad exposure and outcome concepts required extensive search strings, which were refined to maintain a feasible scope while ensuring comprehensive coverage.

2.2.3 Eligibility Criteria and Screening Process

Inclusion and exclusion criteria were established *a priori* to ensure a highly focused synthesis of the literature answering the study's objectives (Table 1). The review targeted peer-reviewed, empirical studies that generated, validated, or evaluated ERS for prenatal exposures or neurodevelopmental outcomes. Eligible studies were required to use prenatal or early postnatal biological samples and report data regarding the predictive power of the constructed ERS. Conversely, non-empirical publication, such as editorials, commentaries, reviews, and conference abstracts, were excluded to isolate primary data from opinion-based or secondary perspectives.

Table 1: *Systematized Review Inclusion and Exclusion Criteria*

Include	Exclude
• Studies developing ERS for prenatal exposures. • Studies developing ERS to predict neurodevelopmental outcomes resulting from prenatal exposures. • Studies using prenatal (e.g. placenta) or early postnatal biological samples (e.g. cord blood)	• Full text unavailable online. • Publication unavailable in English. • Reviews, commentaries, manuscripts, or conference abstracts without original research data. • Tissue or cell type unspecified • Studies only involving animals • Studies analyzing samples collected during adolescence or adulthood, even if investigating prenatal exposures retrospectively, were excluded.

The screening process was conducted independently by the student investigator (Z.N.M.) across two sequential stages: an initial title and abstract scan, followed by a full-text review of potentially eligible papers. No automated screening tools or machine learning classifiers were used. To mitigate single-reviewer bias, any ambiguous records or boundary cases regarding eligibility were marked and resolved via discussions with co-investigators J.N.H. and M.J.

2.2.4 Data Extraction and Synthesis

To guarantee consistent and systematic data capture, a structured data extraction template was developed and pilot-tested on a subset of four included articles. The structural design of this template was reviewed and approved by J.N.H. and M.J. before full implementation. The finalized data extraction template, detailed in Appendix A.2, captured data across several domains: bibliographic information, study design and cohort characteristics, methodological approaches (such as tissue type, DNA methylation platform, and statistical modeling techniques), and predictive metrics alongside how the authors described the performance of their score. Data synthesis was entirely descriptive, focusing on narrating the extracted methodologies and study characteristics.

2.3 PHASE TWO: Focus Groups With Prenatal Genetics Providers

2.3.1 Theoretical Framework: Pragmatism

A pragmatist framework guided the design, execution, and analysis of the focus group phase of this study, which considered how genetics providers' professional experiences and clinical contexts shape their perspectives on prenatal ERS. Pragmatism orients itself primarily toward solving practical, real-world problems (Kaushik & Walsh, 2019). It posits that knowledge is fundamentally derived from action and experience, and that individual perspectives are inevitably shaped by unique professional and social contexts. This framework is highly suited for

exploring how emerging, non-implemented technologies, like ERS might operate within applied prenatal clinical settings.

Methodologically, pragmatism relies on abductive reasoning, an approach that moves iteratively between deductive logic (informed by existing literature and theories) and inductive exploration (driven by raw participant data). This iterative movement allows for a flexible exploration of genetics providers' experiences while keeping the findings grounded in practical clinical realities (Kaushik & Walsh, 2019). Pragmatism aligns closely with the central objective of this study: to capture the firsthand professional perspectives of genetics providers regarding the practical utility and feasibility of ERS within routine prenatal care.

2.3.2 Participant Recruitment and Sampling Strategy

Participants were recruited through professional genetics networks using a combination of purposive, theoretical, and snowball sampling strategies in accordance with eligibility criteria (Table 2). Recruitment occurred concurrently with data collection, establishing an iterative feedback loop that allowed the research team to remain responsive to unique perspectives as they arose.

Table 2: *Focus Group Inclusion and Exclusion Criteria*

Include	Exclude
• Board eligible or board-certified (ACGC or CBGC) GCs and board-certified medical geneticists (CCMG/ACMG) with at least one year of experience in the prenatal discipline practicing in Canada or the United States	• GCs or MGs who have not been practicing in the prenatal setting in any capacity within the last 3 years

• Fluent in English	
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Primary recruitment notices were distributed through several major professional channels

(Appendix A.3). A standard recruitment announcement was distributed internationally through the National Society of Genetic Counselors (NSGC) via its monthly Research Survey E-Blast and was pinned directly to the NSGC Communities digital forum on June 11, 2025 (Appendix A.3.1). Domestically, two email broadcasts were distributed to genetic counsellors through the Canadian Association of Genetic Counsellors (CAGC) listserv (Appendix A.3.2), and medical geneticists via two dedicated email broadcasts sent through the Canadian College of Medical Geneticists (CCMG) listserv (Appendix A.3.3) on June 18, 2025, and July 25, 2025, respectively. Physical and digital recruitment posters were also circulated in person at the 2025 CAGC-CCMG Joint Conference. To reach eligible genetics providers operating outside these specific member organizations, an online recruitment poster was shared publicly on Z.N.M.'s professional LinkedIn account, which was re-posted by others within this online community (Appendix A.3.4).

Interested individuals were directed to contact the student investigator via email, and they were subsequently directed to an online eligibility screening questionnaire using REDCap (Research Electronic Data Capture) tools hosted at the University of Manitoba (15.5.34) (Appendix A.4). The questionnaire was constructed in alignment with the University of Manitoba Guidelines for Demographic Questions and was structurally informed by recent CAGC and NSGC Professional Status Surveys. The instrument screened for participant eligibility and collected specific demographic and professional characteristics to describe the cohort (CAGC, 2024; Hennink, 2007; Mays & Pope, 1995; NSGC, 2024). To verify professional credentials, the candidate cross-referenced all eligible respondents against publicly available registries, including the American

Board of Genetic Counseling (ABGC) "Find a Certified Genetic Counselor" directory and the Canadian Certified Genetic Counsellors (CCGC) professional registry.

While it was important to ensure that the final group captured a broad range of professional perspectives, all eligible providers who met the criteria were invited to participate, based on their availability. To safeguard data integrity against computerized bots and fraudulent submissions, attention-check items were embedded within the questionnaire (Mayer et al., 2025).

Furthermore, unique tracking links were generated for each individual recruitment channel to monitor enrollment pathways.

2.3.3 Focus Group Design and Rationale

Focus groups were designed to explore three key areas with prenatal genetics providers: 1) current practices in environmental risk assessment for prenatal exposures for neurodevelopmental disorders, 2) perceptions of ERS utility, and 3) gaps and future directions for applying ERS in prenatal counselling. Each focus group session began with an educational component introducing ERS, covering its definition, its proposed utility compared to Polygenic Risk Scores (PRS) with which genetics providers are more familiar, prediction goals, and specificity vs. sensitivity. This was followed by a discussion of three hypothetical case scenarios and a closing reflection.

Focus groups are ideal for this inquiry because they leverage the interactional processes of sharing and comparing to observe collective sense-making in real time (Morgan, 1997). Each session was capped at 90 minutes. Due to the limited availability of practicing clinicians across multiple time zones, sessions were structured as three-person triads.

While smaller than traditional focus groups, triads maintain the core methodological strength of participant interaction (Morgan et al., 1997). This format combines the depth of an individual interview with the benefits of a group. Compared to larger groups, the triad increases individual speaking time, minimizes conversational friction, and prevents dominance effects. Moreover, the three-person dynamic provides sufficient interactional space to capture disagreements and alignments, which was important given that the goal was not to reach consensus but to capture participants' true opinions (Bayuo et al., 2026; Morgan et al., 1997)

2.3.4 Development of Hypothetical Case Scenarios

As ERS are not yet integrated into clinical practice and genetics providers receive limited formal training in epigenetic-based risk models, discussing these technologies in the abstract can be challenging. To ground discussions in familiar professional contexts, three hypothetical case scenarios were used to anchor the emerging technology within recognizable prenatal counselling encounters (Appendix A.5).

Case scenario development was directly informed by the preceding systematized literature review (phase 1), incorporating realistic data regarding specific prenatal exposures, neurodevelopmental outcomes, predictive validity metrics, and sample collection methods. To ensure clinical plausibility and withstand participant scrutiny, only exposures and outcomes supported by statistically significant findings in the literature were integrated into the case scenarios. Rather than asking participants to speculate, these case scenarios invited them to apply existing core competencies, such as risk assessment, uncertainty counselling, psychosocial support, and ethical reasoning, to realistic future situations (ABGC, 2023). The structural development of these case scenarios was guided by the Oxford Scenario Planning Approach (OSPA), a framework designed for environments characterized by Turbulence, Uncertainty,

Novelty, and Ambiguity (TUNA conditions) (Ramírez, R., & Wilkinson, 2016). Prenatal genetic counselling for emerging genomic tools fits these conditions precisely, as the science is rapidly changing, clinical validity remains uncertain, and clear practice guidelines do not yet exist.

Initially, four distinct hypothetical case scenarios were developed by Z.N.M. Following review by J.N.H. and M.J., one scenario was removed due to conceptual overlap. Revisions focused on strengthening and clarifying case parameters, and ensuring the case scenarios were sufficiently distinct to prompt diverse lines of discussion. Following this internal review, two formal consultation sessions were conducted with an experienced prenatal genetic counsellor (A.J.) and the study team (Z.N.M., J.N.H., and M.J.). A.J. evaluated the cases to maximize clinical realism and ensure alignment with standard protocols for prenatal exposure counselling. The team adjusted the sequencing of the semi-structured probing question (Appendix A.6) to encourage reflection, balanced technical data with practical counselling elements, and drafted neutral supplemental background information to be used only if participants requested it.

2.3.5 Development of Focus Group Guide

The focus group discussion guide (Appendix A.6) was developed in collaboration with J.N.H. and M.J. and subsequently reviewed with G.H. to ensure participants received sufficient background information, clarify focus group expectations, align discussion questions with the case scenarios, and facilitate smooth transitions between case scenarios by Z.N.M (Stewart et al., 2007).

2.3.6 Instrument Refinement and Pilot Testing

To pilot the discussion guide and case scenarios, the student investigator conducted a 90-minute pilot focus group with six participants. The pilot session provided insights into instrument

refinement and group facilitation. Specifically, it informed how to optimize the wording and sequencing of main and probing questions, transition smoothly between case scenarios, and anticipate the exact clinical information participants might request.

The pilot also established appropriate time allocations for each case (more time for complex, two-part case scenarios compared to single-part test cases). The pilot also highlighted strategies to better balance participant engagement, such as explicitly inviting quieter individuals to share, thanking vocal participants before redirecting the floor, and managing off-topic discussions. Corresponding revisions were made to the discussion guide to improve clarity, pacing, and participant interaction. Finally, following the first formal focus group, in consultation with J.N.H. and M.J., one probing question was removed and replaced with a new question that more directly addressed the study's research aims to maximize relevance.

2.3.7 Data Collection

All focus groups were conducted virtually via the Zoom video conferencing platform (6.6.5). To prepare for data collection and ensure professional facilitation, the Z.N.M completed formal facilitation training (Community Assessment: Conducting Focus Groups) and consulted with A.B. and G.H. for targeted questions regarding facilitation.

Before starting any session, informed consent was secured through REDCap and monitored in real time by Z.N.M.; any incomplete submissions were handled privately and confidentially via the Zoom chat function. No participant was permitted to join the discussion without a verified, electronically signed consent form (Appendix A.7).

During the sessions, Z.N.M. was the facilitator. A student volunteer, R.L., was also present during each group to take field notes. Z.N.M took independent field notes as well. Immediately

following the conclusion of each session, Z.N.M. and R.L. held a formal debriefing session to record immediate interpretations and contextual observations.

2.3.8 Transcription and Data Cleaning

The audio and video recordings of the focus groups were exported from Zoom and transcribed using Microsoft Clipchamp (Online Video Editor by Microsoft Clipchamp, n.d.). Z.N.M. conducted audioverification and converted the transcripts to an intelligent verbatim format, a standard that removes distracting verbal fillers (e.g., "um," "like," "ah") (Isaac, 2015). Video recordings were referenced to resolve any indistinct or overlapping dialogue. This process served as an initial phase of data familiarization, allowing Z.N.M. to deeply connect with the nuances, tones, and recurring patterns across the sessions. During this stage, all institutional and personal identifiers and were stripped from the text. Each speaker was assigned a generic alphanumeric participant code (e.g., Participant 1, Session 1) and text files were imported for analysis into Dedoose (10.0.34), a secure, cloud-based application chosen for its intuitive interface and its capacity to support remote collaboration among team members.

2.3.9 Qualitative Data Analysis of Focus Group Data

Focus group data were analyzed using Reflexive Thematic Analysis (RTA), an interpretive framework that identifies broad patterns of meaning across a qualitative dataset (Braun & Clarke, 2019, 2021). Unlike methodologies designed for developing inductive theories (grounded theory), capturing lived experiences (phenomenology), or counting code frequencies (content analysis), RTA is uniquely suited for exploring how groups collectively negotiate shared meaning (Braun and Clarke, 2021; Wainstein, 2026). RTA allowed the research team to interpret specific group dynamics, such as participants echoing and building on an idea, reactions to divergent views, and implicit assumptions. The analysis followed Braun and Clarke's established

six-phase framework, transitioning systematically from data familiarization to final reporting (Braun and Clarke, 2021; Clarke, 2021).

Coding was primarily inductive whereby any excerpt reflecting a comment on the clinical applicability of prenatal ERS was assigned a descriptive code. Coding was managed using Dedoose, a secure, cloud-based application chosen for its intuitive interface and its capacity to support remote collaboration among team members. To ensure analytical consistency, an initial codebook was developed by Z.N.M. after coding three transcripts. This codebook was reviewed independently by J.N.H. and applied to one focus group to support intercoder reliability.

Discrepancies in code application between Z.N.M. and J.N.H. were to be resolved by M.J.; however, full consensus was achieved, and third-party review was not required. Following this check for intercoder reliability, feedback was provided on the coding process and code definitions, and one new code was added. The student investigator iteratively applied the codebook to the entire dataset to ensure absolute consistency.

Next, the analysis transitioned from descriptive codes to broader conceptual patterns, aligning with Richards (2014). The student investigator grouped related codes into general thematic "buckets" representing shared underlying concepts. The research team then met regularly to move the analysis from a semantic level (describing what participants explicitly said) to a latent level (interpreting the underlying values, professional anxieties, and systemic requirements dictating their stances) (Richards, 2014). Through these collaborative sessions, the team ensured that each emerging theme met Braun and Clarke's standard of possessing a distinct, internally coherent "central organizing concept" that directly addressed the primary research aims (Braun and Clarke, 2021).

Once preliminary themes were established, they were formally defined, named, and finalized. Rigour was supported by ongoing reflexivity, intercoder reliability, and the integration of rich participant quotes to ground the themes directly in the raw data. Finally, a member-checking protocol was implemented: an overview of the three themes and associated Ethical, Legal, and Social Implications (ELSI) findings was shared with participants to ensure the synthesis accurately resonated with their perspectives.

To maintain a transparent and reliable interpretive record, Z.N.M. wrote analytic memos throughout the analytical process. These memos summarized key takeaways from meetings, explored conceptual overlap or divergence between distinct code groups, tracked early theme definitions, and documented Z.N.M.'s thoughts and reflections.

2.3.10 Reflexivity Statement

In reflexive thematic analysis, the researcher is viewed as an active instrument in production of knowledge; clean objectivity is neither possible nor desirable (Braun & Clarke, 2022). It is therefore necessary to explicitly "own one's perspective" by outlining the investigator's personal and social standpoint. The primary analysis was conducted by Z.N.M., a cisgender, able-bodied graduate student in a genetic counselling program. Her perspective is shaped by current training paradigms that emphasize client autonomy, evidence-based practice, and dealing with uncertainty in a clinical context. This background may have contributed to an interest toward exploring the potential utility of ERS, while remaining mindful of the practical constraints faced by clinicians in everyday practice. Throughout the study, Z.N.M. maintained reflexivity to ensure her social position and professional background did not overshadow participant perspectives.

2.3.11 Evaluating Data Adequacy and Saturation

In this study, thematic saturation was defined and deemed achieved when successive focus group discussions yielded no new conceptual patterns or codes, providing a rich, multi-layered understanding of the case scenarios (Hancock et al., 2016). This signifies sufficient data within the specific parameters of the study design rather than an exhaustive cataloguing of all possible perspectives on prenatal ERS (Hancock et al., 2016). This approach aligns with Morgan (2013), who states that three to five focus groups are typically sufficient to achieve thematic adequacy in focused qualitative investigations.

Saturation was used as a practical metric to ensure the dataset captured a sufficient range of different ideas (i.e. breadth), while the research team's iterative, collaborative coding process ensured those ideas were deeply analyzed and interpreted (i.e. depth) (Richards, 2014).

2.4 PHASE THREE: Deductive Content Analysis of Studies Identified in Phase 1

A deductive content analysis was conducted on the discussion sections of the papers identified in phase 1 to extract ERS researchers' perspectives on the utility of their tools (Hsieh & Shannon, 2005). To initiate this process, Z.N.M. coded all papers using the codebook established during the focus group analysis, while inductively generating new codes to capture recurrent topics specific to the published literature. As an intercoder reliability check, J.N.H. and M.J. independently applied this codebook to two discussion sections using this expanded codebook. The research team then reviewed the applications, clarified code definitions, and resolved all coding discrepancies together. Following this, the discussion sections were converted into Word documents and imported into Dedoose and iteratively coded according to the finalized codebook to ensure consistency across the entire literature dataset.

2.5 PHASE FOUR: Integration of Findings

To integrate the findings from the focus groups and the literature review, a comparative analysis of data from phase 2 and 3 was conducted to identify areas of conceptual overlap and distinction. Data were organized into two distinct tables: a convergence table documenting shared codes and priorities across both sources, and a divergence table mapping differing codes. For each code, underlying excerpts were reviewed, and the total number of focus groups and research papers which addressed the concept was tallied. This process facilitated an evaluation of the overarching messages from each group, which were then synthesized into summary points to highlight areas of alignment and divergent.

CHAPTER THREE: RESULTS

Literature Review Results

3.1 Study Selection and Screening Process

A total of 245 records were identified through electronic database searching, including 75 from Scopus and 170 from Ovid MEDLINE. Of these, 11 primary studies met eligibility requirements (7 from Scopus and 4 from Ovid MEDLINE). Secondary screening via citation chaining yielded an additional 2 studies. In total, 13 studies were included in this systematized review. An overview of the screening process, including specific exclusion rationales is illustrated in the PRISMA flowchart (Figure 3) (*PRISMA 2020 Flow Diagram*, n.d.).

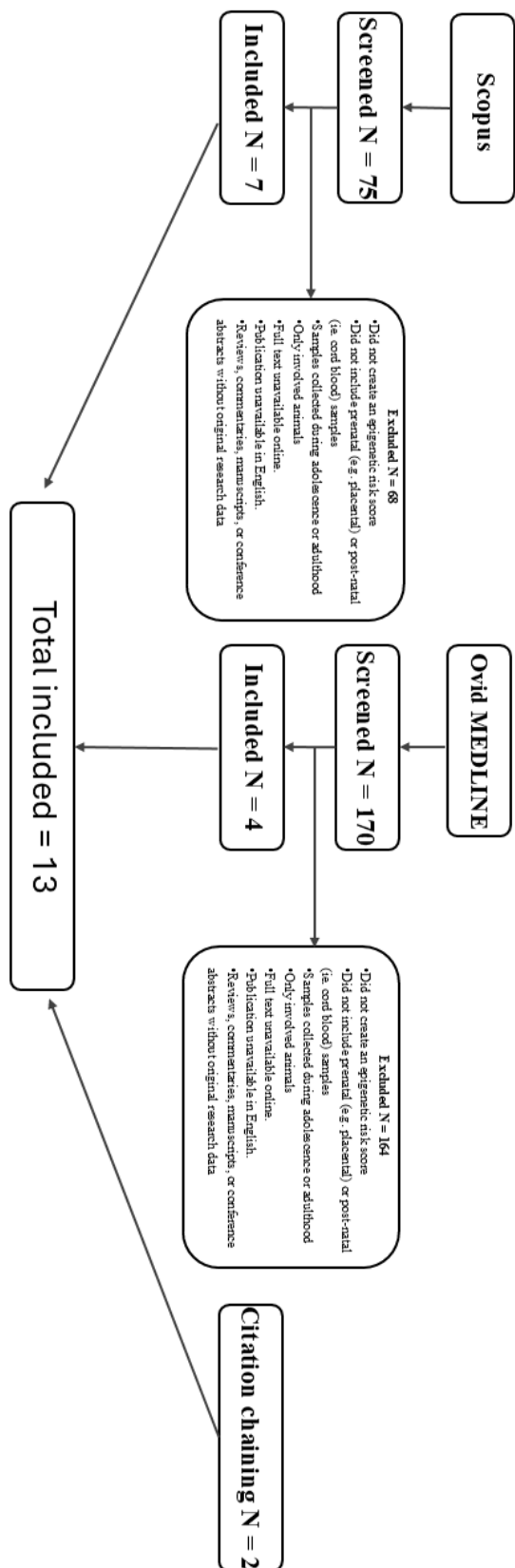


Figure 3: *PRISMA Flow Diagram of Study Screening and Selection via Scopus, Ovid MEDLINE, and Citation Chaining*

The chronological distribution of the included literature (Table 3) demonstrates that while research appeared sporadically between 2017 and 2023, the field experienced a noticeable inflection point in 2024, which accounts for nearly half of the total sample (n = 6, 46.2%). International collaborations were common, with the United States leading contributions and appearing in 76.9% (n = 10) of the papers, followed closely by the United Kingdom (n = 6, 46.2%). Canadian, Finnish, and German institutions each contributed to ~23% (n = 3 each) of the included literature, while the Netherlands and Norway were represented in two papers each (15.4%). South Africa, Brazil, Denmark, and Australia were each represented once.

Table 3: *Summary of Publication and Methodological Characteristics of Included Studies*

Publication Year	Studies N
2017	1
2018	1
2020	2
2022	1
2023	1
2024	6
2025	1
Country of Authors	
USA	10
UK	6
Canada	3
Netherlands	2
Germany	3
Finland	3

Norway	2
South Africa	1
Denmark	1
Brazil	1
Australia	1
Tissue/cell type:	Studies N
Cord blood	8
Placenta	1
Cord blood and placenta	2
Buccal swabs	1
Genetic ancestry	Studies N
European	3
Dutch	2
Finnish	2
White	2
African American/Black	2
South African	1
Asian/Pacific Islander	1
Hispanic and non-Hispanic	1
American Indian or Alaska Native	1
Norwegian	1
Mixed	4
Other	4
Unspecified	1
TOTAL	24
Sex: all papers included samples from male and female infants.	
ERS predicted outcomes:	Studies N
Neurodevelopmental outcomes	2
cognitive, adaptive, socioemotional, and motor domains	1

expressive language, receptive language, visual reception, fine motor, communication, daily living, socialization	1
Psychiatric and diagnostic outcomes	7
Autism spectrum disorder or ASD-related traits	2
mental and behavioural disorder diagnosis	1
psychiatric symptoms (internalizing and externalizing behaviours; total difficulties, emotional problems, hyperactivity/inattention, conduct problems)	3
Psychosis	1
Behavioural outcomes	2
Neurobehavioural outcomes	1
Child total behaviour problems	1
Stress reactivity/neuroendocrine regulation:	1
Enhanced stress response, neurodevelopmental vulnerability	1
ERS predicted exposures:	
Tobacco/Nicotine exposure	7
Maternal smoking/tobacco use	6
Secondary exposure	1
Alcohol/Substance use	2
Prenatal alcohol exposure	1
Prenatal cocaine exposure	1
Psychosocial stress	3
Maternal anxiety and depression	3
Prenatal socioeconomic position (SEP)	1
Infection and inflammation	3

Prenatal infection	2
Neonatal infection	1

Note: For the following variables, some papers spanned multiple options: Country, genetic ancestry, outcome, exposure

3.2 Study Populations and Tissue Types

3.2.1 Demographics, Ancestry, and Sex

All 13 included papers evaluated mixed infant cohorts containing both male and female samples. However, geographic and ancestral bias was a significant limitation identified across all literature reviewed. Cohorts of homogeneous European, Finnish, or Dutch ancestry were the primary focus across 53.8% (n = 7) of the individual papers. While 30.8% (n = 4) of the studies used cohorts labeled as "mixed" or "racially diverse", including African American/Black, Asian/Pacific Islander, Hispanic, and American Indian or Alaska Native participants, true diversity remains narrow, with non-European groups typically appearing as sub-cohorts rather than primary focus populations.

3.2.2 Tissue and Cell-Type Distribution

While the majority of the included literature exclusively used predominantly cord blood (61.5%, n = 8) or placenta (23.1%, n=3 collectively), there was a single study which used post-natal buccal saliva swabs. This focus on fetal and placental tissues is indicative of the types of samples prioritized as informative for ERS construction.

3.3 Methodological Heterogeneity and ERS Architectures

The review revealed substantial methodological divergence in how epigenetic profiles were captured and translated into predictive or descriptive metrics. Studies differed in both the

technological platforms used to generate DNA methylation data and the statistical approaches used to construct epigenetic risk scores.

Earlier studies primarily relied on the Illumina Infinium HumanMethylation450 BeadChip (450K), whereas more recent studies (2024–2025) more commonly used the Infinium MethylationEPIC BeadChip (EPIC) or customized targeted arrays (e.g., Shorey-Kendrick et al., 2024). In parallel, statistical approaches ranged from simple weighted linear combinations of CpG methylation levels to multivariate regression models. Some studies also accounted for cell-type composition heterogeneity by estimating proportions of nucleated red blood cells, granulocytes, and lymphocytes, in order to reduce confounding from variation in cell types and better isolate true DNA methylation signals.

3.4 Characterization of Prenatal Exposures

The exposures investigated by the ERS fell into four primary domains:

Tobacco and Nicotine (n = 7, 53.8%): This represents the most commonly investigated exposure in prenatal ERS literature. Six studies focused strictly on active maternal smoking or tobacco use during pregnancy, while one study extended this measurement to evaluate secondary/passive smoke exposure hours per week.

Psychosocial Stress (n = 3, 23.1%): These studies captured maternal mental health vulnerabilities, specifically targeting gestational anxiety and clinical depression scores.

Infection and Inflammation (n = 3, 23.1%): Studies focused either on systemic prenatal maternal infections (n = 2) and localized neonatal/perinatal inflammatory disorders or encephalopathy of prematurity (n = 1).

Alcohol and Substance Use (n = 2, 15.4%): These studies constructed targeted risk scores to detect prenatal alcohol exposure (PAE) and prenatal cocaine exposure (PCE).

Socioeconomic Position (n = 1, 7.7%): A single study attempted to map the broader macro-environment by designing an ERS tailored to prenatal socioeconomic position (SEP).

3.5 Characterization of Outcomes

Several studies used ERS to predict downstream pediatric clinical phenotypes. The outcomes investigated by these papers targeted four major domains:

Psychiatric and Diagnostic Outcomes (n = 7, 53.8%): The dominant outcome domain. This includes autism spectrum disorder (ASD) diagnoses or associated socio-communicative traits (n = 2), general mental and behavioural health registry diagnoses (n = 1), and broad psychiatric symptoms spanning internalizing/externalizing behaviours, hyperactivity, and conduct problems (n = 3). A single study investigated early childhood precursors to psychosis.

Neurodevelopmental and Cognitive Outcomes (n = 2, 15.4%): These studies used validated clinical scales, such as the *Bayley Scales of Infant and Toddler Development* or the *Mullen Scales of Early Learning*, to track infant performance across cognitive, adaptive, socioemotional, fine motor, and communication/language domains.

Behavioural and Neurobehavioural Profiles (n = 2, 15.4%): Focused on global child behaviour problems, frequently using parent-reported instruments like the *Child Behavior Checklist (CBCL)*.

Stress Reactivity and Neuroendocrine Regulation (n = 1, 7.7%): One study explored the physiological component of risk, linking ERS to enhanced infant stress responses and subsequent neurodevelopmental vulnerability.

In summary, the reviewed papers investigated a range of exposures and outcomes and demonstrated significant methodological variation and demographic patterns across cohorts. The rich data extracted from these 13 papers, specifically the topics surrounding tobacco exposure, prenatal stress, and neurodevelopmental or psychiatric outcomes, directly informed the development of the hypothetical case scenarios analyzed in the following sections.

Focus Group Results

3.6 Focus Group Hypothetical Case Scenarios

The three hypothetical case scenarios developed based on the literature review in phase 1 explored distinct clinical and technical considerations regarding prenatal ERS applications (Appendix A.5). Scenario A focused on a placental alcohol-exposure ERS and explored participant perspectives on biological measures of prenatal alcohol exposure and their potential implications for counselling (Appendix A.5.1). Scenario B examined a tobacco-exposure ERS that conflicted with patient self-report and included a secondary score intended to predict future support needs (Appendix A.5.2). Scenario C involved a stress-related methylation score associated with language delay risk and prompted discussion regarding the predictive value and clinical utility of ERS for complex neurodevelopmental outcomes (Appendix A.5.3).

3.7 Focus Group Participant Characteristics and Recruitment

A total of 34 individuals expressed interest who were eligible for the study. Of these, 27 (79.4%) confirmed their availability to participate in a focus group. Seventeen participants ultimately attended a focus group session, corresponding to a participation rate of 50.0% among eligible

individuals and 63.0% among those who confirmed availability. Table 4 presents the flow of participants through the various aspects of the recruitment and enrolment process.

Table 4: *Summary of participant recruitment and focus group participation*

	NSGC	CAGC	CCMG	LinkedIn	Colleague	CAGC and CCMG Joint Conference 2025	Other
Verified Eligibility	22	5	0	3	3	0	1
Confirmed Availability	19	4	0	0	3	0	1
Participated in FGs	13	2	0	0	2	0	0

3.8 Focus Group Characteristics

Six focus groups were conducted, involving a total of 17 prenatal genetic counsellors. Five focus groups consisted of three participants each, while one focus group included two participants due to a last-minute participant cancellation that could not be replaced. Focus groups lasted an average of 82 minutes (median = 83 minutes), indicating relatively consistent session lengths across groups.

3.9 Participant Characteristics

Seventeen prenatal genetic counsellors (GCs) from Canada and the United States participated in the study (Table 5). Most participants practiced in the United States (70.6%, $n = 12$), while 29.4% ($n = 5$) practiced in Canada.

Participants represented a range of professional experience levels. The mean duration of prenatal genetics practice was 7.9 years (SD = 7.0; range = 1–22 years), while the mean number of years working in a prenatal setting within the previous three years was 6.9 years (SD = 6.7; range = 1–

22 years). The sample included both relatively early-career and highly experienced GCs.

Participants worked across a variety of clinical settings, with academic medical centres being the most commonly reported practice environment. Several participants reported working in more than one employment setting. The sample was predominantly composed of women (94.1%, n = 16). Participants identified primarily as White, although two participants reported additional racial or ethnic identities. Overall, the sample represented a geographically diverse group of prenatal genetic counsellors with varied levels of experience and clinical practice contexts, providing a broad range of perspectives on the potential clinical integration of prenatal ERS.

Table 5: *Focus Group Participant Characteristics*

Years of Experience	Count ((mean ± SD, range)
*Years prenatal experience	7.9 ± 7.0 (1-22)
**Years practicing in prenatal setting last 3 years (mean ± SD, range)	6.9 ± 6.7 (1-22)
	Count
Country	
United States	12
Canada	5
Employment setting	
Hospital/medical facility - academic medical centre	10
Hospital/medical facility - Public	4
Hospital/medical facility - Private	5
Sex assigned at birth	
Female	16
Male	1
Gender identity	

Woman	16
Man	1
Ethnic background	
White	17
Asian	1
Indigenous	1

* This refers to the total duration (cumulative career length) that a participant has worked in the prenatal genetics discipline.

** This reflects recent or ongoing involvement in prenatal genetics in the past three years. It captures recency and continuity of experience, not lifetime accumulation. For instance, a participant with 10 total years of prenatal experience, but who returned to prenatal work only 2 years ago, would report 2 years here.

***Note: Participants could select more than one option for the following variables: employment, gender identity, and ethnic background.

3.10 Data Saturation

Data saturation was achieved after the third or fourth focus group. A total of 25 codes were generated, and no new codes emerged during focus groups five and six. However, these later discussions enriched previously identified codes by providing additional examples and alternative perspectives. Consequently, the final focus groups contributed to the depth and credibility of the findings rather than generating substantially new insights.

Overview of Themes

Three overarching themes on ERS utility were generated and are visually conceptualized as a bridge framework in Figure 4. Currently, genetics providers remain hesitant on the research side of the bridge, calling for more data on validity metrics, tissue types, timing, and appropriate

clinical targets. As illustrated by the tollgate at the centre, transitioning to routine clinical application requires first establishing a robust, actionable justification for "why test" and determining how ERS will alter patient care. Meeting this rationale allows genetics providers to cross into clinical integration, where the focus shifts to helping patients make meaning and navigate decisions through counselling, risk communication, and informed consent. Underpinning this entire framework is a continuous current of ethical, legal, and social implications (ELSI), such as insurance, access, and stigmatization, alongside practical considerations for operationalizing ERS in practice.

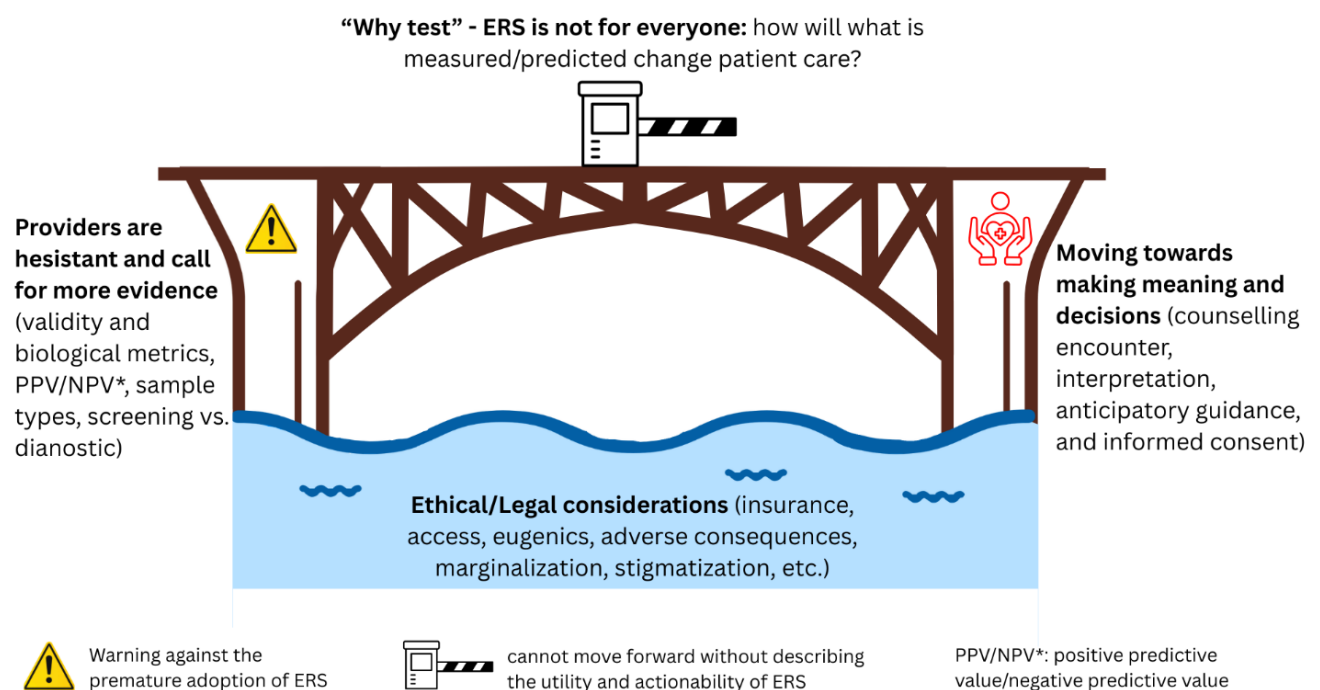


Figure 4: *Overview of Focus Group-Derived Themes on the Perceived Utility of ERS Among Genetics Providers: strengthening the evidence base, addressing clinical needs, and counselling*

considerations for meaning and decision-making, with embedded ethical, legal and social implications

Theme 1: Providers Are Hesitant and Call for More Evidence

All participants expressed broad hesitancy and skepticism toward the current state of ERS evidence regarding its biological and procedural limitations, low predictive values, a lack of longitudinal data, and issues with sample types and test timing. Additionally, participants questioned how to integrate it into existing clinical workflows and emphasized that ERS remains a screening tool, not a diagnostic test.

3.11 Subtheme 1.1: Validity and Interpretive Evidence Needed for Counselling are Missing

Participants broadly questioned the readiness of ERS for prenatal genetic counselling in the absence of stronger evidence, identifying gaps in evidence strength and breadth, clinically appropriate validity metrics, and comparative performance against existing clinical tools.

3.11.1 Overall Attitude on the Current Evidence Base

Across groups, participants repeatedly returned to the absence of foundational evidence on validity measures. From the participants' viewpoint, a lack of solid evidence base is one of the most prohibitive factors in integrating ERS into clinical care.

“I think that a lot of these numbers, I want to understand why we're getting that outcome and how they're getting those numbers to necessarily understand their clinical, technical implications for the patients. And possibly as we start to understand those sort of numbers and causes and influences, maybe that can then make the sensitivity, specificity better. So it could give us a better screening test. But as of right now, I just want more solid evidence overall that I don't think we have currently.” (Participant 9, Session 4)

“I think one thing for me, just a lot more data about the specific scores. What is the timeline for these scores to kind of change. I would need a lot more numbers and data onto how these scores are kind of quantified, what the research is behind them, as far as what factors would be missing for me to feel confident in using these clinically.”

(Participant 13, Session 5)

Some participants spoke of the importance of collecting data over the years to be able to establish a more robust link between exposures and outcomes or clinical presentation. Moreover, longitudinal data may have the potential to inform the kinds of services and the timeline at which these services were accessed:

“If this tool were applied in a longitudinal pediatric study, and you just had a cohort of kiddos who didn't have this tool or this assay, and then a cohort that did, I would love to see like it, 5, 6, 7, 8 years down the road. Did this result in an easier, quicker route to care, to access to services?” (Participant 8, Session 3)

3.11.2 A Desire for Clinically Relevant Metrics

There was also a preference among almost all participants for the kinds of metrics and study designs that make a tool usable in counselling (e.g. positive predictive value [PPV], negative predictive value [NPV], severity correlations, and longitudinal outcomes across diverse populations.). They were less interested in specificity or sensitivity as they are not as meaningful to patients. For example, the following participant commented on how predictive values provide important context relating to risk (personal and population) for outcomes and exposures such as alcohol exposure:

“I think just data in general, I think it will be tricky because outcome data in general is hard to get, but also coming back to our, what do we do with sensitivity, specificity of these scores to get a positive predictive value? I keep coming back to, we don't have a great way to calculate on the front end what the baseline risk of somebody who has alcohol exposure, what's the risk of fetal alcohol spectrum disorder. So then how do we adjust that with these epigenetic risk scores? Would need more data in all the places, I guess.” (Participant 12, Session 5)

Furthermore, another participant expressed the importance of PPV and how they prefer to receive results that speak to positive predictive value rather than specificity or sensitivity. This indicates a difference between the patient-centred outlook of GCs and the test-centred outlook of the researchers.

“I don't know that [testing on amniocytes] changes it too much in my mind. Like, either way, it's a screen, right? Depending on whatever cell type we're screening, it's still a screen. And maybe it changes the sensitivity or specificity a bit. But I think for most patients, those numbers are not super helpful, or at least not as helpful as like PPV potentially.” (Participant 15, Session 6)

Another participant explained the underlying reason for this rationale, highlighting the impact on patients' understanding of their results:

“... I think when we're doing prenatal counseling, PPVs are much more understandable and applicable for patients when they're understanding their risks, than sensitivities and specificities. Because as we know with NIPT, that can over, if you're looking at sensitivity numbers, that can overestimate what - that's not the right assessment of what

that risk actually is. So I think that that would be a measure that would be helpful in this space to probably make this tool...have some more clinical utility and ease of explanation.” (Participant 6, Session 3)

3.11.3 PPV is Not Enough: Predictive Power Needs to be Better Than Existing Tools

Participants also expressed that ERS needs to perform at high or higher than the existing available testing and information used in clinic care for risk assessment. For example, participant 7 compared ERS to other measures such as MSS or NIPT. These numbers do not exist in silos:

“Information that we're able to get about risk for pregnancy. They don't have to just be good on their own, but they have to be better or comparable to information we already have.” (Participant 7, Session 3)

This further was described when discussing the sensitivity or specificity for the case scenarios. Participants felt that in order to even consider offering ERS through an invasive procedure, the sensitivity and specificity of the ERS must be high:

“Offering a invasive procedure with a risk of miscarriage for a screening test with not a high sensitivity and specificity, I can't imagine many genetic counsellors or geneticists would consider that a great option.” (Participant 1, Session 1)

Some participants explained that not only does the predictive value matter but also whether there is a way to confirm the ERS results through diagnostic testing after, which would depend on the indication. Therefore, the crucial step of getting more definitive answers is missing with ERS.

“I come back to that not being a very high specificity. Like 72% doesn't feel great for me when we're thinking about something that's potentially being used in pregnancy decision

making. And it's so hard because normally when we have a screening test, we think about what is your diagnostic test step, but we don't have a diagnostic test for FAS prenatally...Sure, there's a test that's been run, but those sensitivity and specificity figures still aren't extremely high.” (Participant 10, Session 4)

In summary, across participants, the current evidence base for ERS was seen as insufficient in several areas: the quantity and type of available evidence, the absence of clinically relevant metrics, and the failure to match or surpass existing clinical tools. Participants consistently indicated that further research would be needed before ERS could be considered ready for clinical application.

3.12 Subtheme 1.2: Issues Persist Even With Stronger Evidence

Even when considering a hypothetical future with stronger supporting evidence, participants identified several caveats to the clinical utility of ERS, including its role as a screening tool, the dependence of clinical relevance on exposure and outcome selection, the insufficiency of statistical performance alone to confer clinical meaning, and the complexity of integrating ERS into clinical decision-making.

3.12.1 Ultimately, ERS is a Screening Test and Not a Diagnostic One

Many participants argued that even despite plausible evidence and statistically robust ERS (e.g., high specificity/sensitivity, strong PPV), it will always remain a screening, rather than a diagnostic test. They worried about framing probabilistic outputs as determinate, thereby blurring the lines between screening and diagnosis. Further, participants expressed this could potentially increase the likelihood of false reassurance, especially with “low-risk” results, or cause excessive worry, with “high-risk” results.

In speaking about the downstream impacts on patients, one participant expressed that one reason they would not offer ERS without other tests and assessments was because a normal or low-risk result would not be reassuring or sufficient to inform next steps of care:

“...I'm sitting here thinking no matter how great that PPV and the NPV, if I know there's been alcohol exposure, I'm not relying on this methylation test to rule out or rule in. Like, you're right, it could be a great flag for who needs screening later on and that, but let's say her methylation test in this situation was normal or whatever, or low risk for FASD. I don't, that's like I have an AV canal and a low risk NIPT for Down syndrome and I don't order karyotype after delivery. I'm not going to rely on any screen, because this will never, I mean, this will always be a screen.” (Participant 8, Session 3)

One participant echoed this sentiment and went one step further, questioning the overall utility of this tool, particularly in the realm of outcome prediction, because of this limitation:

“I think it's better as part of an answer to something that has come up rather than trying to be predictive. I think, to me, there's no value in trying to make these predictive for a few reasons. Number one, the test is never going to be a test. It's always going to be a screen. Epigenetics cannot ever be diagnostic or predictive. And number two is because there's nothing you can do about it. So in all of the case scenarios that we talked about, today, there's nothing that you could change about that exposure, right? So I don't really see any value in it being predictive ever.” (Participant 11, Session 4)

A few participants drew parallels with counselling approaches they use with current screening tools like Non-Invasive Prenatal screening (NIPS), to explain how they would move forward in the event of an ERS result being discordant with other evidence:

“Even with something as good as NIPT is for Down syndrome...if you have another strong indicator that contradicts it, that goes right out the window anyway. So I really don't know that it's ever going to qualify as a standalone test unless it's also considered diagnostic.” (Participant 6, Session 3)

3.12.2 Participants Had Strong Views on Exposure and Outcome Types

Participants also reflected on how the specific exposure and outcome being targeted by an ERS is important to its potential utility in prenatal counselling. Most participants opposed or saw limited utility in ERS targeting exposures such as maternal anxiety, where the target was perceived as too subjective, too stigmatizing, or too weakly linked to a discernible phenotype, qualities that undermine both interpretability and ethical acceptability.

“I wouldn't want anything with their mental health. I feel like that just, you're just already dealing with so many emotions and so many stressors. I just don't think that that's necessary.” (Participant 17, Session 6)

Moreover, some participants wondered about the purpose of ERS for exposures with commonly known harms. One participant was opposed to such ERS and urged for consideration of broader social, mental health, economic, etc. factors.

“We don't need an epigenetic test to tell someone that drinking during pregnancy could have a bad impact. Like it's not, ‘oh, now that we have the result, okay, now I'll stop drinking.’ That clarifies it like that. There were other factors going on where either there's addiction concerns or they didn't know they were pregnant or they were struggling for whatever other reason. They don't need the epigenetic result to tell them that exposure has the potential to be harmful.” (Participant 10, Session 4)

In contrast, several participants suggested that ERS predicting exposures or measuring outcomes with clearer biological mechanisms and management implications, such as medications, infections, toxic exposures like lead, or ultrasound anomalies, might more directly support clinical decision-making and follow-up care.

“I mean, my gut is something...like anticonvulsants or something, but like those are things we counsel and we know there are risks. There are tests we have to identify a lot of the biggest manifestations, at least neural tube defects if we're worried about those, potentially, even fetal intervention...For me, that's one where it's a little more concrete. It's a much more defined population. It's a little less nebulous. People are unlikely to inaccurately report anticonvulsant use. We have tests for it. We have treatments, we have delivery planning, neonatal planning that we do.” (Participant 16, Session 6)

The broader sentiment was that, at least within the domains most relevant to prenatal counselling, the field would benefit from prioritizing building ERS that establish a clear, less ambiguous link between exposure and clinical outcome.

3.12.3 Statistical Performance Does Not Equal Clinical Meaning

Participants questioned whether ERS can credibly link exposure to epigenetic signature to phenotype, warning against mistaking correlation for causation and that even strong statistical performance may not translate into clinically meaningful prediction of severity, presentation, or developmental trajectory. They expressed that any future prenatal ERS research would need to provide strong evidence for clear or quantifiable outcomes that are well-defined. One participant used the outcome of language delay in one of the case scenarios, to make their point:

“I mean, there could be so many reasons that a baby had, a toddler has language delay. I feel like you can always look back on things and be like, oh, yeah, that that was what it was... That's the cause. But it's just I mean, you can't say that that's causative. It could... just be correlation. I still don't like it, and I don't think I would want to use it. So I don't know that it would change anything for me.” (Participant 17, Session 6))

3.12.4 How ERS Might Affect Clinical Decision Making

Given the issues described, most participants were unlikely to put a clinical decision solely on ERS result. One participant drew on her experience teaching teratology in a genetic counselling program, explaining that even with a low-risk result, they are never fully comfortable with fully reassuring patients that the exposure is no longer a concern:

“We always talk about when is a patient off the hook from an exposure, like with Accutane or something? If somebody did have an early Accutane exposure, okay, their early anatomy screen's normal. That's reassuring, but let's wait a few more weeks till we can complete the anatomy. Okay, that's normal, but we don't know about neurocognitive effects. And when are we gonna know about those? Three years of age, six years of age, ten years. There's just not really an end point. So you don't have a way to rule it really in or out. You see a heart defect, you can't say, oh, okay, well, that's because you had this alcohol exposure. And if you don't see it, you can't say, okay, good, you're off the hook, everything' fine.” (Participant 16, Session 6)

Other participants expressed that even with a high-risk ERS, they would continue to seek more confirmatory evidence before drawing conclusions about causality.

“...if the sensitivity and specificity were just outstanding, we would not stop there. We would continue the workout for IUGR. It would not be sufficient for us to say we're not going to go after all the other possible etiologists.” (Participant 8 Session 3)

Another participant expressed that even if ERS becomes a widely accepted screening tool, they have concerns offering such a tool for which there is no diagnostic test to provide clarity in the risks for the outcomes and exposures screened for:

“It reminds me of [NPT] in terms of, it's really early, it's a screen, it's not diagnostic. But the difference is we don't have a diagnostic test for FASD. So I wouldn't feel great about offering NIPT if I didn't have a diagnostic test to offer as a follow up. And I think that's what makes me uncomfortable about this possibility. (Participant 15, Session 6)

Taken together, participants' reflections on these caveats suggest that even a well-evidenced ERS would require careful consideration before clinical adoption, not only in terms of what the score can statistically demonstrate, but in what exposures and outcomes are measured, how its results can be meaningfully predict the different aspects of an outcome (e.g. severity, trajectory) and applied to the clinical decision making process.

3.13 Subtheme 1.3: Feasibility of ERS for Prenatal Counselling is Limited by Biological and Procedural Constraints

Participants expressed uncertainty due to biological and procedural constraints. This includes questions about technical factors such as stability and sample type and the invasiveness of collection, the fraction of phenotypic variance explained by ERS, and ultimately whether ERS is “worth it”.

3.13.1 What Fraction of the Phenotypic Variance is Explained by the ERS?

When considering the multifactorial nature of developmental outcomes, participants expressed concern not only about over-reliance on a score that accounts for only a fraction of a given outcome. They mused situations where outcomes are multifactorial, and that even a high ERS result may not have a significant impact on the overall clinical decision making and patient counselling.

“And this risk score is another piece of the puzzle that we can't use to solely attribute to the language development. And that there's so many different things that kind of lead into this picture. So just the risk score itself doesn't give us the whole picture and we can't just base all of our understanding on that.” (Participant 4, Session 2)

One participant gave specific examples of what other influences may make up the rest of the phenotypic variance, ultimately affecting risk assessment:

“I hesitate to quote the 25% or any number that they find from this epigenetic risk score, because I would want to know how they isolate that finding versus multifactorial influences. Because a child might have an anxious mother, but they might come from a house that is bilingual. There might be other kids. They might be raised by multiple people. Like there's so there's so much that goes in the language development within the environment, but also internally, that I don't think you could isolate that number taking out other factors to know that this is only caused by maternal anxiety, and therefore this is the number, and therefore this is a good test, would be my hesitation towards it.”

(Participant 9, Session 4)

Another participant explained how this limitation would affect their counselling:

“I think I'd probably still keep it pretty general and overview about how there's many reasons that contribute to what causes a toddler's development and early language skills and what helps promote them. And I don't think I would really focus too much on this score because it doesn't really contribute the majority of what influences a toddler's early language skills...I don't think this would influence my counselling too much.” (Participant 14, Session 5)

When it came to the potential for false-reassurance for a low-risk ERS, some participants pointed out that ERS would act as one input among several in their clinical risk assessment, in conjunction with other factors such as family history. They expressed their desire to appropriately describe the proportion of variance in ERS scores with patient:

“...if she wants to do an ERS assessment for this pregnancy or even like this newborn on cord blood and it comes back with a low risk, are we not going to monitor as well and not offer early intervention services, knowing there's already a family history of a sibling with language delay?...Would it give false reassurance if we had the other type of result when there could be many other factors at play here?” (Participant 12, Session 5)

3.13.2 How Stable are DNA Methylation Signatures and Can They Be Relied Upon Long-Term?

Several participants raised questions about whether DNA methylation signatures are sufficiently stable (e.g. can results obtained at one stage of pregnancy be generalizable to the rest of the pregnancy?) to support prenatal prediction, noting dynamic methylation patterns:

And then my other thought too was, what are the different gestational ages? Would we need to measure this methylation test at various time points in the pregnancy? And kind

of like you were saying before, methylation patterns can change. So are we just going by what's measured in the first trimester or close to delivery? (Participant 12, Session 5)

Some wondered if testing at multiple timepoints will be required, will testing be limited to the duration of the pregnancy or extend to time periods following birth, including the postnatal period, childhood, and beyond:

“...if this was testing you did prenatally, on amnio or CVS, then would there be a recommendation to repeat it at birth? Because this is something that hypothetically changes over time with exposures. If someone's tested at birth and has this, do they repeat it five years in the future or 10 years? Is there any sort of utility? If somebody has a high risk or low risk result at one point, do we then repeat it in the future?” (Participant 4, Session 2)

Another participant compared it to a diagnostic test, highlighting that repeated testing may be another difference between ERS and other established clinical tests:

“Would you get it more than once prenatally? Typically for a diagnostic test, for like a microarray, we're not doing that more than once. We just need one amniotic sample, but something that could theoretically change over the pregnancy figuring out how it's changing, if that helps in the postnatal period.” (Participant 5, Session 2)

One participant expanded this one idea, expressing their specific concerns about an ERS that is done at a single timepoint and how this may affect risk assessment:

“I think for me, it depends on what the data looks like about how long these methylation profiles kind of stick around, what the timeline is on those changing. I think I agree with [participant 12] that I think would be most helpful to have kind of a picture of this

methylation throughout different stages of the pregnancy. So I think limiting the timeline of when we have this data does kind of further limit the utility. Because if we're talking about data from the last month of the pregnancy versus at 13 weeks, like in this scenario, I think that that's a lot more limited in what it tells us about a picture of the pregnancy as a whole, if that makes sense.” (Participant 13, Session 5)

3.13.3 What is the Most Appropriate Sample Type?

Participants were also curious about which sample method would be best-suited (amniocytes vs placental tissue) for testing, whether placental-fetal discordance may undermine confidence, and expressed a need for having validated data on the sample type being used for ERS:

“I mean, I think I would certainly be more cautious if it's not a sample type that it's been validated on or regularly used on. I think that makes me even more cautious of how I'm interpreting this information. You know, again, I don't know either what that methylation profile looks like with amniocytes versus placental tissue, just in general, what the difference is there. And so I think it's something I wouldn't feel super comfortable with not having the information validated for the sample type.” (Participant 13, Session 5)

One participant desired specific research data on the differences in DNA methylation patterns between placental and fetal tissue:

“[Is] placental methylation shown to be the same as the fetus in the literature?”
(Participant 1, Session 1)

Some also wondered if ERS done on placental tissue would need to be confirmed on fetal tissue such as cord blood.

“If we did this on CVS and there's a high risk, do we then have to confirm with amniocytes? Like, what would that look like? Based on one result, right? Would we then all like for everyone do cord blood testing to confirm?” (Participant 4, Session 2)

3.13.4 Participants Were Seldom Willing to Accept an Invasive Procedure for a Screening Test

Many participants expressed hesitations about patients undergoing an invasive procedure for what remains ultimately a screening test rather than a diagnostic one. One participant expressed this sentiment directly, “I can't see a patient accepting a risk of an invasive procedure to do a screen that's not going to be able to change anything.” (Participant 11, Session 4). This points to a general preference for non-invasive methods for obtaining ERS. Given the unresolved biology and validity questions, participants struggled to justify an invasive ERS procedure, especially on its own.

“I was thinking about the invasive diagnostic test, CVS, just in general, or amnio, usually patients are weighing doing this invasive procedure to get a diagnosis. And this is more of a scenario doing an invasive procedure that does have some risks associated with it to get more screening information...that does give it a very different feel.” (Participant 12, Session 5)

A participant from a different focus group drew on their experience, noting that even a well-validated ERS test with meaningful predictive power might face limited patient uptake if delivery required an invasive procedure:

“I mean, I practice where CVS is available...a lot of our patients do not do CVS, even when it's, there's all kinds of clinical or fetal indications for that. So I think it's an interesting question to ask a patient to do a test that's invasive, to try to find a biomarker

for something they may have had control over...I think with something that's got some prediction, but not diagnostic, that might be a harder sell for a CVS. It's sometimes hard enough to sell diagnostic testing in amniocentesis or CVS to patients. So a predictive test may be a harder sell when you've got a test that has a risk tied to it.” (Participant 6, Session 3)

Other participants echoed this sentiment and asked whether ERS alone would be sufficient to justify the risk of an invasive procedure:

“...are we doing these invasive tests for only these purposes? And is that justification enough for the risk?” (Participant 3, Session 1)

Across all focus groups, participants raised questions about the stability of DNA methylation signatures, the most appropriate sample type, and phenotypic variance explained by ERS. Lastly, the majority of participants were not able to justify ERS in the form of an invasive screening test. Overall, this subtheme focuses on the biological and technical limitations that must be addressed before clinical integration of ERS in prenatal risk assessment.

3.14 Theme 1 Summary

Overall, this theme suggests that, from participants' perspectives, ERS currently lacks the evidentiary, biological, and interpretive foundation needed to be integrated into prenatal genetic counselling in a way that is robust, safe, and able to meaningfully support decision-making. Even assuming a technically well-performing score, participants expressed concerns about counselling patients about a result that accounts for only part of a specific outcome, and doubting the effect of positive ERS results on their clinical approach. How the sample is collected posed an

additional barrier, with participants finding it difficult to justify the risks of an invasive procedure when obtaining an ERS would be its sole indication.

Theme 2: “Why test” – ERS is Not for Everyone

This theme focuses on the cross talk needed between clinicians and researchers to develop ERS that are clinically useful. Participants evaluated prenatal ERS through a pragmatic lens: a test is worth offering only if it meaningfully changes clinical decisions, recommendations, or patient care pathways. While theme 1 addresses whether there is sufficient evidence to use ERS in clinic, this theme focuses on how ERS results could alter care in ways that directly benefit patients.

3.15 Subtheme 2.1: Clinical Utility is the Threshold for Offering Prenatal ERS

Across focus groups, genetic counsellors repeatedly highlighted the same core challenge. ERS for prenatal exposures linked to NDDs currently feels misaligned with clinical needs, because the results often do not translate into clear, specific, actionable next steps. For genetics providers to offer prenatal ERS to their patients, there needs to be strong justification for its utility beyond existing tools, whether that is by informing clinical decision-making, diagnostic evaluations, recommendations, or management planning.

3.15.1 A Thorough Medical History Interview May Be Sufficient

For certain exposures, many participants expressed that collecting a thorough, detailed medical history would gather sufficient evidence of an exposure to counsel on the possible effects, and might be more cost- and time efficient. In other words, knowledge of the exposure itself is enough. “I think a more careful clinical evaluation might have disclosed this information without the need for an invasive procedure.” (Participant 3, Session 1)

3.15.2 What is a Label With No Next Steps?

Several participants worried that an ERS result can risk functioning as a label (e.g., “high-risk pregnancy”) that adds psychological burden for patients without meaningfully altering their care. This highlights a mismatch: when the exposure is already known, and the ERS cannot reliably predict a specific outcome, severity, or trajectory, it only contributes to more uncertainty and makes it difficult to justify the cost, time, or resource burden:

“I think how would the patient then take that information? Would it just be like, oh, good to know, now I feel more prepared. Probably not. I feel like a lot of times people end up feeling guilty or they end up feeling like then it just becomes one other thing to be anxious about, right?” (Participant 4, Session 2)

Others saw limited utility in a screening tool which detected outcomes that would take time to manifest. One participant noted that the outcomes discussed in the focus groups were not ones that would threaten the life of the fetus in the immediate neonatal period, and went on to explain:

“...for all of these, you kind of just have to see how the child does anyways and assess their development and their language skills and whatnot, and then provide support based on those factors. It's not something you would use to automatically assign a newborn a label that they are going to be developmentally delayed when they're one month old...and I don't see a situation where they could ever get to that point, really definitively at least because these are, your methylation is changing throughout your life.” (Participant 1, Session 1)

3.15.3 Finding a Place for ERS Within Standard Diagnosis and Management Pathways

Participants also emphasized that standard approaches to diagnosis and management already used in the clinic (e.g., ultrasounds, placental Dopplers, microarray testing, or other genetic investigations) would still be carried out alongside an ERS result. A “high-risk” ERS would not replace established investigations or clinical judgement, and a “low-risk” ERS would not ethically justify stopping evaluations when clinical indications are present (e.g., phenotypic or biochemical findings). Participants placed greater weight on the presenting indication, the child’s needs and developmental profile after birth, and the reason for referral than on an ERS result. As currently envisioned, ERS is therefore positioned, at best, as an adjunct that sits alongside routine care.

“I almost would see this as a more useful tool in the neonatal or pediatric period than prenatally when we have no other pieces of information... You want to combine that screen ideally with other pieces of information. And if we don't expect ultrasound findings for FAS, that's going to be really hard during a pregnancy to combine them with other pieces of information” (Participant 10, Session 4)

Indeed, justifying the value of an ERS was easier when participants imagined it combined with other clinical tests, rather than a standalone tool:

“So the best possible way for something like that to fit in would be when it can be done, at a time in pregnancy or on a type of sample that we would be obtaining regardless or that we're getting alongside other results that more traditional forms of testing... rather than considering offering new invasive procedures for tests that I think have limited utility on their own.” (Participant 10, Session 4)

One participant expressed pessimism about whether this would change management after birth, especially given Canada's healthcare system:

"I don't know how useful this would be because again, we'd just be treating the child for what they're showing us after they're born. We're not, like in Canada, we don't take an overly proactive approach for providing kids with medical management. It's often, you know, what does this child need? This is what we will give them." (Participant 14, Session 5)

3.15.4 What Are the Testing Criteria?

When considering utility, a substantial proportion of participants reflected on how patients would be referred for ERS in the first place. They raised questions regarding whether there should be defined clinical thresholds or presentations required to prompt ERS testing, how eligible patients would be identified, and what standards must be met to justify pursuing the test in the first place.

"You get into sticky situations of if we were to say, these indications are what we want to offer this testing for, say, alcohol exposure and pregnancy, drug exposure or maternal anxiety, how do we quantify what's quote unquote enough for us to offer this testing? Is it mom had one beer like or a glass of wine at 9 weeks? Is that enough for us to say, okay, we have to do this testing? Or is it somebody that's had two to three drinks a day for three weeks? You know, is it something where if mom was exposed to secondhand smoke at a party, is that enough for us to think we should offer it?" (Participant 9, Session 4)

In discussing testing situations, one participant drew on existing, established screening criteria and was unconvinced that ERS currently meets that bar:

“The question of the purpose of screening and the Wilson and Jungner criteria for why are we doing screening, and some of those principles being not clearly present for this type of screening, that there should be a treatment, there should be...a diagnostic test or something that you can do. And so, I think this type of test fails to meet sort of the threshold for offering population-based or screening to people in general sort of as it is presented in this way.” (Participant 1, Session 1)

One participant considered how ERS might fit into their clinic’s existing referral pathways, noting the uncertainty around whether the certain exposures measured by ERS would meet the services offered by the clinic:

“...right now with how we practice, we have a very hard line of when we offer diagnostic testing for what indications...we have, at least in all the clinics I've practiced in, there's a risk to the fetus that's greater than the amniocentesis risk. And for these types of exposures, I can see how we could maybe quantify risks for, this mom had X amount units of alcohol for this many weeks in a pregnancy, there was an exposure to this teratogen. But for anxiety, I don't really know how we would quantify that. And it's very much like a subjective feeling. Like I felt more anxious this day over the next day.”
(Participant 14, Session 5)

The following participant provides a perspective expressed by most participants, describing what ERS would accomplish, for it to be a valuable and clinically relevant tool:

“Utility is: what is that diagnosis going to change? What is knowing that going to change? If you tell me my child has alcohol syndrome, but there's nothing, there's no additional resources that that diagnosis gets them plugged, gets accessibility for them, if

there's not something with their interventions or things that we are going to be doing, then what does that actually do for me other than, again, maybe reinforcing some guilt that that mom had for an exposure she had during her pregnancy...It's what does that diagnosis do to improve outcomes for that child? And if there's not anything that's going to radically change in that, you have to ask, well, what's the utility of even doing an assessment for this?" (Participant 6, Session 3)

3.15.5 Provider Optimism and Utility Beyond The Prenatal Setting

Despite some participants not seeing value for ERS in the prenatal space, due to a perceived lack of actionability or other factors, a considerable number of participants held an optimistic view. One expressed that if the ERS could help pregnant individuals make decisions about their pregnancy, there would be value in that:

“So if we're getting this information in a pregnancy, then possibly this could be useful for how the parents might want to manage the pregnancy if they want to continue or stop the pregnancy based on expecting their child to need additional, I guess, need additional medical services or have additional needs postnatally.” (Participant 14, Session 5) Some participants indicated they could more readily support the integration of ERS if it could help prevent diagnostic delays, particularly in cases where a "wait and see" approach is not ideal and alcohol exposure is suspected:

“If we can do cord blood, if we have a child that we're suspicious for FAS, and we don't want to play that wait and see game of how are they reaching their milestones, when they're having behavioural issues, then yeah, I think that could be helpful for sure.” (Participant 9, Session 4)

Other participants focused on positive possibilities postnatally, expressing support for an ERS that could facilitate earlier access to early childhood intervention services, evaluations and assessments, and inform postnatal management:

“I think that if you were in a situation where you did have access to resources, if they were needed, then if this score had data behind it that said we know these kids typically need additional assistance, we may want to start some type of screening earlier and then be able to plug them into those resources when they need them or we have data that shows that if we start these interventions earlier, the outcomes are better, then there may be value in doing this.” (Participant 6, Session 3)

The same participant evaluated utility from a different lens:

“...another way you could think about utility is if postnatally children are having trouble getting evaluations because of prenatal exposure. If this tool could help get, be a reason to support the need for those evaluations or support insurance coverage for those evaluations. There may be some utility there with it, but I think you have to show, how are we changing care with this?” (Participant 6, Session 3)

Another participant highlighted ERSs’ potential value in changing care for those without a diagnosis:

“I mean, in genetics, we know all about the diagnostic odyssey. And if this helps patients get access to the services that they need without having a diagnosis, then that would be great. Yeah, I guess I don't want to get caught up in how realistic that might be, but yeah, we know there can be a long time sometimes or a long delay for people to get a diagnosis. So if this provides access, then great.” (Participant 15, Session 6)

In discussing the utility of ERS, some participants gave specific examples of what management recommendations could look like:

“If there was something that said that there was a higher risk for leukemia in childhood, right? Maybe you'd want, there'd be more recommendations about having a CBC every year of life that might typically not be indicated otherwise.” (Participant 4, Session 2)

While there was a more prominent focus on the fetus' wellbeing after birth or pregnancy decision-making, some individuals also considered the utility of ERS for the pregnant individual themselves, particularly in the context of mental health:

“...now that we know that there was some impact for that, like what are some referrals like to psychiatry or psychology or other ways to manage to reduce that anxiety?”
(Participant 5, Session 2)

3.16 Subtheme 2.2: ERS May Be the Most Valuable in Targeted Scenarios to Fill a Gap

Where participants did see potential value was in narrower, clearly justified situations, especially when ERS could fill a genuine information gap. Rather than supporting broad testing, participants envision ERS meeting specific, unmet needs within current prenatal genetic counselling. Specifically, they highlighted four main criteria: narrowing phenotypic variability to gain outcome clarity, supplementing incomplete exposure histories, measuring responsiveness to interventions, and establishing a clear link between test results and clinical next steps.

3.16.1 Participant Preference for Discrete Outcomes

Screening for conditions with a discrete outcome seemed to be more readily accepted by participants, such as the presence/absence of a condition or birth defect and are less comfortable with outcomes that have variable or poorly described presentations.

“I think when the outcomes are very definitive and tangible, like if it was looking at risk for an oral cleft or risk for a specific birth difference or something like that, then that's something that I think is a little bit easier to maybe measure outcomes on versus things like developmental delay...if the outcome is a little bit more of a definitive yes or no. I think that from a data standpoint feels like it would be maybe more solid to me.”

(Participant 13, Session 5)

One participant was clear that it would be difficult to justify pursuing ERS if a high-risk result did not fill a gap in understanding the spectrum or presentation of the condition:

“So even if the test was saying there's a higher risk for this condition, it doesn't really tell us much about how that would manifest. It just doesn't seem any more useful than the patient's reported alcohol consumption to me.” (Participant 2, Session 1)

Some participants expressed interest in the types of outcomes being investigated but wanted the predicted outcome to be more specific, providing patients with more meaningful information about their child's expected presentation after birth:

“If there was research or data that was like...when the alcohol consumption is in this trimester and this window, and these methylation factors are present, then the outcome is this version of fetal alcohol syndrome. That would be a way to then have a conversation with a patient and be like, okay, so it was going to be this range.” (Participant 5, Session 2)

3.16.2 ERS As a Tool to Complete Missing History

Several participants also volunteered situations for which they could see ERS being useful, for example when it came to incomplete exposure history:

“I think it could maybe be a stand-in or an option for the diagnostic criteria when we don't know, for example, for patients that are adopted...Maybe this can be a way to learn more about some of that prenatal history that we might not be able to know about otherwise.” (Participant 4, Session 2)

“I could see that being potentially beneficial, particularly if a patient themselves maybe is not aware or hasn't identified certain risks or exposures or just wasn't aware of something that should have been disclosed.” (Participant 1, Session 1)

3.16.3 Measuring Response to Interventions

Others questioned the value of the specific exposures being investigated in their current framing. While they did not see utility in ERS that simply quantifies exposure risk, they were open to the concept if it were used to measure intervention response. They proposed that an ERS capable of predicting whether a treatment or pharmacotherapy is likely to be effective could offer the kind of actionable information that would make the tool clinically meaningful:

“I think anxiety is something that a mom can't do anything about. So I think the only utility here is this knowledge that, the fact that anxiety could increase the chance of poor or poorer outcome for a baby or for a child. So that's, to me, that's all you need to know, because then you can compare, anxiety versus taking some kind of pharmacotherapy during a pregnancy and what are the risks of that pharmacotherapy. So being able to compare a certain medication that might work to help her with her anxiety versus having a pregnancy where your anxiety is untreated. So sure, perhaps research about this and information is helpful, but I would not ever be interested in giving a mother some kind of risk score based on her level of anxiety during pregnancy.” (Participant 11, Session 4)

3.16.4 There Needs to Be a Next Step After ERS

In defined and focused cases, participants felt that ERS could potentially guide monitoring intensity, help anticipate needs, or support earlier access to services and interventions, especially if other features are absent, such as in FASD where many infants do not display obvious symptoms and remain undetected. Participants were in favour of defined and focused cases only if there is a clear or quantifiable link between a positive ERS result and the next step.

“...if we have a structural anomaly on ultrasound, one of those that can have such variable outcomes, probably in part because of multiple factors, I'm thinking Dandy-Walker variant or something like that, where it could be anywhere on the spectrum. So again, in an ideal setting where we had all this data that we've gathered and knew how the ERS correlated, I could see it potentially being helpful there in the context of we have a finding that we know can have such a variable outcome. Is this another metric we can use to help better assess where that outcome might be?” (Participant 12, Session 5)

“I guess expression of genetic disorders, right? That's a big clarification point that we, it's so hard prenatally to predict phenotype, but if epigenetic risk scores could help predict phenotype or clarify phenotype for parents, that would be super interesting.” (Participant 2, Session 1)

In cases where ERS established a link between the predicted outcome and follow-up recommendations, one participant clarified that the score would need to speak to specific health concerns and explain not just what to expect, but why:

“...if there was data about, well, 85% of kids who have this finding end up needing to follow with nephrology. I think that's informative. I think it's more informative to have

the reason why they're following with nephrology, like specifics about what the exact health issues are versus the supports and interventions that they're needing.” (Participant 13, Session 5)

Ultimately, participants based their support for ERS on meeting specific clinical needs, whether by substituting for missing prenatal histories in adoption cases, narrowing a variable phenotypic spectrum, or predicting specific health needs (such as explicit organ-system involvement) that require targeted intervention.

3.17 Theme 2 Summary

This theme highlights a translation gap between ERS research and clinical practice, and ultimately centres on the “who test” and “why test?” question. Participants ask under what circumstances would a genetic counsellor offer prenatal ERS, and what would ERS results actually change in clinical management of a pregnancy or individual? Participants want researchers and clinicians to co-develop ERS with clinical actionability in mind, which includes clear definition of who would benefit from testing, what tangible benefits patients would gain, presentation of scores that can be meaningfully interpreted in counselling, and integration into a defined care pathway that specify what recommendations, interventions, monitoring, referrals, or services would follow from a “high-risk” result. Meeting these requirements could improve ERS utility such that it can be used for clinical decision-making.

Theme 3: Moving Towards Making Meaning and Decisions

This final theme addresses what participants anticipated the counselling encounter would involve, spanning the discussion of ERS capabilities and limitations during pre-test counselling, the informed consent process, collaborative interpretation of results in the post-test encounter,

the psychosocial dimensions embedded within both, and ultimately patients' perceived capacity for agency and actionability in response to their results.

3.18 Subtheme 3.1: Anticipatory Guidance as the Foundation of Meaningful Consent

Participants emphasized the importance of an informed consent process. They described consent as also requiring an explicit exploration of uncertainty, what the test can and cannot answer, and the possible implications of results before testing occurs. Without building this foundation, they worried patients may over-interpret or misinterpret ERS results, leading to misinformed expectations and emotional responses. Participants framed anticipatory guidance as integral to the process, both for risk interpretation and for emotionally and cognitively preparing patients for the kinds of results they may receive and the kinds of conclusions that can and cannot be drawn from those results.

3.18.1 Facilitating Patient Autonomy in Evaluating ERS Value

Beyond their own assessments of ERS utility, participants also reflected on factors that may affect whether patients choose to pursue ERS testing. One participant shared that the value of a result ultimately depends on what the patient stands to do with it, and that if a result amounts only to a label, it falls to the patient to determine whether that label holds meaning for them:

“...for me, a diagnosis alone is not necessarily always a good reason to do a test if there's not going to be something I can do because of that diagnosis. Because if it's only going to be a label, then the patient has to decide, does that label have any value for me or not?”

(Participant 6, Session 3)

Another participant focused on a patient's motivation to do the ERS, noting that a patient who sought out an appointment with the genetics provider out of worry may require a very different

counselling approach than one whose physician provider was concerned about the exposure without the patient having any prior concern:

“I guess my first thought is like about the motivation for this consult, like whether this was something that the patient's worried about. And that's why she presented, because I think maybe that's a very different counselling scenario than someone who was maybe not worried about this.” (Participant 15, Session 6)

A different participant shared that their counselling would invite the patient to focus on the value of the test for that specific individual:

“I counsel my patients, I say, let's begin with the end in mind. And every time we look at a tool in our toolbox, remember that we have to walk ourselves through: what is that tool telling us? How can it help us? Is that useful information?” (Participant 8, Session 3)

3.18.2 Transparent Counselling Acknowledging ERS Limitations

Thorough discussion of test limitations was a considerable priority for participants for informed decision making. They emphasized setting realistic goals and tempering expectations about what information could be obtained from an ERS. One participant expressed their concern about this, while also acknowledging that despite its limitations, there was still value in the test for some patients:

“I think there would also have to be good counselling about, there's a difference between the chance of presenting with features and being able to predict what those features are ultimately and the spectrum of what can be seen. Unless there's data that ties this to being able to predict a certain level of severity of presentation...there may still be some limitation in what that provides for patients. But I could see some patients potentially in a

situation like that, having some interest in a test that might give them a little bit more information to go on.” (Participant 6, Session 3)

The discussion of test limitations was a challenge many participants foresaw in the pre-test counselling encounter, particularly with patients who are feeling vulnerable and want to pursue every available test for reassurance. For this reason, a detailed and transparent discussion of what the test can and cannot deliver was seen as essential to minimizing potential harm:

“I definitely have a population of parents who are like, ‘any test you have that can give me any information, I want to have access to’. And very often, those can be some of the most challenging patients to talk about. While we could do this, you have to understand the limitations of the information and the potential confusion that some of this information may provide and how it may not ultimately be useful.” (Participant 6, Session 3)

3.18.3 Considerations on the Drivers of Patient Uptake

Some Participants also considered the perspective of their patients, reflecting on what might influence uptake. A recurrent question among participants was how much procedural risk patients would be willing to accept in order to obtain a sample for ERS. In envisioning a pre-test counselling encounter, one participant explained:

“I still think anytime you're talking about a prenatal test that has a risk, whether it's CVS or amniocentesis, patients are going to consider it if it's going to help change management, if it's going to make a big difference. If it's not, I don't know that they're going to be willing to take that risk.” (Participant 6, Session 3)

An Informed Consent Process

There were other aspects of informed decision making that patients wondered about. One participant asked, “is this something that parents have to opt into? Is it automatic?” (Participant 4, Session 2), pointing out the importance of having a clear, pre-defined ERS consent model. Some were adamant about wanting an opt-in model from an ethical standpoint, “I think people should have the right not to know this information if they don't want to know it.” (Participant 8, Session 3)

3.18.3 Drawing on Existing Parallels for Post-Test Anticipatory Guidance

Pre-test counselling was not the only context where participants found themselves navigating uncertainty. Participants also reflected on how post-test counselling sessions might unfold, drawing on their experience with other genetic situations to consider how they might frame developmental risk and its implications for the fetus post-birth. One participant questioned whether the counselling approach used for conditions with variable symptoms could be applied, such that the counsellor will acknowledge the potential for the outcome and link the results to some kind of early intervention could serve as a parallel:

“...thinking about how EI [early intervention] is, how therapies work for these kiddos, oftentimes we need evidence of some sort of either delay or a predisposition to a delay with a genetic finding. Could this fall in that same basket of say they have Klinefelter syndrome. And that's something where we talk about, hey, they could have developmental delays. It's not a guarantee. If they present with delays, let's start them in early intervention. Could we counsel this the same way?” (Participant 9, Session 4)

One participant summarized the various facets of anticipatory guidance succinctly when describing how they were envisioning the pre-test counselling encounter:

“I think it would be a big conversation. I would certainly want to make sure that it's something that we discuss in detail. What are the possible types of results from this test? How would we use those results? Thinking through with patients with that shared decision-making kind of counselling about why are we doing this test? What are the outcomes? What is this going to give us? What is this not going to give us? How could this make us feel? Kind of all of those things. So I think it is kind of a complicated discussion when it's information that maybe feels like it would be a little bit less clinically actionable to me.” (Participant 13, Session 5)

3.19 Subtheme 3.2: Agency, Actionability, and the Risk of Burden

Almost all participants expressed concern regarding patient perception, desiring a deeper understanding of how patients might internalize responsibility for measured exposures and predicted outcomes. This included concerns over whether an ERS result would empower or diminish a patient's perceived agency to alter their circumstances.

3.19.1 Is Action Always Possible?

Many participants felt that even when ERS results generate recommendations and urge action, action may actually not be possible. For instance, environmental exposures and social determinants are not easily modifiable, such as living with a parent who smokes:

“...I don't know if it's going to have much utility in changing the environment, the context for this patient, right? So, it's not she herself who's smoking. This is an elderly parent who she may not have a choice of being able to get away from. And we all know we can't change anybody else's decisions with what they do. So while, yes, you could,

you could try to use that to persuade a family member to not smoke, that that may or may not be useful.” (Participant 6, Session 3)

Indeed, other participants highlighted additional external factors that may be out of patients’ control:

“And they can't help most of those exposures where you live, your air quality, your access to clean water. I live in a capital city that's had a water crisis now for a decade.”
(Participant 8, Session 3)

3.19.2 Psychosocial Impact Differs Depending on Patient Circumstances

This inability of a person to change their circumstances or not have a clear roadmap made participants feel uneasy and less enthusiastic about ERS implementation:

“I think it would place people in a very hard situation knowing what to do with that information...I can see that causing a lot of distress for patients if this is implemented without us being able to really know what's next.” (Participant 14, Session 5)

In such contexts, ERS may produce a sense of urgency or responsibility when the patient has limited agency, contributing to guilt and burden. Moreover, where ERS target exposures that carry stigma, such as maternal anxiety or depression, a score could be a hindrance to empowerment and have the opposite effect. Indeed, considering the potential for guilt and blame, some participants expressed, is especially important in the prenatal space, as there are many other external and internal factors that may complicate interpretation of results and patients’ perceived role in how they may have harmed their pregnancy:

“...what's unique to the prenatal realm is that you're, especially when you're talking about exposures or maternal health conditions, is those are just pre-loaded to make mom feel bad about things that she may or may not be able to control...And so I think anything that looks at these without at least addressing the implications that could have for mom's self-perception is shortsighted.” (Participant 8, Session 3)

For this reason, they emphasized that any recommendations attached to ERS must be realistic and contextualized within available supports and resources.

3.19.3 Does ERS Imply a Sense of Personal Responsibility?

Some participants distinguished ERS from other genetic tests on the grounds that epigenetic risk may be perceived as partially attributable to behaviour or lifestyle choices which may be within someone's control. Unlike inherited genetic variants, which carry no implication of personal responsibility, ERS results may implicitly assign agency:

“I feel like we spend a lot of time telling and explaining patients that this random thing is not your fault...We're trying to reassure the patients that there was nothing you could have done to prevent or cause in most circumstances...this feels like the blame game...I don't know if...I'd want to utilize this tool is to make a patient who has anxiety feel worse about having anxiety in pregnancy and then questioning all their choices.” (Participant 17, Session 6)

A few participants noted that while measuring epigenetic patterns may hold value in principle, the specific exposures being targeted could evoke a very different sense of agency, actionability, and perceived fault, with implications for blame, self-perception, and the broader pregnancy

experience. One participant drew a comparison between alcohol and tobacco exposure and maternal anxiety, expressing that:

“If she had significant anxiety and she was taking medication, she's got her own guilt from that. If she was not taking medication, she has her own guilt from that. So it feels like she's already got a significant burden that she's carrying with her psychiatric diagnosis and then exacerbated by her worries about how that may have harmed her baby. And so, telling her this feels like kicking her when she's already down...you can not smoke, you can not drink, you can't just not have anxiety, and people who have anxiety are allowed to have pregnancies.” (Participant 16, Session 6)

Some went as far as to suggest that epigenetic results may hold little value for patients precisely because of the implied role of the expectant parent in shaping those outcomes:

“With a genetic result, there's always... quite a bit of guilt and shame that we find for patients. And that's something they can't control... You're born like that... But with epigenetics, it's screening for something that patients may feel like is within their control... I can't think of any kind of factor that would influence epigenetics that would help parents.” (Participant 11, Session 4)

Therefore, this makes the clinical rationale for testing and how results are communicated even more consequential.

3.19.4 Empowerment May Still Be Possible

In contrast, some participants were more optimistic, especially if the ERS results helped the patients make lifestyle adjustments, be more proactive about their health, or encouraged them to change their environment:

“Maybe there's some evidence that people can take action. Say I'm at high risk for diabetes based on this. And so maybe I'm going to change my lifestyle. Maybe there's some utility there of, if the whole point of epigenetics is that it is changeable throughout our lifetime, and also heritable. I mean, maybe this could be pre-conceptual, like, ‘hey, I can change these things about myself and it can benefit my health’.” (Participant 3, Session 1)

Many participants tied the clinical benefit of ERS to how it affects a patient's sense of agency. Depending on the test results, an ERS risk score could either induce guilt, blame, and shame, or empower patients to take control of their pregnancy outcomes. However, because epigenetic patterns are linked to environmental and modifiable factors, participants noted that ERS carries an underlying message of personal responsibility not typically found in traditional genetic testing.

3.20 Subtheme 3.3: ERS Interpretation and Meaning-Making in the Counselling Encounter

Participants expressed that the real consequences of ERS would not be determined at the point of score generation, but in the counselling encounter where results are interpreted and communicated. Even a technically robust ERS only becomes meaningful, or harmful, when a patient receives and makes sense of it. This includes understanding its limitations, integrating it with other clinical information, and using it in ways that support how patients approach and interpret risk, planning, and decision-making.

3.20.1 Appropriate Framing of ERS Results Is Critical

Some participants felt that how a provider frames and communicates an ERS would have a noticeable impact on how patients interpret and internalize it:

“...with good counselling, you can frame it in the context of, I don't want you to feel bad because you have anxiety, but because we know you have anxiety, we have access to the, you could frame it, but that requires a provider to be good at communication with their patient and that.” (Participant 6, Session 3)

3.20.2 Participant Perspectives on Patient Risk Interpretation

However, most participants were concerned that patients would not engage with ERS results with neutrality. Counselling in the prenatal setting is already an emotionally charged context in which many patients are seeking certainty, and participants anticipated that this would shape how results are interpreted. Low-risk results risk producing false reassurance and reduced vigilance, while high-risk results risk being received as a diagnosis or verdict rather than a probabilistic estimate, potentially amplifying anxiety, guilt, or decisional urgency and driving decisions about additional testing, pregnancy termination, mental health support, or lifestyle modification. Collectively, such responses may reflect perceived rather than actual risk. Indeed, a perspective that recurred throughout the focus groups was that regardless of how carefully a genetic counsellor presents a result, patients may still interpret and process it in ways that are beyond the GC's control. This highlights a potential source of unintentional harm that participants identified as an inherent risk of ERS:

“I feel like a lot of people would read between the lines and be like, ‘I caused my child to have this bad grade and bad future’ or something and just feeling like it's very deterministic. Like ‘I already messed up’.” (Participant 2, Session 1)

One participant raised concern that a high-risk result could drive patients toward decisions that exceed what the evidence actually supports, especially when patients are motivated by a desire

for certainty and actionability, which can lead them to over-interpret what the score actually says:

“I think that patients I've talked to...are just desperate for answers, right? And struggling so much with the uncertainty. And I do worry that, even with clear counselling that this is not a diagnostic test, that, well, if it's the only tool we have, especially at this early gestation, then I think of course patients are going to kind of cling to whatever information they can get. And so, yeah, I guess as a clinician, I worry that we're suddenly using the screening test to make decisions that it wasn't really built for.” (Participant 15, Session 6)

3.20.3 Participants and Their Own Risk Assessment

At the same time, participants described their approach to patient risk assessment as integrative. In other words, ERS would be one data point among many, rather than a standalone tool, and it would need to be contextualized within each patient's unique circumstances.

When it came to conveying risk, many participants were concerned about patients over-interpreting a risk score and making consequential decisions based on it, whether the result was high or low risk. They were cautious about counselling with confidence on what a score ultimately means for the pregnancy, and whether patients could be considered truly informed when making decisions about pregnancy management on the basis of such information:

“From a decision-making standpoint, I would be very hesitant to either alone or combined encourage a patient to make decisions about it, other than that if they would, if the risk knowing of the exposure itself is too much for them to choose to continue the pregnancy, which of course is certainly their right. So if just knowing that this exposure

may have complicated the long-term health or development of the baby, then of course, that's their right. But I would be hesitant to be like but don't worry because if we do this test and it's normal, then there's no reason to be worried. And if we do this test and it's high risk, then I think that just further confirms that if you were leaning towards termination, that it makes sense. I think where I get hesitant is to use it too, specifically as a decision making tool.” (Participant 16, Session 6)

Another participant also cautioned against an alarmist approach, expressing the importance of framing an ERS result within the context of its multifactorial nature:

“What if ultrasound is normal? What if everything's looking normal? We still have this high-risk score and the patient would consider termination on this high-risk score, especially if it is used alone rather than as part of an overall diagnosis and kind of saying, we won't really know until baby's born if there is any effect. This is just like one more piece of the puzzle. (Participant 17, Session 6)

They also added that their counselling about risk would focus on minimizing blame and guilt to ensure that the patient does not overinterpret the results:

“I would probably be really reassuring in that, hey...there could be a lot of reasons that your baby had language delay, and we don't know that it was the score. Again, you can't blame yourself. You did the best that you could.” (Participant 17, Session 6)

In considering a reassuring ERS result, one participant stated that a low-risk score would not necessarily translate into a sense of relief:

“What patients and providers would have to understand is just because you don't get an abnormal result on this test doesn't mean that there's not going to be an issue.”

(Participant 6, Session 3)

When it came to being reassuring, some participants explored other reasons why they would feel comfortable not relying on ERS results for decision-making, beyond the fact that epigenetics is only part of the picture (i.e. multifactorial). One participant explained that even when a score is high-risk, the magnitude of the actual developmental impact may be small enough that its clinical or functional manifestations go undetected:

“High risk, if that just means that we think there's a high chance that there was, because of the methylation, there is some potential impact on development, but that could be something that is so negligible, nobody would notice it. Because again, my gut is, I'm pretty reassuring to these people, not completely, but pretty reassuring. And I think appropriately so.” (Participant 16, Session 6)

A few participants were cognizant of how their own reactions and biases, toward ERS as a tool, toward the exposures and outcomes being measured, and toward the counselling encounter itself, might shape the way they discuss results with patients. This self-awareness points toward the potential for countertransference, where the provider's internal response to the topic risks influencing the counselling dynamic:

“My initial response was, oh, that made me sad for her that she's already anxious and now she's getting this really tough news. I mean, I guess that plays in because we have to recognize our own reactions to things to make sure that we are counselling appropriately.” (Participant 12, Session 5)

3.20.4 ERS Needs to be in the Context of Other Data Points

Participants explained that their comfort level with attributing findings to an ERS result would be contingent on the results of other investigations. This broader clinical picture would change how they assess the patient's risk and interpreted the risk score:

“I think if we ruled everything else out. If we said, oh, you had negative CMA, negative exome, you're not showing signs of placental dysfunction, preeclampsia, we have nothing else to explain it. Well, most likely it could be due to your second-hand smoking exposure. But without all that information, I wouldn't stop the diagnostic workup. And I wouldn't say that's definitively the answer.” (Participant 17, Session 6)

Another participant noted that their interpretation of an ERS result would be shaped by whether the score aligned with or diverged from the clinical history:

“Now if the patient's clinical history that they gave didn't match that methylation test, then that might change how we perceive risk a little bit more in my mind.” (Participant 13, Session 5)

One participant noted that their interpretation of a result would depend not only on the score itself but also on its validity metrics, showcasing the number of clinician considerations that go into making sense of a score and communicating that interpretation to a patient during a post-test counselling encounter:

“I feel like I would then kind of interpret it case by case. If this was a low-risk result and the specificity was only 58%...I mean, that's pretty close to 50/50 with like whether a low risk is actually a low risk.” (Participant 4, Session 2)

Another participant offered a more nuanced perspective, noting that how much weight they would place on a score would depend on the direction of the result:

“...if the epigenetic risk score was actually low risk, that I could see being helpful. But the high risk, I think we're always counselling to prepare for a worst-case scenario, right? So I think the high risk doesn't change the counselling as much, but maybe the low risk would.” (Participant 15, Session 6)

3.20.5 Conveying Recommendations

When it came to post-test management recommendations, the participants often felt it was harder to justify very specific recommendations based on a particular ERS score and felt more comfortable discussing with patients less specific or more tentative plans:

“We can't say that oh, yes, they'll definitely need speech or occupational therapy. But, some kids with this result might need some extra occupational therapy or speech therapy and talking through how they would get that care if they end up needing it. So, it wouldn't really be a specific follow up recommendation. It would just talk about, it'd be talking about what that would look like with the sort of care that their child is already going to be getting.” (Participant 4, Session 2)

One participant described the tension between wanting to use ERS to inform management and provide patients with choice that aligns with their beliefs and priorities, while at the same time avoiding overreliance on and overconfidence in the results, ultimately maintaining a balance that respects the ethical weight of the situation, a tension that is familiar to genetics providers:

“But in a pregnancy, I can maybe see a benefit to parents if they were quite liberal and open with who can access termination of pregnancy. So, I could see somebody saying,

‘well, this risk is too much for me. I’m choosing to stop the pregnancy.’ But of course, that also comes with the ethical concern of how confident are we in these results. But, we’re also counselling people about that uncertainty for fetal anomalies all the time. And people choose to stop a pregnancy without 100% guarantee that their child will need extra needs after they’re born. So could be seen pretty similarly to that.” (Participant 14, Session 5)

3.20.6 Impact on Provider-Patient Relationship

An additional potential challenge participants identified in the post-test counselling encounter was the strain that discordant results could place on the provider-patient relationship. One participant wondered how they would navigate a situation where a patient's reported clinical history does not align with the ERS result, and what message that discordance might send to the patient:

“...would this somehow be putting patients in a position where somebody might be implying, ‘oh, you’re not being truthful. You’re not telling us what really happened,’ which feels like a tricky place to be, especially when we’re thinking about exposures, because there’s already layers of do patients feel self-blame if there’s been an exposure and it’s caused enough, teratogens just have their own psychosocial part built into that, too.” (Participant 12, Session 5)

Indeed, maintaining patient rapport was viewed as more important than offering a screening test that could directly contradict the patient's self-reported history. Another participant also echoed the sentiment and phrased it as:

“...I don't want to find out about the smoking example for moms who are telling me that they're not worried about smoke exposure, that they don't smoke. I don't want to have contradictory information that maybe destroys our relationship or destroys that trust.”

(Participant 15, Session 6)

3.21 Theme 3 Summary

Overall, participants argued that successful integration of ERS into prenatal genetic counselling requires designing ERS with counselling considerations in mind: a clear and transparent consent process that anticipates how both patients and genetic counsellors will interpret risk, communicates strengths and limitations in a useful way, and offers clinically actionable steps that are realistic in practice.

3.21 Overarching Ethical and Legal Considerations

Nearly all participants raised concerns about potential harms associated with ERS testing, including social and legal implications, impacts on patient wellbeing, perceived capacity to care for oneself or a child, and feelings of guilt or blame, particularly when exposures are framed as controllable.

3.21.1 Potential Legal Repercussions of ERS

Participants emphasized the need for robust policy and regulatory frameworks to govern ERS use, including protections against epigenetic discrimination, alignment with existing health policy and service delivery structures, and clarity around regulatory jurisdiction at the provincial or state level.

“There's that concern that the information can be used more negatively by, what have you, insurance companies or something, because we have seen that with, there are laws I know now in place to prevent genetic discrimination. Are we going to have to expand that to no epigenetic discrimination?” (Participant 1, Session 1)

In a similar vein, a few participants wondered about with whom ERS results would be shared and the potential consequences across social, financial, and personal life domains. One participant asked:

“Who has access, right?...employers, schools, is this used by colleges to decide who to admit and who not? Is it used by the military? Is it used by labs looking at egg donors and sperm donors and embryo transplantation?” (Participant 1, Session 1)

Broader social and legal risks were also flagged, such as child protective services involvement, discrimination in adoption or healthcare contexts, and stigmatization in cases where results implicate substance exposure.

“You've then got patients who are worried, probably from like a social services standpoint, could they be at risk to lose their, lose custody of their child if it's proven, depending on how good the science is, that they drank during the pregnancy.”
(Participant 16, Session 6)

One participant put herself into her patients' shoes and echoed this sentiment:

“If I were a patient, I would be concerned about, is my baby going to be potentially taken away from me? I know we don't act that way with alcohol, but we do with other

exposures sometimes. Or at least we get CPS [Child Protective Services] involved.”

(Participant 8, Session 3)

Another participant expressed concerns about how ERS could impact adoption practices:

“...we certainly wouldn't want to have this testing be utilized, for to justify why a certain child should be adopted or not.” (Participant 3, Session 1)

3.21.2 Potential Adverse Societal Impacts of ERS

While the broader focus group discussions addressed participants' perspectives on the utility of ERS for maternal anxiety and other mental health-related exposures, some participants also reflected on ethical challenges specific to this domain. They were concerned about the potential for an ERS result to inadvertently compromise a mother's self-efficacy, self-worth, and perceived capacity to care for her child. Participants emphasized that maternal mental health extends far beyond pregnancy, noting that undermining a mother's confidence during the critical "fourth trimester," which could lead to negative developmental and psychological outcomes. As one participant cautioned, if a clinical tool unintentionally causes a mother to "harbor guilt", the resulting harm could outweigh the risk of the condition being screened for:

"... if you just withdraw any confidence in her ability to be a mother, even if it's unintended, that could have far more disastrous impacts on that baby than her having mild anxiety and an increased risk for an expressive language. " (Participant 8, Session 3)

Moreover, a few participants highlighted that if a high-risk score imposes a psychological toll and "jeopardizes a woman's sense of self or self-worth", there is potential for increased risk of severe postpartum depression and maternal suicide. They urged that

these risks "have to be weighed against any potential benefits of these tools." (Participant 8, Session 3)

Finally, a small number of participants raised concerns regarding social stigma. Because ERS reflect environmental and behavioural exposures, they feared a high-risk result could introduce maternal blame, leading to pregnant individuals being socially "ostracized" or subjected to systemic "othering" for an outcome deemed potentially avoidable.

3.21.3 Risk of Eugenics

Several participants further cautioned against the potential for ERS to be used for eugenic purposes or to pathologize normal variation in the human population:

“I think it also makes me more uncomfortable because it feels like it's feeding into a little bit of this witch hunt that's happening against neurodiversion. It starts to feel a little eugenic if we're finding more ways to identify people at risk for language delays...with everything that's gone on with the whole Tylenol autism thing. It just feels like we're finding more and more ways to scare people earlier about their babies...it just starts to feel so othering and...negating the benefit of the existence of people with different ways of thinking and expressing themselves and pointing the blame at people, at the mother. So, it just feels dangerous.” (Participant 16, Session 6)

Participants also raised discrimination concerns in cases where the exposure being measured could be attributed to the pregnant individual's own behaviour:

“Could this be a reason to deny this child insurance or something because of something that the mom did while they were in utero?” (Participant 1, Session 1)

3.21.4 Impact on Marginalized Communities

Many participants also considered the broader societal implications of ERS, particularly for populations whose baseline risk is elevated by circumstance. Examples included patients carrying the effects of chronic stressors, generational trauma, or adverse personal experiences. For these groups, participants questioned whether ERS might systematically overestimate risk, and conversely, whether it might underestimate risk for other populations. One participant raised concerns about the social implications of ERS validation, a point that also speaks to subtheme 1.1 in terms of how the breadth and strength of the available evidence base shapes the applicability and generalizability of the tool. Specifically, they questioned whether ERS would carry the same predictive power for patients from marginalized communities, and whether the populations in which these scores have been validated are sufficiently broad to support their use across diverse groups. Ensuring that validation extends to a wide range of populations was seen as essential to minimizing future harm to these communities, whether in the form of psychosocial consequences or potential legal repercussions:

“...with epigenetics and the buildup of methylation stress, I feel like we know that some of our patient populations are just more vulnerable to that already...my worry would be that our patients who are from marginalized groups are going to be more likely to get high risk scores because they're carrying epigenetic damage from other stressors, generational trauma, things they've gone through, that it may be overestimating risk for them or underestimating risk for other people” (Participant 16, Session 6)

A few participants expressed concern about the risk of further stigmatizing communities that are already marginalized, thus making them more vulnerable:

“Also, when we're thinking about exposures during pregnancies, I think some of our most vulnerable populations are populations that do have higher frequencies of exposures. And is that another way of just kind of targeting, not targeting, but kind of just calling out?”

(Participant 6, Session 3)

Ultimately, participants emphasized that ERS adoption cannot be separated from its broader legal, societal, and systemic implications. Addressing equity, access, and the intersectional impacts on marginalized communities remains a concern and introducing these tools without carefully weighing their ethical consequences risks exacerbating existing clinical inequities.

3.21.5 Equity and Access

Concerns about equity surfaced around access to downstream services or interventions following ERS screening, with insurance coverage identified as a key barrier. One participant raised concern that a low-risk ERS result could be used to justify denying access to services:

“If a test like this exists that's able to identify children who may need early childhood intervention and a particular child doesn't score high on that test, will it then be harder for them to access those services?” (Participant 7, Session 3)

Another participant raised the question of equitable resource distribution, not only for pregnancies flagged as high-risk by ERS, but for those requiring intervention for other reasons, and how the introduction of ERS might affect access in that broader context:

“...from a use of resources standpoint, if there are finite resources and the science isn't actually as good as it seems and this puts a big long queue in for the babies who really need these services because we're evaluating these kids who had these scores that the

scientific support for what they mean is not necessarily rigorous, as rigorous as it is for these other kiddos, there are other systematic problems it causes if this alone is used as criteria to get early intervention services but from an individual standpoint, I don't have a problem with it. It's more on the larger scale.” (Participant 16, Session 6)

3.21.6 Integrating ERS Into the Current Healthcare System

They also raised logistical concerns about the volume of referrals for genetic counselling or clinician support that ERS could generate and how the system would absorb them:

“How are we going to be accepting these cases? I could see us just getting a massive influx of referrals because mom was anxious. And anxiety is like the number one mental health disorder.” (Participant 14, Session 5)

One participant had doubts and skepticism about whether Canadian provincial governments, given the existing constraints on the public healthcare system, would support early intervention for individuals based solely on their ERS results, as it is ultimately a screening, and not a diagnostic, tool:

“... if there was some kind of magical provincial government that would take this screen and be like, yes, absolutely, we are on board...I think patients would, totally go for that. I just don't think that a screen would ever, in a public healthcare system, would ever equate to just being given early intervention hours, right?” (Participant 1, Session 4)

Though raised by only a few participants, the distinction between Canada's public healthcare system and that of the United States was noted as an important factor, one that could produce noticeably different patterns of ERS uptake, integration, and access across the two systems:

“But you need to have some demonstration of what that utility is, especially if you're trying to implement this in a system that doesn't have as many resources. Even if you're thinking about in Canada where there's probably, there's more kind of equal access, and it's not kind of as piecemeal as it necessarily is in the States. But definitely if you're thinking about here in the States where it's as piecemeal, you really have to have good data to try to shoehorn that into a system that's broken.” (Participant 6, Session 3)

Insurance coverage was another topic that a few participants expressed concerns about. One participant questioned whether ERS would be covered under public health screening or would remain an out-of-pocket expense, thus limiting test access to only those with the financial means or insurance coverage. Beyond the test itself, the same participant extended this concern to publicly funded early intervention services, questioning whether the introduction of ERS might introduce or deepen existing inequities in that space.

3.22 Additional Operational Factors to Consider Prior to ERS Integration

While not frequent or overarching enough to be included in the thematic description of the focus group findings, the following considerations were provided about collaboration with other stakeholders, provider education, and how ERS reports convey results, which nonetheless merit attention given their significance for the integration of ERS into clinical practice:

3.22.1 Discussions With Other Stakeholders

Numerous participants noted that for ERS to reach its clinical potential, a fuller representation of relevant stakeholders will be required before implementation. They recommended ERS researchers consult with other providers in this space, including obstetricians, gynecologists, and pediatricians.

“...while it's definitely helpful to get genetic counsellor input on this, the people who are going to be actually talking about anything like this are going to be your OB [obstetrician] providers. And you have to have buy-in from them to actually get that really implemented into prenatal care.” (Participant 6, Session 3)

They also noted that provider buy-in would have a huge impact on how patients in the prenatal realm would perceive ERS and its value for them:

“I do think patients very often they have to have a lot of trust in their prenatal providers. Ideally, they're able to have trust in their prenatal providers. And if they do have a good relationship, that provider's perspective is going to drive things a lot.” (Participant 6, Session 3)

It was clear that a notable number of participants valued multidisciplinary collaboration to maximize the utility and applicability of ERS for patient risk assessment. They suggested involving stakeholders from various medical specialties during the development phase to ensure future scores align with clinical priorities.

3.22.2 Healthcare Provider Education

Some participants also raised the lack of formal or informal education on epigenetics and ERS among healthcare providers as a concern. Participants wondered how other providers without expertise in genetics would interpret and respond to such information. One participant highlighted that across maternal fetal medicine units, some may have an in-house GC, whereas others do not, and as such may not have expertise available for interpretation

“...we do run the risk of misinterpretation of the result, where we might have a provider that receives a result back that says increased risk for FAS [fetal alcohol spectrum], for

example. And the OB [obstetrician] or the MFM [maternal fetal medicine specialist] might interpret as like, ‘hey, baby does have FAS, this is something that's going to happen for your pregnancy.’” (Participant 9, Session 4)

The participant went on to explain that because of this very reason, “a lot of provider education and information would be needed before this was implemented, widespread across practices as well.” (Participant 9, Session 4)

Another participant called for more prescriptive and directive counselling guidance around ERS, emphasizing that any clinical integration would need to be accompanied by solid healthcare provider education that answers, “how do you interpret these test results? What do they mean? What don't they mean? When do you act on them? When should you not, solely rely on them if ever should you? So, I think their education would be huge ahead of ahead of implementation and then continuing throughout implementation of this.” (Participant 6, Session 3)

3.22.3 ERS Report Language and Presentation

Participants offered several reflections on what they would want to see in a clinical ERS report to support their counselling. One participant had suggestions about the importance of contextualizing a score using frequencies rather than figures. For a patient to relate to the data, they argued that the report should state the population, so that predicted outcomes could be grounded in something patients could meaningfully relate to:

“...for 100 women who have the same epigenetic risk score, these are the outcomes...hopefully that means something to them where we can say ‘maybe I'm in the, you know, 90 out of 100 women who are probably going to have this outcome’.”

(Participant 15, Session 6)

One participant called for greater transparency about how these scores are generated, wanting the ERS report to explicitly outline the evidence and biological mechanisms behind the numbers:

“When this is within research, when they're mentioning these numbers, how are they getting to those numbers?” (Participant 9, Session 4)

Rather than percentiles or raw numbers, which one participant felt uncomfortable applying to a seemingly healthy newborn, preference was given to qualitative categories (e.g., “low exposure, moderate exposure, high exposure” along with specific, actionable recommendations: “the test results predict that this newborn would especially benefit from X, Y, and Z recommendations.” (Participant 2, Session 1)

A few participants noted that while genetic counsellors are comfortable counselling on the nuances of multifactorial outcomes, other specialties may default to a binary interpretation (e.g., “low risk, you're good”). Drawing a parallel to NIPT, one participant emphasized that for ERS to be used responsibly by non-genetics providers, the reports must feature “really well written, very clear language” supported by comprehensive training materials (Participant 8, Session 3).

To conclude, successfully integrating ERS into clinical practice requires expansions of future research to capture the perspectives of non-genetics providers who will use these tools. It also requires provider education regarding ERS capabilities and limitations. One way to prepare ERS for clinical practice is through clear, accessible reports with actionable recommendations.

3.23 Literature Review: Deductive Content Analysis Results

Analysis of the thirteen papers revealed a nuanced perspective on ERS among researchers, generating a total of 21 codes. Researchers view these scores as promising, objective biomarkers with translational and clinical potential. Researchers found value in ERS to uncover underlying

biological mechanisms and as an opportunity to collaborate. Yet, they remain cautious about their current readiness, acknowledging that these scores are not yet fully developed to explain significant phenotypic variance or demonstrate long-term stability. Thus, there is a gap between their optimism about clinical potential and the real-world performance of their scores, owing to a complex interplay of internal and external limitations.

3.23.1 Researchers Believe in ERS' Translational Potential

Some researchers highlighted the potential of ERS to have clinical impact by offering meaningful information about health risk, and filling gaps that other measures may not. The overall pattern assumed across all papers was: a prenatal exposure (smoking, glucocorticoids, infection, socioeconomic position, etc.) → a lasting methylation signature → a downstream health outcome (language delay, mental disorder severity, white matter integrity, etc.).

Researchers position ERS as a tool to overcome the limitations of subjective or incomplete clinical data. For example, in prenatal research, self-reported smoking relies on patient recall and is prone to reporting bias, medical records are frequently incomplete or binary, and short-lasting serum biomarkers (like cotinine) only capture a brief snapshot of time. Literature supports that an ERS may be able to bypass these boundaries, offering a robust, longer-term exposure window that reflects the continuous "allostatic load" of sustained biological impact across gestation (Reese et al., 2017). In this light, research teams suggest that highly predictive ERS "may offer an opportunity to develop predictive and prognostic tools to optimise neonatal care" (Conole et al., 2023), allowing clinicians to identify at-risk newborns early, provide targeted early intervention services, and suggest preventative lifestyle changes.

3.23.2 Proxies for Exposure vs. Predictors of Outcomes

Despite this translational optimism, research teams were able to demonstrate a link between exposure to methylation more frequently than a link between methylation and outcome. For instance, a prenatal tobacco exposure MRS was deemed to be “highly predictive of PTE [prenatal tobacco exposure]” but did not significantly establish an association between the exposure and child neurodevelopment (Abrishamcar et al., 2022). Similarly, an ERS designed for C-Reactive Protein (MPS-CRP) demonstrated an “adequate” ability to predict cord blood CRP levels at birth but showed null correlations with psychiatric symptoms tracked across childhood (Suleri et al., 2024). Overall, most studies positioned ERS as indicators of prenatal or environmental exposure, with limited evidence supporting its use for predicting downstream clinical outcomes.

In contrast, a few studies reported associations between ERS and measures of clinical severity. For instance, a polyepigenetic glucocorticoid (GC) score was successfully linked to the severity of child mental disorders, where lower scores directly correlated with "more days spent in inpatient or outpatient treatment" (Suarez et al., 2020). However, because these findings are rare, researchers remain conservative in their risk interpretations.

3.23.3 Methodological Drivers of ERS Performance

To address the lack of success with linking exposures to outcome prediction, researchers point to the specific methodological components to build the scores. ERS validity is sensitive to three primary internal factors: tissue type, timing, and CpG site selection.

3.23.3.1 Tissue Type:

The choice of biological tissue was an important consideration for researchers. Some positioned cord blood as capturing “a direct reflection of the in-utero environment” that is free from postnatal confounding (Deng et al., 2024). Others expressed that placental DNA methylation could have larger effect sizes and better reflect cumulative gestational exposure than blood (Shorey-Kendrick et al., 2024). Others discussed how saliva is a more accessible sample type (Conole et al., 2023). Conversely, maternal blood was noted to be problematic as it can potentially conflate fetal exposure with the pregnant individual’s biological state (Deng et al., 2024). This sensitivity to tissue specificity creates a barrier. Researchers are forced to use easily accessible sample types (e.g., blood, saliva) which may not accurately reflect the pathology of inaccessible target organs (e.g., fetal brain). While this limitation does not stop ERS development, none of the reviewed papers could confirm whether the construct being measured remains stable across different tissue types.

3.23.3.2 ERS Timing:

Timing shapes both the magnitude and the durability of the DNAm signal. Researchers view ERS as temporally sensitive; it does not merely detect the presence of an exposure but provides clues about the specific gestational window during which the exposure occurred. For example, "sustained maternal smoking during pregnancy has a much greater effect on newborn methylation than smoking that ceased early in pregnancy" (Reese et al., 2017).

Additionally, these signals fade. CpG associations are often “attenuated with the passage of time,” meaning newborn methylation signals may persist into childhood but with drastically reduced effect sizes (Reese et al., 2017). Because the predictive reach of an ERS across a lifespan is still unknown, associations established at birth cannot be assumed to hold in later

adolescence when complex psychiatric or neurological phenotypes emerge. To overcome this single-point-in-time limitation, teams are calling for multi-trimester assessments and longitudinal studies tracking the postnatal, pediatric, and adult periods (Suleri et al., 2024).

3.23.3.3 CpG Sites:

The number of CpG sites also made a difference in ERS performance. More is not always better; expanding the number of CpG sites often introduces noise and dilutes the true biological signal. One study demonstrated that an extended methylation score using roughly 1,500 CpG sites performed significantly worse than a parsimonious seven-site score (AUC [area under the curve] of 0.53–0.55 vs. 0.72–0.76), concluding that the DNAm signal of CRP at birth is better captured by a targeted score (Suleri et al., 2024).

3.23.4 The Generalizability Problem

ERS is vulnerable to the components and conditions that are used to generate it, meaning that generalizability is lacking. The confounding factors most often discussed included the context in which ERS was applied, the array platforms used, training and testing conditions, and sample characteristics.

When researchers validate their scores on external data, performance drops, a known limitation widely acknowledged across many research teams. A score optimized on a specific discovery cohort typically exhibits metrics that degrade when applied to independent datasets. This lack of generalizability stems from two main barriers: technical sensitivity and cohort/sample characteristics. First, ERS performance is highly sensitive to technical variables, including variations in microarray platforms (such as the 450K vs. EPIC arrays) and whether data used was normalized or unnormalized. Second, models are highly sensitive to their training populations.

An ERS trained on a predominantly active-smoker sample underperforms in populations with lower smoking prevalence. Additionally, ancestral diversity significantly impacts ERS accuracy. Models trained on homogenous cohorts drop in prediction accuracy when applied to ancestrally diverse populations.

3.23.5 Researchers are Motivated by Scientific Purpose, Beyond Score Performance

Given the methodological challenges of ERS, one may view the current stage of ERS research from a purely critical perspective. However, the analysis revealed that there are several motivators that seem to be driving the development of ERS that extend beyond creating strong scores that can capture the epigenetic footprint of prenatal exposures on developmental outcomes. For many researchers, the ERS serves to understand underlying biological mechanisms and facilitate collaboration across teams. Researchers expressed a deep interest to uncover how prenatal exposures become embedded in the epigenome. In one study of prenatal cocaine exposure, the authors noted that individual CpG sites did not provide sufficient information on their own. To obtain a more interpretable signal, they conducted gene ontology analysis on CpGs incorporated into their epigenetic analyses, which identified altered GABAergic synaptic pathways and suggested potential effects on inhibitory synaptic function. This example illustrates how epigenome-wide analyses and downstream aggregation approaches, including ERS, are used in combination with one another to go beyond individual CpG effects and support interpretation of complex neurodevelopmental outcomes.

As constructing ERS is a huge endeavour, research teams approach ERS development with an open, collaborative mindset. From presenting their CpG weights to model specifications in supplementary tables, they invited other researchers to apply the score directly in their own datasets for validation purposes, at points claiming, “little loss of performance” (Reese et al.,

2017). The same team also mentions that their score would be “simple to compute in other newborn datasets”, and purposefully not batch-correcting their training and test sets “to better approximate how the score will behave in other studies” (Reese et al., 2017). This transparency shows that researchers are making their current scores as accessible as possible for the broader scientific community.

3.23.6 Summary

The analysis of the papers revealed that from researchers' perspective, despite ERS' vulnerability to biological and technical constraints (e.g., tissue type, ancestry) and unmeasured environmental confounders, they believe in its utility as an objective proxy for exposures and a mechanism for investigating biological pathways.

CHAPTER FOUR: INTEGRATION OF LITERATURE REVIEW AND FOCUS GROUP RESULTS

4.1 Convergence of Concepts Discussed by Focus Group Participants and Researchers

When comparing the focus group transcripts with the discussion sections of the research papers, the high degree of alignment between participants and researchers was striking. Despite their differing roles as the "builders" and the future "users" of ERS, both groups frequently positioned their arguments in the same core concepts. These convergent codes function in Figure 4 as the pillars of a bridge connecting basic research to clinical practice, proving that both sides are ultimately building toward the same destination: positively impacting patient care. Table 6 describes where researchers and focus group participants converged, and provides important context to each group's respective priorities, highlighting just how frequently their clinical and research interests overlapped.

Table 6: *Overarching Convergent Topics Between Focus Groups and Reviewed Literature. A summary of the frequency of convergent codes and shared topics across focus groups (phase 2) and the discussion section of reviewed papers (phase 3) is presented. Note that the final row encompasses an overarching convergent topic rather than a single matching code; while the specific codes assigned to each data source were distinct, they conceptually outline the same area of interest from parallel perspectives.*

Code	Focus Groups (FGs)		Reviewed papers	
	Key points/issues	No. of FGs	Key points/issues	No. of papers
Breadth and depth of ERS research	Most participants had strong discomfort with integrating ERS before large-scale, blinded, or longitudinal studies confirm validity, especially across diverse populations. Some cited the accumulation of decades of clinical data for other established tools such as NIPT and were concerned that premature integration without strong evidence may have negative consequences and put a strain on the healthcare system.	5	Studies positioned ERS within a broader literature and noted that the body of ERS literature is still in its early stages. Thus, they called for multi-tissue analyses, larger longitudinal cohorts, and follow-up data, especially in light of a lack of gold standard for ERS development and the variation in array platforms, tissue types, statistical methods, and populations.	11
ERS validity metrics	High PPV and NPV, rather than sensitivity and specificity were the preferred metrics for clinical use by almost all participants. There was a desire to better understand what they were based on and populations they were derived from.	6	Most research teams used AUC, sensitivity, specificity, and concordance with known health outcomes as their primary validity indications and were more likely to be preoccupied with questions related to the technical aspects of ERS validity (training and test sets, the effect of sample size on sensitivity and specificity, as well as the number of CpG sites).	10

ERS- presentation link	• Most participants were not confident that an ERS can establish a causal or even correlational link between a specific exposure and clinical presentation given the multifactorial nature of many NDD outcomes and that many NDD outcomes manifest years later. Moreover, they felt that a normal ERS does not rule out exposure effects.	6	• While some studies documented associations between ERS scores and health outcomes including language delays and behavioural disorders, with some dose-dependent relationships, researchers cautioned that methylation signatures are not exposure-specific, as multiple prenatal exposures may be involved in the same epigenetic pathways; and heterogeneity in study populations and exposure types introduces variation in the direction, strength, and specificity of associations. Some also emphasized that ERS captures correlation with outcomes rather than causal mechanism.	11
Potential ERS benefits	• ERS was viewed as potentially most valuable when it filled a knowledge or clinical gap, changed care pathways, facilitated access to early intervention services, pregnancy decision making, or motivated behaviour change.	6	• Researchers saw ERSs being used as an objective biomarker, to distinguish sustained from intermittent exposure, to complement epidemiological studies of other prenatal risk factors, to identify at-risk newborns before clinical symptoms appear, and to advance our understanding of the Developmental Origins of Health and Disease (DoHaD).	9
Clinical actionability	• The most recurring concern for all participants was how would ERS change clinical management and struggled to identify a scenario where a low-risk result would offer reassurance or a high-risk ERS result would	6	• While some papers provided examples of ERS' clinical actionability potential, such as validating self-reported exposure history, identifying newborns who warrant closer developmental surveillance, and monitoring the	8

	prompt a management change beyond what is already standard practice, especially given the emotional weight of a high-risk ERS result.		efficacy of prenatal interventions, most papers acknowledged that translating ERS findings into concrete clinical protocols remains an area that requires more research.	
ERS prediction limitation	Participants pointed out some current limitations of ERS, such as the dynamic nature of methylation patterns that may change postnatally, inability to specify outcome severity or distinguish between direct and indirect exposures, the multifactorial cause of certain outcomes, that could impact risk assessment and counselling.	6	This was primarily discussed as ERS predictive power being constrained by technical limitations including recall bias in training data, biomarkers that cannot capture exposure timing or duration, population homogeneity in discovery samples, unmeasured confounders, and small sample sizes.	10
Timing of ERS	Many participants raised questions about when and how often ERS should be measured, weighing the need to capture exposure effects at the most biologically relevant time point against the potential for psychological harm from poorly timed or repeated testing.	6	Most papers collected ERS at birth, which aligned with the postnatal preference expressed by some focus group participants. According to several research teams, this appears to be a biologically meaningful window. They showed that sustained prenatal exposure produces stronger methylation signals than intermittent or early-cessation exposure, in utero signals may persist into childhood, and neonatal ERS may be able to predict developmental outcomes as late as 36 months.	8
Sample collection method	Many participants were curious to see the data on different tissue types to better understand their applicability and comparability. Regardless of the evidence, almost all participants preferred non-invasive or postnatal approaches as they tend to be more	5	Overall, researchers expressed that tissue type critically shapes ERS results: cord blood is the most common and directly reflects the in-utero environment, but methylation patterns vary across biologically relevant tissues. One paper noted that the placenta may offer greater	11

	acceptable to patients and less ethically challenging, especially for a screening test.		precision for certain exposures compared to blood-based ERS.	
Placenta-fetus concordance	Participants raised concerns that placental methylation from CVS may not align with fetal methylation, that testing a different tissue than the one validated in research limits applicability and interpretability of ERS results, and that a high-risk CVS result may need confirmatory amniocentesis, an additional invasive procedure for a screening test.	4	Some studies showed that methylation changes in placental tissue and cord blood show different patterns for the same exposure. Overall, similarly to focus group participants, they cautioned against cross-tissue interpretation of ERS results without proper, tissue-specific validation.	4
Outcome clarity	Most participants were interested in an ERS that specifies outcome severity, phenotypic features, or predicted functional implications for the fetus. A discrete, clearly defined outcome was deemed most valuable for anticipatory guidance, compared to a broad outcome.	6	A few researchers acknowledged that there may be limitations in how clear an outcome ERS may be able to predict. For instance, shared biochemical responses across multiple exposures may influence DNAm signatures, thereby impacting outcome specification. Confounding factors (nutrition, infection, lifestyle, environment, etc.) were also stated to limit outcome clarity.	3
Bias/ethics	Many participants brought up ethical concerns such as potential legal and custody-related repercussions for patients, further stigmatization of marginalized populations that may already be carrying epigenetic “burden”, eugenics, inequitable access to services following a high-risk ERS result, the ethical risks of predicting certain exposures such as prenatal alcohol use and maternal	4	There was very little discussion on the ethical challenges and factors surrounding ERS development, aside from concerns about serial blood sample in preterm neonates (ethical challenges of that, discomfort, etc.) as well as potential harm to vulnerable groups given that the data used to train and test ERS is based largely on individuals of European ancestry.	1

	mental health, as well as ethical challenges during the consent and disclosure process.			
Risk interpretation	Overall, most participants felt that they would treat each ERS result on a case-by-case basis, factoring in other possible causes and investigations. Some felt was a low- or high-risk result would impact their risk interpretation, with the former being potentially more useful for some and the latter carrying more uncertainty. A few felt that they would be reassuring for most teratogen-exposure scenarios, regardless of ERS results.	5	Researchers pointed out a few factors that would limit risk interpretation. They noted that small effect sizes explain only a portion of outcome variance and cumulative exposure scores may mask which specific exposures drive associations.	4
Type of exposure/outcome	The majority of participants distinguished between exposures that carry inherent stigma (substance use, mental health conditions) and those that do not such as toxic teratogens. In terms of outcomes, there was a preference for outcomes with discrete, definable clinical management implications.	6	The range of exposures studied in the literature is wide and continues to expand. Researchers seemed to view the various types of exposures and outcomes that are measured as progressive steps towards ERS expansion. They did not ethically differentiate between the different exposure types in the same way that focus group participants did.	10
Collaboration is key to building successful and relevant ERS*	Focus groups participants expressed curiosity about unknown perspectives from different health providers such as obstetricians, who may be involved in the care of pregnant individuals or may be involved in ordering ERS and delivering the results. They thought it was critical to include their voices in ERS development, as well as those of people involved in policy.	3	While research teams also cared about collaboration, their focused lay heavily on working with other researchers. Collaboration, from their perspective, was geared toward validation of their findings and advancing research forward, and less so on implementation and conversing with various stakeholders. In short, researchers' focus is on building and validating the tools. Indeed, they	13

	• Relevant codes: Other Providers Should be Consulted and Provider Education		seemed to focus more on ERS predictive power, in other words, how well the test performed, and the various technical, training, and test factors that limited or strengthened its performance. • Relevant codes: Applicability and Comparability Across Studies, Data Sharing and Accessibility and Future Directions, Diversity as Strength, ERS Performance Level, ERS Training and Testing	
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4.2 Divergence of Concepts Discussed by Focus Group Participants and Researchers

Although many topics converged between the focus group transcripts and the discussion sections of the included articles, each group also exhibited unique priorities as described in Table 7.

Table 7: *Overarching Divergent Topics Between Focus Groups (Phase 2) and Reviewed Literature (Phase 3): Summary of Codes Unique to Each Data Source*

Focus Groups	Reviewed Papers
• Other Providers Should be Consulted • Provider Education • Diagnostic vs Screening • Follow-Up/Recommendation Regardless of ERS • Targeted Clinical Evaluation Over ERS • Mismatch Between ERS and Clinical Need • Work-Up Regardless of ERS • Knowledge of Exposure Is Enough • ERS Alone Doesn't Justify an Invasive Procedure • Testing Indication • Insurance Coverage • Policy and Regulation • Access and Equity • Report Language and Presentation” and Informed Consent • Factors Influencing Patient Uptake • Impact of ERS on Patient Behaviour • Patient ERS Interpretation • Potential Adverse Consequences • Eugenic concern	• Applicability and Comparability Across Studies • Data Sharing and Accessibility • Future Directions • Diversity as a Methodological Strength • ERS Performance Level • ERS Training and Testing

Fundamentally, while researchers are focused on constructing and validating the tool, genetics providers are anticipating the practical realities of its clinical utility. This section examines

differences in how each group viewed the value of collaboration, focus group participants' concerns regarding the clinical and human side of ERS, and researchers' distinct perspectives on the broader value of ERS research.

4.2.1 Does ERS Actually Produce the Kind of Knowledge That Is Useful in a Clinical Encounter?

While the usefulness of ERS in a clinical encounter was a topic that came up repeatedly across all focus groups, it was largely absent in the published papers. In themes one and two, focus group participants expressed a recurring concern that ERS cannot function as a screening tool without defined confirmatory or diagnostic investigations available to pursue should a “high risk result” be identified. This concern was compounded when participants considered outcomes like neurodevelopmental conditions, where epigenetics may only explain a fraction of a clinical presentation. Adding to this, in some cases, the result would simply confirm what a thorough clinical evaluation had already suggested. While clinical actionability was a code that both groups touched upon, focus group participants discussed the concept of reason for testing more holistically and comprehensively. They wondered about the utility of ERS in cases where the work-up proceeds the same way regardless, the exposure is already known, or the procedure required to obtain the sample carries more risk than the information justifies. Together, these concerns highlight a mismatch between what ERS is proposed to offer and what is required for clinical decision-making.

4.2.2 The Necessary Infrastructure and Governance Has Not Yet Been Established

Not surprisingly, considerations regarding the health infrastructure needed before ERS could be used in clinic were uniquely described in the focus group data. Participants had questions about who could decide to offer ERS and under what circumstances, with what consent process? What protections exist against the result being used by insurers or in legal proceedings? How are

results communicated in the report? Participants expressed that even if ERS belong in clinical practice, the necessary systems do not yet exist for successful clinical integration. As discussions surrounding clinical governance and infrastructure are typically outside the scope of biomarker discovery studies, these issues were unsurprisingly absent from the discussion sections of the reviewed papers.

4.2.3 The Human Being on the Receiving End of ERS

Central to all focus group participants' key issues and priorities were the impact on patients. They discussed, from their own perspective, how patients might perceive the value, clinical utility, and safety of the test. They also discussed the emotional reactions patients may have, and the ethical and logistical implications ERS may propose for patients. Many participants were curious about how patients would interpret their own risk and perceived control following disclosure, ultimately affecting their decision-making. These were issues or topics that were absent from reviewed papers.

Moreover, focus group participants were also concerned with the potential of who bears the cost if things go wrong. They wondered about who is most likely to be impacted, what specific worries or concerns we may have to address proactively, and what harms we would need to mitigate as we make progress.

4.2.4 Broader Benefits of ERS Research

A topic prominent in the research literature was the value of ERS beyond direct clinical application. Researchers expressed two justifications that focus group participants did not raise. From their perspective, ERS has value as a research tool independent of clinical utility. Researchers described ERS as a means of objectively capturing prenatal and early-life exposures, generating resources for future investigations, and supporting the study of exposure-outcome

relationships in child health. Second, researchers saw practical viability in ERS development, expressing that targeted methylation assays may be more cost-effective and scalable than genome-wide approaches. Together these codes reflect a research goal focused on building and justifying the knowledge base around ERS, rather than toward the clinical questions that were at the centre of focus group discussions.

Considering the disproportionate number of codes unique to each source, it was clear that the clinical questions focus group participants brought to ERS about patients, governance/policy, and harm, extend beyond what researchers focusing on prenatal ERS may have so far engaged with. Such asymmetry is to be expected, as it naturally reflects the distinct priorities each group holds regarding ERS development and application. Researchers are primarily focused on building and validating the bridge, whereas genetics providers are concerned with what happens when people are asked to cross it.

CHAPTER FIVE: DISCUSSION

This is the first study to examine genetics providers' perspectives on the utility of ERS in prenatal genetic counselling for exposures linked to neurodevelopmental outcomes. The study is unique in its design, which compares provider perspectives collected via focus groups to the language used by ERS researchers in discussion sections of published papers. The perspectives are important to investigate, particularly in the era of fast advancement in genomic and epigenomic technologies, rapid development of ERSs, commercialization of these tests, and direct-to-consumer efforts which bypass clinical workflows and go straight to the general population (Gronowski & Budelier, 2020; Jarry, 2020; Javitt & Hudson, 2006; Panacer, 2023).

Both groups expressed concerns regarding the strength of the evidence base, technical limitations of ERS, and the characteristics of the exposures and outcomes being measured. However, their professional roles shaped how they interpreted these issues. Researchers tended to emphasize analytical validity and scientific advancement, whereas genetics providers focused on clinical validity, utility, and the practical realities of implementation. Consequently, divergence between the groups was less about whether ERS should be developed and more about the relative importance assigned to different forms of evidence and the rationale for selecting particular clinical variables and neurodevelopmental outcomes.

5.1 What Constitutes Progress: Analytic Validity or Clinical Validity?

The core area where the two groups diverged seemed to centre on the underlying purpose of doing ERS research. Researchers were largely focused on technical performance: biological mechanisms, comparison to previous literature, score construction, and training and test set characteristics. Their main focus was to establish whether ERS demonstrates strong predictive performance, as evident in the values presented in the literature: specificity, sensitivity, and AUC, which align with analytic validity rather than clinical validity (Khoury et al., 2007; *Regulation of Genetic Tests*, 2024). Focus group participants focused on validity data, such as PPV and NPV, to find the application of ERS convincing. Without these metrics, they struggled to see how ERS could be clinically useful. This is not surprising as the FDA's review template lists clinical validity, including PPV and NPV, as a required component of genetic test evaluation (Kaul et al., 2001).

Another marker of progress for focus group participants was whether ERS is clinically actionable. What would counselling of this tool look like? Would an ERS result change pregnancy options or postnatal and follow-up care for their child? Their experience and training allowed them to speculate the impact of ERS results in a clinical encounter distinguish situations where it may add value beyond the current standard of care from those where its benefit is limited.

5.2 Evaluating the Evidence Base for ERS

For researchers, a stronger evidence base meant strengthening specificity, sensitivity, AUC, and other measures of analytic and clinical validity, and advancing the ERS field along those metrics. For focus group participants, analytic validity was less important than clinical validity and utility, including explaining ultrasound findings, informing treatment response, and improving pregnancy and postnatal health outcomes, ultimately aiming to determine what recommendations, interventions, or treatments might follow an ERS result.

5.2.1 Existing Frameworks for Assessing Clinical Readiness

It is interesting that themes from the focus group data and the ERS literature align with longstanding debates about laboratory performance in genomic medicine regarding how to appraise newly developed genetic tests. One framework that has been widely used in these evaluations is the analytic validity, clinical validity, clinical utility and associated ethical, legal and social implications (ACCE) model (Sanderson et al., 2005). Analytic validity refers to test performance in the laboratory: can the test consistently and accurately detect the presence or absence of what it claims to measure (Sanderson et al., 2005)? Clinical validity asks how well the test result relates to the exposure, outcome, or trait of interest, while clinical utility asks whether the result will meaningfully change patient management and improve health outcomes (*Regulation of Genetic Tests*, 2024). This distinction matters for ERS because there is currently no regulatory oversight for clinical validity in the United States or in Canada. Centers for Medicare & Medicaid Services (CMS) oversees analytic validity in the United States, but no agency systematically reviews clinical validity for most genetic tests (*Regulation of Genetic Tests*, 2024). In Canada, the framework is less clear cut. Health Canada assesses the analytical validity of commercial kits and pharmacogenetic devices, while provincial health ministries and accreditation bodies oversee the analytical accuracy of in-house laboratory-developed tests (LDTs) (Holloway et al., 2019). The fourth ACCE domain, ethical, legal, and social issues, has

been described as the most difficult to evaluate, in part because the relevant literature tends to address general principles of genetic testing rather than test-specific concerns (Sanderson et al., 2005).

5.2.2 Are Current Evaluation Frameworks Sufficient for ERS?

One might suggest that the ACCE model, along with comparable frameworks such as EGAPP (Evaluation of Genomic Applications in Practice and Prevention) and GETT (Genetic Testing Evidence Tracking Tool) could be applied to assess the clinical readiness of ERS. However, whether these frameworks can be applied directly to ERS remains uncertain (National Academies of Sciences et al., 2017; *Regulation of Genetic Tests*, 2024). Unlike traditional genetic tests, which often assess relatively stable inherited variation, ERS is intended to capture the biological effects of environmental exposures that may change over time and may be modifiable through intervention. Consequently, evaluating ERS may require consideration of additional factors, including the stability of scores across developmental periods, the extent to which scores respond to environmental or clinical interventions, and whether modifying an ERS ultimately leads to meaningful improvements in health outcomes. These considerations are not explicitly addressed within many existing genomic evaluation frameworks, raising questions about whether adaptation of current approaches may be required. While a detailed examination of how existing frameworks might be adapted for ERS is beyond the scope of this study, these findings highlight the need for future work to establish appropriate evaluation criteria through engagement with relevant stakeholders. Such efforts may help determine whether existing frameworks can be adapted for ERS or whether new approaches to evaluation are needed.

5.3 Technical Limitations Must be Addressed

Both groups agreed that ERS faces certain limitations that are addressable, while others may be inherent to the tool itself. These included the multifactorial nature of phenotypic variance,

including confounders, lifestyle, family history, and environment, along with the dynamic nature of DNA methylation patterns and tissue specificity. Researchers largely framed these limitations as solvable through further study and score generation, whereas genetics providers more often viewed certain constraints as features of ERS that may always be present.

Previously published literature on environmental epigenetics supports these concerns. In their 2023 publication, Lappé and Hein interviewed epigenetic researchers investigating the longitudinal and tissue-specific validity of epigenetic markers and found that perceptions of the evidence needed to address technical limitations varied according to researchers' areas of expertise. For instance, a developmental psychologist studying maternal mood sought to test DNA methylation stability over time by collecting samples across multiple developmental stages, while a pediatrician aimed to collect specimens across multiple tissue types within the same patients to strengthen confidence in epigenetic signals (Lappé & Hein, 2023). While these studies focus on broader epigenetic research rather than ERS specifically, they demonstrate the importance of identifying priorities relevant to the end users of ERS.

These priorities were reflected in focus group participants' suggested solutions, which included expanding and diversifying exposure and outcome measures, population samples, and tissue types. However, participants also acknowledged that some limitations may persist, including the proportion of phenotypic variance explained by ERS. This residual uncertainty may complicate interpretation and could introduce challenges for clinical communication, regardless of future improvements in evidence generation.

5.4 Prioritizing Exposures and Predicted Outcomes for ERS

Both groups treated exposure and outcome type as meaningful considerations in ERS development, though they did so for different reasons. Genetics providers drew a clear

distinction between stigmatized exposures, such as substance use and maternal mental health, and those perceived as more neutral or less socially contested, such as teratogens or infections. They also preferred discrete, clinically actionable outcomes over those that might generate uncertain or ambiguous results. This reflects their professional training: providers are trained to consider the whole person, not only the test result, which means they anticipate how an ERS framed around a stigmatized exposure will function in a counselling encounter (ACGC, 2023; Veach et al., 2007). Researchers, by contrast, did not differentiate between exposure or outcome types on ethical or social grounds in the literature reviewed. Expanding ERS to new exposures and outcomes was framed as scientific progress. It is worth noting that no literature reviewed for this study addresses how exposures or outcomes should be selected for ERS specifically, or for epigenetic research more broadly. This absence may reflect the early stage of ERS development, where much of the literature remains focused on establishing technical feasibility and predictive performance. As the field moves toward clinical translation, greater attention may be needed to determine how exposures and outcomes are selected and to consider the potential ethical, social, and clinical implications of these choices.

5.5 Structural Barriers to Clinical Translation

It is worth mentioning that the divergence between researchers and genetics providers may also reflect a broader structural gap, perhaps partly shaped by funding incentives. Studies have shown that translational research moving tools from validation toward clinical practice has historically received less investment than discovery research, contributing to a well-described “valley of death” between early-stage findings and clinical implementation (Butler, 2008; Khoury et al., 2018). Funding models often favour smaller, short-term studies that are feasible within limited timeframes, whereas the larger, longitudinal studies required to establish clinical utility are more difficult to support (Seyhan, 2019). This structural gap may contribute to an emphasis on demonstrating ERS’s biological or statistical validity, such as predictive performance, rather than advancing tools toward assessments of clinical usefulness.

5.6 Regulation, Consent Frameworks, Insurance, and Access

One area that was almost entirely absent in the ERS research publications reviewed was regulatory and policy-related considerations. Focus group participants raised questions about the practicality of integrating ERS into clinical care: what constitutes informed consent for this kind of test, who will have access to it, how will post-ERS interventions be handled, will it fall under public health coverage or require private insurance, and how will results be reported? These questions align closely with concerns raised in the broader literature on technology assessment for genetic tests, where social impacts include informed consent, individual privacy, and the risk of stigmatization or discrimination, alongside resource allocation questions about who bears the cost of providing test-related services (Giacomini et al., 2003). None of these concerns, however, were found when analyzing the discussion sections of the ERS research papers.

The absence of these considerations from the literature is noteworthy because they represent important preconditions for clinical integration. Several explanations may exist. ERS researchers

are simply less likely to encounter these issues directly, since they sit closer to the laboratory than to the clinical space. Alternatively, discussion section space limitations may lead authors to prioritize methodological and scientific considerations over downstream implementation challenges. It is also possible that these conversations are occurring in less visible formats that were not captured by this analysis. Regardless of the reason, regulatory and policy considerations should be addressed alongside scientific development rather than deferred until ERS reaches a technical threshold of readiness.

Regulatory agencies and policy stakeholders will play a critical role in determining whether and how ERS is incorporated into clinical practice. There is precedent for government advisory committees (e.g., Advisory Committee on Genetic Testing, Clinical Laboratory Improvement Advisory Committee) and interdisciplinary roundtables (e.g., the Institute of Medicine) collaborating with professional organizations to establish genetic testing oversight (Institute of Medicine, 2011; Kaelin et al., 2001; Voelkerding, 2000). As ERS moves toward clinical application, regulatory agencies such as the FDA and Health Canada may need to determine how existing oversight mechanisms apply to ERS.

Overall, both groups agree that there may be some potential for ERS in the clinical space; however, the current body of literature is insufficient to provide enough supporting evidence to move forward to the next step of translating this research tool into clinic. This is consistent with a broader pattern in genomic medicine, where lack of evidence is often described as the primary obstacle to moving a tool from research into clinical practice (Khoury et al., 2008). As illustrated by the ERS bridge in Figure 4, participants viewed the evidence base as a foundational support of the bridge that remains underdeveloped. Researchers are primarily responsible for strengthening this foundation through the generation of robust evidence regarding validity,

predictive performance, utility, and actionability, while genetics providers are focused on how ERS information can be meaningfully integrated into patient care and decision-making. The findings suggest that greater collaboration between these groups is needed to bridge the gap between evidence generation and clinical application, ensuring that future ERS research addresses clinically relevant questions and produces the evidence necessary to support safe and effective implementation.

5.7 RECOMMENDATIONS FOR FUTURE RESEARCH AND CLINICAL TRANSLATION OF ERS

Data from all four phases of this study have culminated in the recommendations described in Table 8. There are a number of actionable items for both clinicians and researchers to consider on the path of translating ERS from a research tool to a clinical one (Table 8). Efforts are required in a collaborative fashion to advance the evidence base, establish clinical utility, and address the practical and ethical considerations necessary for the responsible translation of ERS into prenatal care.

Table 8: *Recommendations for Researchers and Clinicians to Support the Advancement and Responsible Integration of ERS into Prenatal Genetic Counselling Practice*

Researchers	Clinicians
Engage providers (e.g., genetic counsellors, OBGYNs, pediatricians) and patients before, during, and after study design and score generation, using a structured mechanism such as a community consult team to advise on recruitment, materials, and study design. This collaboration should be long-term rather than a one-time consultation.	- Genetic counsellors, OBGYNs, pediatricians, and other relevant providers should participate in and consult on ERS studies, contributing their expertise during score generation and data collection and interpretation rather than only at the point of clinical translation. - Before ERS tools become widely available to the public, clinicians and professional

• Incorporate clinical utility metrics, including PPV and NPV, alongside the analytical performance metrics already prioritized, such as sensitivity, specificity, and AUC. • Build equity considerations into exposure and outcome selection at the design stage to mitigate potential downstream adverse impacts of poorly selected exposures/outcomes. Consider developing ERS that predict provider-prioritized exposures and outcomes, including environmental teratogen exposures, infection risks, intervention responses, and ultrasound findings. • Communicate ERS findings transparently and proactively to the broader scientific, clinical, and media community, to foster an honest discussion and narrative around ERS and its impact on people's health. • Advocate for or participate in cross-disciplinary evidence synthesis efforts for ERS, modeled on EGAPP or similar frameworks, to support responsible clinical integration of this tool.	organizations must engage with regulatory bodies to address the risks of premature or unregulated rollout, including via DTC pathways. • Related to the previous point, the NSGC and CAGC should consider issuing position statements on ERS that incorporate the clinical adoption considerations identified in this study, including but not limited to clinical evaluation of ERS, clinically actionable exposures and outcomes, and ethical considerations (eugenics, access, informed consent processes, etc.) • Healthcare Provider training programs and continuing education bodies should consider developing and sharing a single learning module on epigenetic mechanisms and ERS across programs, rather than each program building separate content independently.
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5.8 The Translational Research Pipeline Model Could be Applied to Move Forward

These recommendations can be further interpreted using the translational research pipeline as a framework for organizing different stages of evidence translation (Khoury et al., 2007). As illustrated by the bridge analogy (Figure 4), this pipeline describes how scientific discovery (the evidence-base pillar) is eventually implemented in routine clinical practice (the meaning- and decision-making pillar of the counselling encounter). Khoury and colleagues describe this framework in four phases: T1 research translates a basic discovery into a clinical application, which includes diagnostic tools; T2 research assesses the validity and utility of that application

and produces evidence-based guidelines; T3 research translates those guidelines into clinical practice through dissemination and implementation; and T4 research evaluates real-world health outcomes once the application is in use (2007). According to these phases, ERS are currently best understood as sitting at the T1 stage: researchers are establishing the field of ERS and generating evidence for its feasibility as a biological marker. Aligned with the goals of this study, focus group participants were focused on T2 and T3 questions: what would it take for this tool to be valid enough to use, and what would using it look like in practice? Moving ERS from T1 toward T2 will therefore require structured mechanisms for collaboration between researchers, clinicians, and end-users to define what constitutes clinical validity and utility for this tool. This could include Delphi consensus processes to establish evidence thresholds (Nasa et al., 2021; Visram et al., 2025) co-development of standardized reporting and interpretation frameworks (Brouwers et al., 2010; Moher et al., 2010) and prospective studies embedded within clinical settings to evaluate how ERS results influence counselling and decision-making (Pearson et al., 2020; Pieters et al., 2009). Table 9 illustrates potential research examples across the translational framework and summarizes the field's current progress (Adapted from Khoury, et al., 2007).

Table 9: *ERS Translational Research Continuum: Types and Examples in the Prenatal Space*

Phase	Definition (Khoury et al., 2007)	Research Type	Potential Example	Progress on ERS Research
T1 Discovery	Discovery to candidate health application	ERS score generation, longitudinal birth cohort studies, Epigenome-wide association studies	Are prenatal exposures (e.g., tobacco smoke, air pollution, gestational stress) associated with differential methylation at	This is where current ERS research is most active.

		(EWAS); candidate CpG site analyses;	specific CpG sites in cord blood or placental tissue? Do these DNAm signatures associate with later neurodevelopmental outcomes such as ASD or ADHD? Can generated ERS establish a link between exposure and outcome?	
T2 Validation	Health application to evidence-based practice guidelines	Independent cohort replication and validation studies; systematic reviews and meta-analyses; clinical validity assessment; adapted ACCE framework evaluation, with modification required for DNAm patterns rather than genetic variants	What is the analytic and clinical validity (AUC, sensitivity, specificity) of an ERS for NDD? What is its clinical utility (PPV, NPV) for the target populations?	Emerging but incomplete. Researchers report the first set of metrics; the second, which providers require, is largely absent.
T3 Implementation	Practice guidelines to health practice	Dissemination and implementation research; provider knowledge and attitudes surveys; barriers and facilitators studies; health technology assessment	What proportion of prenatal care providers and genetic counsellors are aware of ERS and prepared to integrate them into clinical workflows? What are the structural, informational, and ethical barriers to ERS uptake in prenatal genetic counselling?	Largely absent for ERS specifically. Existing surveys on genomic technology readiness among genetic counsellors did not include

				epigenomic technologies (Farwell Hagman et al., 2020; Gronowski & Budelier, 2020; Haga et al., 2012). This study contributes early evidence toward this phase.
T4 Impact	Practice to population health impact	Outcomes research; population-level surveillance of risk and benefit; long-term birth cohort follow-up; monitoring of equity and access to services	Does ERS-informed prenatal care or early intervention reduce the incidence or severity of NDDs at a population level? What are the long-term clinical benefits, harms, and costs of routine prenatal ERS screening?	ERS research has not yet reached this stage.

5.9 Ethical, Legal, Social Implications (ELSI)

Larger ethical questions remain about who benefits, who is harmed, and what responsibilities clinicians and researchers carry in relation to this emerging technology. The four foundational principles of biomedical ethics by Beauchamp and Childress first published in 1979 and widely applied in genetics practice, provide a useful framework for examining these concerns: respect for autonomy, beneficence, non-maleficence, and justice (Beauchamp, 1979).

5.9.1 Eugenics: History Should Not Repeat Itself

Issues of justice and non-maleficence surface in several distinct concerns raised by participants, beginning with the profession's own history. The field of clinical genetics has a dark history of

eugenic underpinnings, as the origins are tied to a movement that justified reproductive decisions by deciding which traits were considered undesirable. Although present-day genetic counsellor practice models steer clear from that intent, this concern is understandable given a historical context of racism and structural oppression (Veatch et al., 2007; Zuckerman, 2021). This is important because the decision to study certain exposures and outcomes identified by ERS over others is not neutral. Measuring some exposures and outcomes while leaving others unmeasured may place implicit value on certain traits and behaviours among families and clinicians (Boardman, 2014; Zerres et al., 2021)

A related violation of non-maleficence has been raised about epigenetics more broadly: framing the field as a basis for progressive, inclusive policy does not prevent its findings from being used to support older eugenic arguments. A 2009 study published in the American Journal of Human Biology linked lower birth weight among African Americans to the long-term effects of slavery (Jasienska, 2009; Meloni, 2016). The finding was meant to support investment in addressing structural harm, but the same data, some argue, could be misread as evidence of “acquired inferiority.” ERS that focus on vulnerable populations carry a similar risk, and researchers need to think about how their findings may be interpreted, not only whether the findings are accurate.

5.9.2 Epigenetic Surveillance: ERS as Evidence of Behaviour

ERS developed for exposures such as substance use or maternal mental health raise a distinct concern: they make a pregnant person's behaviour biologically traceable in a way that current clinical tools do not. This traceability can invite moral scrutiny and, in some contexts, legal consequences for behaviours that were previously private. This risk is in direct conflict with the principle of non-maleficence and the literature on environmental epigenetics suggests that it is not hypothetical. Studies on epigenetic mechanisms during pregnancy have already been used to

support individualized narratives of blame, and these narratives compromise justice by disproportionately affecting Black, Brown, and Indigenous individuals (Lappé et al., 2022; Saldaña-Tejeda & Wade, 2019; Valdez & Deomampo, 2019). Valdez (2021) argues that epigenetic findings can either redistribute responsibility toward the structural conditions that shape pregnancy or be used to justify greater surveillance and monitoring of pregnant individuals based on race, gender, and other social traits. Which direction ERS research takes will depend on which exposures are selected for, how results are communicated, and whether structural and systemic factors are built into interpretation of findings. Lack of attention to these issues for ERS could potentially perpetuate aforementioned harms, especially for marginalized individuals.

5.9.3 Is Non-Directiveness Possible With ERS?

Offering ERS challenges patient autonomy in ways that may not be as neutral as it appears on the surface. Certain genetic counsellor researchers have argued that offering a test implies, at minimum, that the test is worth taking, and offering a test for risk of a poor outcome implies an implicit recommendation about what to do if that risk is found (Clarke, 1991; Clarke, 2017). This pressure, some believe, will hold true irrespective of a counsellor's individual intentions, because it comes from the structure of the clinical encounter itself rather than from anything the counsellor says. In offering ERS, providers would, in effect, be putting their stamp of approval on the idea that this information is something a reasonable person would want. Providers must consider this risk to autonomy before it becomes part of routine prenatal care.

5.9.4 Equal is not Equitable: The Concern of Systemic Barriers

Access and equity raise additional questions about justice. Even before follow-up care is considered, there is uncertainty about who would be offered an ERS in the first place and whether individuals or families would be able to afford testing if it is not publicly funded or fully covered by insurance. Beyond test access, there is no guarantee that appropriate counselling,

referral, or monitoring pathways following a high-risk ERS result would equate to equitable distribution of interventions and services. Literature shows that genetic test evaluation is tightly linked to resource allocation, raising equity concerns about who has access to the resources needed to manage an uncertain result, and who is left to handle that uncertainty alone (Adair et al., 2009); National Academies of Sciences, Engineering, and Medicine [NASEM] et al., 2017). The National Society of Genetic Counsellors (NSGC) has taken the position that regulation should prevent barriers to accessing genetic tests for underrepresented and underserved communities, but access to the test itself is only part of the concern (NSGC, 2025). Depending on the jurisdiction, variable coverage and reimbursement policies can produce unequal access to the follow-up care a result might require, which would further widen existing health disparities.

5.9.5 Outpacing Utility: The Risk of an Over-the-Counter ERS

A further concern worth discussing involves beneficence and non-maleficence: whether ERS would reach the public through direct-to-consumer (DTC) channels regardless of whether clinicians consider it ready for clinical use. This concern has precedent. Companies have already begun marketing epigenetic tests directly to consumers, including tests related to epigenetic aging (Aubrey, 2024; Ibáñez-Cabellos et al., 2026; Jarry, 2020). This growth has occurred in the absence of clinical consensus about validity or utility, and there is little reason to expect ERS would be treated differently (Apsley et al., 2025). If ERS reaches consumers through direct-to-consumer companies before the clinical and communities decide on its readiness, providers may end up managing the consequences of a test they did not endorse.

Epigenetic aging tests offer a useful preview of what ERS may face if it reaches the public before its clinical value and diagnostic pathways are fully described. These tests are already commercially available and present consumers with results derived from epigenetic data, often

communicating conclusions, such as the benefits of reducing alcohol use or quitting smoking, that are already available for free through public health guidance (Jarry, 2020). The evidence on whether this kind of risk communication is beneficial and changes behaviour is not encouraging. A systematic review and meta-analysis found no significant effect of communicating DNA-based risk estimates on smoking cessation, diet, physical activity, or alcohol use (Hollands et al., 2016). If ERS are rolled out as DTC tests, this could violate non-maleficence by generating cost and anxiety for patients without a clinical benefit, which strengthens the case for establishing clinical utility before, rather than after, these tests reach the public.

Bearing in mind these issues and using the principles of biomedical ethics as a guide, Table 10 depicts a set of considerations in the case of premature adoption of ERS in prenatal genetic counselling. This responsibility does not rest with a single group; rather, it requires collaboration among researchers developing ERS, clinicians who will interpret and communicate results, and regulatory and policy bodies responsible for oversight and equitable implementation in clinical practice.

Table 10: *Core Bioethical Principles Applied to Prenatal ERS: Examples of Fulfilment and Non-Fulfilment*

Core ethical principle	Fulfilled	Not Fulfilled
Autonomy	• May offer pregnant individuals access to probabilistic information about prenatal exposures and NDDs, supporting decision-making for the pregnancy period and beyond. • May meet the right to know for families seeking to understand	• Informed consent is compromised when clinicians and patients lack adequate understanding of the probabilistic, tissue-specific, time-sensitive, and potentially reversible nature of ERS • Without structured pre-test counselling, families are likely to conflate ERS with deterministic

	environmental contributors to neurodevelopmental risk	genetic risk, undermining informed decision-making • The right not to know is not protected if ERS results are returned without opt-in consent processes or disclosure counselling. • A maternal ERS carries implications for the child's "right to an open future", as a third party who bears risk without agency, known as relational autonomy (Feinberg, 1980) . • ERS generated from cord blood or placental tissue at birth epigenetically profile children who cannot consent to testing.
Beneficence	• May enable early identification of children at elevated NDD risk, facilitating timely developmental monitoring or referral • Could motivate reduction of modifiable prenatal exposures if results prompt behaviour change in pregnant individuals and broader systemic change resulting in improved environments (e.g. reduced pollution, improved working conditions, cleaner neighbourhoods, reduced stigmatization, etc.)	• Without established clinical validity, ERS cannot reliably distinguish high- from low-risk individuals. • In the absence of validated interventions tied to ERS results, returning scores may generate distress without improving health outcomes. • Causal relationships between ERS-indicated DNAm changes and NDD development are not established; the assumption that the score reflects biological risk is unsubstantiated. • Early monitoring benefits are premised on ERS having actionable clinical utility, which is a threshold the field has not yet reached.
Nonmaleficence	• If ERS identifies modifiable prenatal exposures, clinical follow-up could support exposure reduction in future pregnancies	• Without validated thresholds, ERS risk high false positive and false negative rates, false reassurance or unwarranted alarm with no established clinical path forward. • Labelling a child with a probabilistic ERS, prior to established clinical validity, may cause lasting psychological harm through parental

		anxiety, stigma, and altered caregiving expectations • Cord blood DNAm does not reliably reflect brain tissue methylation; risk estimates derived from surrogate tissue may be systematically inaccurate in ways that cannot be detected without validated reference standards • Epigenetic data encodes sensitive information about a person's lived environment and health history, creating privacy and data misuse risks in the absence of robust governance frameworks • ERS tied to prenatal exposures may amplify unwarranted maternal guilt and blame, disproportionately directed at pregnant individuals rather than the structural conditions that shape exposure
Justice	• May draw clinical attention to environmental contributors to NDD disparities, highlighting structural determinants of neurodevelopmental health	• ERS developed predominantly from European birth cohorts may perform poorly in racially, ethnically, and socioeconomically diverse populations, introducing systematic bias in risk stratification • Communities bearing the greatest environmental exposure burdens, racialized, low-income, and Indigenous populations, may be most likely to receive elevated ERS, pathologizing the epigenetic consequences of structural inequity without addressing root causes • Without equitable access to genetic counselling for result interpretation, marginalized populations face greater risk of misunderstanding, misuse, or unexplained anxiety from ERS results

		• Epigenetic risk data could be accessed by insurers, employers, or child welfare systems and used in discriminatory ways in the absence of legal protections • Resource expenditure on clinically unvalidated ERS diverts from evidence-based NDD services, with disparate impact on underfunded healthcare systems serving higher-need populations
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5.10. Study limitations

Several factors influenced the generalizability and applicability of the study findings. First, due to the limited existing literature on ERS for prenatal exposures and neurodevelopmental outcomes, only a small number of relevant studies were available for inclusion. This reflects the early stage of the field; as such, the available data are restricted in both depth and breadth. This scarcity limited the variety of hypothetical case scenarios that could be meaningfully developed for the focus groups. Furthermore, given the small number of available articles, ZNM was unable to explore researcher perspectives in substantial depth, particularly as this was a secondary analysis of published research papers in which the written content was not intended to address the specific research question of this study. Since discussion sections of empirical papers are already limited in scope by convention, this compounded the constraints on the qualitative analysis that was possible, narrowing the interpretive range and depth of that component of the study. However, it is important to note that this reflects how ERS is currently being communicated and disseminated into the field, as researchers developing these tools are not typically engaging in primary qualitative studies such as focus groups. As such, although this approach has limitations, it is an appropriate method for examining how ERS is currently represented in published literature.

Focus groups were chosen to account for both the time constraints during a 90-minute session and existing knowledge gaps regarding ERS, ensuring that participants could engage meaningfully with a topic that is still relatively early in its development. Although surveys and direct interviews may appear to provide the most straightforward way to elicit opinions about emerging risk assessment tools, such approaches assume that participants possess sufficient familiarity and experiential grounding to offer well-developed views. In the case of ERS, this assumption is problematic, as many stakeholders have limited exposure to the concept, and there is no ERS-specific clinical experience on which to draw. As such the knowledge about ERS among participants may be directly informed by the information presented in the hypothetical case scenarios, and participant responses may have anchored by the specific exposures, outcomes, and predictive values that were presented. Additionally, hypothetical case scenarios cannot be expected to fully replicate how genetics providers would respond in real clinical encounters with actual patients, despite efforts to make the case scenarios as realistic as possible. While the case scenarios served effectively as anchors for structured discussion, they represent only a subset of the clinical situations that genetics providers might encounter in practice. As such, they may serve as a template or source of inspiration for future studies seeking to explore a broader range of ERS-related clinical contexts. Further, the case scenarios were focused on prenatal exposures and neurodevelopmental outcomes. Thus, this may have shaped participants' framing of ERS utility in ways that would not necessarily be generalizable for other exposures and outcomes. As such, participants' views should be understood within that context rather than as a general commentary on the ERS field.

As with most focus group-based studies, the number of participants may be insufficient to capture the full diversity of perspectives across the profession, and any attempts to generalize

beyond the sample should be approached with caution. Moreover, despite deliberate efforts to reduce social desirability bias and to balance dominant and quieter voices during facilitation, the small size of each focus group may have nonetheless contributed to a narrower range of expressed opinions or the suppression of dissenting views (Nederhof, 1985). Additionally, the participant pool was composed exclusively of Canadian and U.S.-based genetic counsellors, which limits the transferability of findings to genetics providers practicing in other healthcare systems, such as those in the United Kingdom or Australia, where structural, regulatory, and cultural contexts may differ meaningfully. Indeed, the absence of other genetics providers, specifically geneticists, from the participant pool may have also shaped the data and, by extension, the themes that emerged from the focus groups. Finally, participants were majority female, which may impact the diversity of perspectives; however, this reflects the broader demographic profile of the profession, where over 90% of genetic counsellors identify as female according to recent NSGC and CAGC professional status surveys (CAGC, 2024; NSGC, 2024).

During the analysis of focus group data, body language and nonverbal communication were not captured, which can at times provide meaningful context for interpreting verbal responses. However, this limitation was partially mitigated by the researcher replaying audio recordings when excerpts were ambiguous, allowing for closer attention to tone and nuance in order to better capture the essence of participants' contributions.

Finally, the focus group facilitator's positionality may have shaped the development of the focus group guide, the coding process, and the interpretation of emerging themes. However, this was mitigated through continuous reflexivity practice and the application of the rigour strategies described in the methods section, which were employed throughout data collection and analysis.

A further limitation concerns the difference in focus area between the two participant groups with respect to ERS and its potential. Genetics providers may possess more extensive knowledge of the clinical dimensions of patient care and the genetic counselling of genomic technologies, whereas researchers may have more in-depth familiarity with ERS methodology and its technical parameters. This difference in baseline knowledge complicates direct comparisons of perspectives across groups, as differences in viewpoints may partly reflect differences in professional exposure to ERS rather than substantive disagreement about its clinical utility.

It is important to note that this study is exploratory in nature and is intended to contribute foundational understanding within an emerging area of research, rather than to serve as a guide or roadmap for clinical utility. The limitations described above reflect the boundaries of what is currently possible in this emerging area of research and point to the directions that future research could take to build upon and extend these findings.

5.11 Future Directions

The limitations outlined above offer several meaningful directions for future research, many of which emerged organically from the focus group discussions themselves.

Although genetic counsellors are among the provider groups with the greatest expertise in counselling patients on genomic technologies such as ERS, focus group participants identified other providers whose perspectives would offer valuable and critical insights into the utility and applicability of ERS in clinical practice. These include obstetricians and gynecologists, geneticists, pediatricians, and other providers who may be involved in the care of children identified as high risk by ERS, or who may be called upon to counsel patients on this tool. Engaging these groups would require both more targeted recruitment strategies and a broader

recruitment reach. Bioethicists represent another group of particular note, given their capacity to contribute important insights into the ethical frameworks that would be necessary for the safe and responsible implementation of ERS in clinical settings. Additionally, conducting dedicated focus groups or in-depth interviews with researchers, rather than relying primarily on the discussion sections of published papers, could yield richer and more nuanced information on their perspectives, and would allow for a more balanced and direct comparison with the views of clinical providers.

“Two, do we think that patients are actually going to uptake if it's feasible? And then definitely needing to get OB input on that. The poor OBs have so much to talk about to their patients. And just this week now they're having to remind patients that Tylenol is actually safe during pregnancy. All of the OBs that I work with this week are like, you've got to be kidding me, right?” (Participant 6, Session 3)

While understanding the perspectives of the scientific and healthcare communities is essential, it is equally important to more directly explore the perspectives of individuals who may receive ERS results and experience this tool firsthand. Neither the literature reviewed nor the focus group data directly represent the perspectives of pregnant individuals; instead, genetics providers anticipate patient responses, which is not equivalent to patients expressing their own views. This absence has important implications for both research and clinical translation. For researchers, excluding patient voices risks the development and validation of ERS in ways that do not reflect patient-defined outcomes, values, or priorities. For clinicians, it limits the ability to design meaningful clinical protocols and counselling approaches without direct input from those who would ultimately receive and interpret the test. While inferences about patient perspectives can

be useful, particularly in emerging areas where direct data are limited, they cannot substitute for empirically grounded patient engagement.

Future research should therefore prioritize the inclusion of patient perspectives on uncertainty and probabilistic risk information in the context of ERS, including how patients interpret and respond to results, how they navigate informed consent for risk-prediction tools, and how they experience potential stigma associated with high-risk results. Equally important are the psychosocial dimensions of ERS, including perceived responsibility or control, impacts on reproductive decision-making, effects on mental health such as anxiety, and how ERS may shape individuals' experiences of pregnancy and their relationship with the developing fetus. Centering the patient perspective in this way would be essential to ensuring that ERS, if implemented, is both clinically meaningful and aligned with the needs and experiences of those it is intended to serve.

Future literature reviews could also be expanded to include all ERS developed for the prenatal period, regardless of the specific exposure or outcome under investigation, rather than restricting inclusion to ERS linking prenatal exposures to neurodevelopmental outcomes as was done in the current study. Such an expansion would supplement and contextualize the data presented here, while also broadening the pool of available evidence from which hypothetical case scenarios for future focus groups or interviews could be developed, allowing subsequent studies to explore a wider range of clinically relevant ERS applications.

Taken together, the cumulative findings of these future areas of research could contribute to the development and establishment of practice guidelines as the evidence base grows and our understanding of how ERS could be responsibly implemented continues to improve. Future work could also help evaluate and inform training needs among genetic counsellors and other

providers with respect to ERS, further supporting the practical integration of this tool into clinical workflows. Additionally, such research could inform how ERS results are communicated and presented in clinical reports, a point that several focus group participants raised as a meaningful and unresolved consideration.

There are many promising and important avenues for future research in this area. Given the emerging nature of this field, it is important to pursue these directions early, so that ERS tools are developed and refined with the perspectives of both providers and patients meaningfully incorporated from the outset, thereby maximizing their relevance and utility in clinical practice.

CHAPTER SIX: CONCLUSION

This study set out to explore the clinical utility and feasibility of epigenetic risk scores (ERS) for prenatal genetic counselling by comparing perspectives from genetics providers, collected through virtual focus groups with Canadian and American genetic counsellors, and researchers developing ERS, as represented in the published literature. The findings indicate that the two groups share some priorities, particularly the need to expand and strengthen the ERS evidence base. However, they diverge in how they define progress, with researchers primarily emphasizing analytic validity and predictive performance, while clinicians place greater weight on clinical validity and utility. The study also identified ethical, legal, and social implications such as eugenics, insurance, access, and stigmatization, that require consideration prior to clinical integration.

The findings of this study show that the field is not yet aligned on what constitutes meaningful evidence for clinical use. Without clearer agreement on evidence standards and closer integration of researcher, clinician, and patient perspectives, there is a risk that technical development will

continue to outpace clinical readiness. Addressing this gap is essential if ERS are to move beyond promising research tools and become responsibly implemented in prenatal genetic counselling practice.

In light of these findings, and situated within the translational research pipeline, this study highlights the need for coordinated efforts to bridge the gap between early-stage development and clinical application. It invites collaboration among stakeholders, including clinicians, ERS researchers, regulatory bodies, and end-users, to support the generation of evidence and development of frameworks necessary to evaluate and responsibly translate ERS from research into clinical practice.

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APPENDICES

A.1: Systematized Literature Review Search Strategies

A.1.1 Scopus Search Strategy

TITLE-ABS-KEY (("methylation profile score" OR "polyepigenetic biomarker" OR "methylation risk score" OR "epigenetic risk score" OR "epigenetic score" OR "methylation score" OR "epigenetic risk predictor" OR ("epigenetic" AND "risk score")) AND ("prenatal exposure" OR (development* W/2 (disorder* OR delay*)) OR neurodevelopment* OR neurobehav* OR praxi* OR dysprax* OR (global W/2 delay*) OR schizophreni* OR autis* OR asd OR "attention deficit" OR adhd OR neurogen*))

A.1.2 Ovid MEDLINE Search Strategy

("methylation profile score*" or "polyepigenetic biomarker*" or "methylation risk score*" or "epigenetic risk score*" or "epigenetic score*" or "methylation score*" or "epigenetic risk predictor*" or "epigenetic signature*" or (epigenetic and "risk score*")).ti,ab. and (prenatal exposure*.mp. or ((development* adj2 (disorder* or delay*)) or neurodevelopment* or neurobehav* or apraxi* or dysprax* or praxi* or (global adj2 delay*) or schizophreni* or autis* or asd or ("attention deficit" or adhd) or neurogen*).ti,ab. or exp Neurodevelopmental Disorders/ or exp Autistic Disorder/ or exp Schizophrenia/ or exp Attention Deficit Disorder with Hyperactivity/) [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms, population supplementary concept word, anatomy supplementary concept word.

A.2: Data Extraction Template

Database	STUDY METADATA						STUDY METHODOLOGY		POPULATION DETAILS				OUTCOME AND/OR EXPOSURE						DISCUSSION SUMMARY	KEY FINDNGS	Extracted by	Extractor Notes
	Article Title	Year	First Author (Last Name)	Journal	Country of Study	DOI	Score created	Epigenetic Platform/ Technology	Sample Size	Tissue/c ell-type	patient sex (Male or female)	genetic ancestry	Outcome predicted (e.g. ASD, ADHD, FASD)	Outcome Measurement Tool	Type of Exposure detected (e.g., environmental toxins, maternal diet, smoking, stress)	Exposure Measurement Tool	Exposure Detection or Outcome Prediction Power: How well the ERS identified or associated with exposures/outcomes	statistical method(s) used (e.g., linear regression, mixed models)	Researchers' perspectives on the utility of (their) ERS	According to researchers and/or identified by the extractor		

A.3: Recruitment Materials

A.3.1 Email invitation for NSGC's research survey blast:

Study title: Share Your Views on an Emerging Prenatal Risk Tool

Are you a genetic counsellor with at least 1 year of experience in the prenatal setting? We'd love to hear from you! This study at the University of Manitoba is conducting focus groups to explore how a **promising new tool**, called epigenetic risk score, could help enhance prenatal counselling for neurodevelopmental disorders in the future.

Next steps: If interested, please complete this quick eligibility questionnaire. [\[LINK HERE\]](#)

Questions?

Please contact Zahra Nasser Moghaddam [\[LINK TO EMAIL\]](#), BSc, MSc candidate

A.3.2 Email invitation for CAGC's research survey blast:

Study title: Share Your Views on an Emerging Prenatal Risk Tool

Are you a genetic counsellor with at least 1 year of experience in the prenatal setting? We'd love to hear from you! This study at the University of Manitoba is conducting focus groups to explore how a **promising new tool**, called epigenetic risk score, could help enhance prenatal counselling for neurodevelopmental disorders in the future.

Epigenetic risk score is an emerging approach that uses information about prenatal exposures (like stress, alcohol, smoking, or pollutants) to help assess potential risks for neurodevelopmental disorders. It could offer a new way to support risk assessment and patient counselling in the future.

As part of my MSc thesis, I am conducting virtual focus groups to discuss realistic case scenarios and your thoughts on the integration of this tool. Your input will help shape how this new approach could be used to improve care for pregnant individuals and their families.

Who can participate?

- Genetic counsellors (ABGC or CBGC certified) with at least 1 year of prenatal experience (you don't need to currently work in prenatal counselling).
- Based in Canada or the United States.
- Available for a 90–120 minute virtual focus group via Zoom.
- Fluent in English.

Next steps: If interested, please complete this quick eligibility questionnaire [[LINK HERE](#)].

Questions?

This study has been approved by the University of Manitoba Health Research Ethics Board. Questions about this survey can be directed to the Student Researcher, Zahra Nasser Moghaddam, or the Principal Investigators, Jessica Hartley and Meaghan Jones (contact information below).

Zahra Nasser Moghaddam, BSc, MSc candidate: [[LINK TO EMAIL](#)]

Jessica Hartley, MS, CGC: [[LINK TO EMAIL](#)]

Meaghan Jones, PhD: [[LINK TO EMAIL](#)]

A.3.3 Email invitation for CCMG's research survey blast:

Study title: Share Your Views on an Emerging Prenatal Risk Tool

Are you a board-certified medical geneticist (CCMG) with at least 1 year of experience in prenatal genetics? We'd love to hear from you! This study at the University of Manitoba is conducting focus groups to explore how a **promising new tool**, called epigenetic risk score, could help enhance prenatal genetics care for neurodevelopmental disorders in the future.

Epigenetic risk score is an emerging approach that uses information about prenatal exposures (like stress, alcohol, smoking, or pollutants) to help assess potential risks for neurodevelopmental disorders. It could offer a new way to support risk assessment and patient counselling in the future.

As part of my MSc thesis, I am conducting virtual focus groups to discuss realistic case scenarios and your thoughts on the integration of this tool. Your input will help shape how this new approach could be used to improve care for pregnant individuals and their families.

Who can participate?

- Board-certified medical geneticists (CCMG) with at least 1 year of experience in prenatal genetics (currently active or within the past 3 years).
- Based in Canada
- Available for a 90–120 minute virtual focus group via Zoom.
- Fluent in English.

Next steps: If interested, please complete this quick eligibility questionnaire [\[LINK HERE\]](#).

Questions?

This study has been approved by the University of Manitoba Health Research Ethics Board. Questions about this survey can be directed to the Student Researcher, Zahra Nasser Moghaddam, or the Principal Investigators, Jessica Hartley and Meaghan Jones (contact information below).

Zahra Nasser Moghaddam, BSc, MSc candidate: [\[LINK TO EMAIL\]](#)

Jessica Hartley, MS, CGC: [\[LINK TO EMAIL\]](#)

Meaghan Jones, PhD: [\[LINK TO EMAIL\]](#)

A.3.4 Social Media Post: LinkedIn

Calling Prenatal Genetics Providers! Share Your Expertise in an Innovative Study

Are you a genetic counsellor or medical geneticist with at least 1 year of experience in the prenatal setting? We'd love to hear from you! This study at the University of Manitoba is conducting focus groups to explore how a **promising new tool**, called epigenetic risk score, could help enhance prenatal counselling for neurodevelopmental disorders in the future.

Epigenetic risk score is an emerging approach that uses information about prenatal exposures (like stress, alcohol, smoking, or pollutants) to help assess potential risks for neurodevelopmental disorders. It could offer a new way to support risk assessment and patient counselling in the future.

As part of my MSc thesis, I am conducting virtual focus groups to discuss realistic case scenarios and your thoughts on the integration of this tool. Your input will help shape how this new approach could be used to improve care for pregnant individuals and their families.

Who can participate?

- Medical geneticists (CCMG/ACMG) and genetic counsellors (ABGC/CBGC) with at least 1 year of prenatal experience (you don't need to currently provide prenatal genetic care).
- Based in Canada or the United States.
- Available for a 90–120 minute virtual focus group via Zoom.
- Fluent in English

Check out our poster below for more information!

#GCChat #geneticcounselling #geneticcounseling #medicalgenetics #clinicalgenetics



University
of Manitoba

Calling Prenatal Genetics Providers!



Join a 90-120 minute virtual focus group and share your perspectives on the integration of a promising new risk assessment tool

Eligibility:

- Medical geneticists (CCMG/ACMG) and genetic counselors (CBGC/ABGC) with 1+ year prenatal experience
- Based in Canada or the US
- Fluent in English

This study has been approved by the University of Manitoba Health Research Ethics Board. Questions about this survey can be directed to the Student Researcher, Zahra Nasserli Moghaddam, BSc : nasseriz@myumanitoba.ca



Scan the QR code or visit
<https://shorturl.at/6blFs>
to check your eligibility!

Version 2 - June 18, 2025

A.4: REDCap Eligibility Questionnaire

Appendix A.4.1 For Medical Geneticists

Study Title: Assessing Genetics Providers' Perceptions of Epigenetic Risk Scores for Prenatal Exposures: A Feasibility and Scenario-Based Study

Dear Participant,

Thank you for accessing the eligibility questionnaire for the study titled “*Assessing Genetics Providers' Perceptions of Epigenetic Risk Scores for Prenatal Exposures: A Feasibility and Scenario-Based Study*”. This eligibility questionnaire will help determine whether you meet the criteria to participate in the research. If eligible, the demographic information you provide here will also be aggregated and presented in de-identified form to describe participant characteristics in study findings. Before proceeding, please review the following consent information. You are welcome to print or save this page for your records.

Participation in this questionnaire is completely voluntary and you may choose to exit this form at any time. The risks associated with completing this form are minimal. Your email address will be used exclusively to notify you of your eligibility status and, if applicable, to coordinate further study activities (e.g., scheduling Zoom focus groups). All provided information will be de-identified and stored securely on password-protected systems at the University of Manitoba. We estimate that this form should take no longer than 10 minutes to fill out.

Questions?

This study has been approved by the University of Manitoba Health Research Ethics Board. Questions about this survey can be directed to the Student Researcher, Zahra Nasser Moghaddam, or the Principal Investigators, Jessica Hartley and Meaghan Jones (contact information below).

Zahra Nasser Moghaddam, BSc, MSc candidate: [LINK TO EMAIL]

Jessica Hartley, MS, CGC: [LINK TO EMAIL]

Meaghan Jones, PhD: [LINK TO EMAIL]

By proceeding with and completing the online survey, you are consenting to participate in this eligibility questionnaire.

Thank you for your interest in this project!

- 1) Email address: _____
“This email address will be used to contact you about all study-related activities.”
- 2) Please confirm your email address: _____
- 3) Are you board-certified medical geneticist (CCMG/ACMG)??
 - a) Yes
 - b) No [end survey]

- 4) Do you have at least one year of experience involving prenatal genetics (e.g., prenatal diagnosis, fetal medicine consultations)?
- a) Yes
 - i) Please specify the number of years: _____
 - b) No *[end survey]*
- 5) Have you been actively involved in prenatal genetics care or consultations within the past three years?
- a) Yes
 - i) Please specify the number of years: _____
 - b) No *[end survey]*
- 6) Do you provide medical assessments, risk counselling, or consultations regarding prenatal exposures (e.g., smoking, alcohol, medications, environmental risks) in your clinical practice?
- a) Yes
 - b) No *[end survey]*
- 7) Which country do you currently live in?
- 8) What is your current time zone?
- a) Atlantic Time
 - b) Central Time
 - c) Eastern Time
 - d) Mountain Time
 - e) Newfoundland Time
 - f) Pacific Time
- 9) Are you comfortable and proficient in English?
- a) Yes
 - b) No
- 10) To confirm your attention, please select the answer that says “Not Applicable.”
- a) Pre-test counselling
 - b) Post-test counselling
 - c) Not applicable
- 11) How would you describe the setting(s) where you are currently employed? (select all that apply)
- a) Hospital/medical facility – academic medical centre
 - b) Hospital/medical facility – Public
 - c) Hospital/medical facility – Private
 - d) Laboratory – commercial
 - e) University, college or training program
 - f) Other
 - i) Please specify: _____

12) What sex were you assigned at birth?

- a) Female
- b) Male
- c) Intersex
- d) Don't know
- e) Other
 - i) Please specify: _____
- f) Prefer not to answer

13) How would you describe your current gender identity?

- a) Woman
- b) Man
- c) Transgender
- d) Non-binary
- e) Genderqueer
- f) Gender fluid
- g) Gender non-conforming
- h) Agender
- i) Questioning
- j) Prefer to self-describe
 - i) Please describe: _____
- k) Prefer not to say

14) How would you describe yourself? (select all that apply)

- a) White
- b) Asian
- c) Hispanic or Latine
- d) Black, African American, or of African descent
- e) Middle Eastern or North African (MENA)
- f) American Indian, Alaskan Native, or Indigenous Peoples of Canada
- g) Native Hawaiian or Other Pacific Islander
- h) Other
 - i) Please specify: _____
- i) Prefer not to answer

15) How did you hear about this project?

- a) CAGC listserv
- b) NSGC listserv
- c) CCMG
- d) Genetics Journal Newsletter
- e) Social media (e.g. LinkedIn)

- f) Sponsored Facebook ad
- g) Forwarded by a colleague
- h) Other
 - i) Please specify: _____

Appendix A.4.2 For Genetic Counsellors

Study Title: Assessing Genetics Providers Genetic Counsellors' Perceptions of Epigenetic Risk Scores for Prenatal Exposures: A Feasibility and Scenario-Based Study

Dear Participant,

Thank you for accessing the eligibility questionnaire for the study titled “*Assessing Genetics Providers' Perceptions of Epigenetic Risk Scores for Prenatal Exposures: A Feasibility and Scenario-Based Study*”. This eligibility questionnaire will help determine whether you meet the criteria to participate in the research. If eligible, the demographic information you provide here will also be aggregated and presented in de-identified form to describe participant characteristics in study findings. Before proceeding, please review the following consent information. You are welcome to print or save this page for your records.

Participation in this questionnaire is completely voluntary and you may choose to exit this form at any time. The risks associated with completing this form are minimal. Your email address will be used exclusively to notify you of your eligibility status and, if applicable, to coordinate further study activities (e.g., scheduling Zoom focus groups). All provided information will be de-identified and stored securely on password-protected systems at the University of Manitoba. We estimate that this form should take no longer than 10 minutes to fill out.

Questions?

This study has been approved by the University of Manitoba Health Research Ethics Board. Questions about this survey can be directed to the Student Researcher, Zahra Nasser Moghaddam, or the Principal Investigators, Jessica Hartley and Meaghan Jones (contact information below).

Zahra Nasser Moghaddam, BSc : [LINK TO EMAIL]

Jessica Hartley, MS, CGC: [LINK TO EMAIL]

Meaghan Jones, PhD: [LINK TO EMAIL]

By proceeding with and completing the online survey, you are consenting to participate in this eligibility questionnaire.

Thank you for your interest in this project!

1. Email address: _____
“This email address will be used to contact you about all study-related activities.”
2. Please confirm your email address: _____
3. Are you a board eligible or board-certified (ABGC or CBGC) genetic counsellor?
 - a. Yes
 - b. No [*end survey*]
4. Do you have at least one year of experience in the prenatal discipline?
 - a. Yes

- i. Please specify the number of years: _____
 - b. No *[end survey]*
- 5. Have you been practicing in the prenatal setting in any capacity within the last three years?
 - a. Yes
 - i. Please specify the number of years: _____
 - b. No *[end survey]*
- 6. Do you assess and counsel on exposure risks in pregnancy (e.g. smoking, alcohol consumption, hot tubs) within your scope of practice?
 - a. Yes
 - b. No *[end survey]*
- 7. Which country do you currently live in? *[open text box]*
Your response must be at least 2 characters long.
- 8. What is your current time zone?
 - a. Atlantic Time
 - b. Central Time
 - c. Eastern Time
 - d. Mountain Time
 - e. Newfoundland Time
 - f. Pacific Time
- 9. Are you comfortable and proficient in English?
 - a. Yes
 - b. No
- 10. To confirm your attention, please select the answer that says “Not Applicable.”
 - a) Pre-test counselling
 - b) Post-test counselling
 - c) Not applicable
- 11. How would you describe the setting(s) where you are currently employed? (select all that apply)
 - a. Hospital/medical facility – academic medical centre
 - b. Hospital/medical facility – Public
 - c. Hospital/medical facility – Private
 - d. Laboratory – commercial
 - e. University, college or training program
 - f. Other
 - i. Please specify: _____
- 12. What sex were you assigned at birth?
 - a. Female
 - b. Male
 - c. Intersex

- d. Don't know
 - e. Other
 - i. Please specify: _____
 - e. Prefer not to answer
13. How would you describe your current gender identity?
- a. Woman
 - b. Man
 - c. Transgender
 - d. Non-binary
 - e. Genderqueer
 - f. Gender fluid
 - g. Gender non-conforming
 - h. Agender
 - i. Questioning
 - j. Prefer to self-describe
 - i. Please describe: _____
 - k. Prefer not to say
14. How would you describe yourself? (select all that apply)
- a. White
 - b. Asian
 - d. Hispanic or Latine
 - e. Black, African American, or of African descent
 - f. Middle Eastern or North African (MENA)
 - g. American Indian, Alaskan Native, or Indigenous Peoples of Canada
 - h. Native Hawaiian or Other Pacific Islander
 - i. Other
 - i. Please specify: _____
 - j. Prefer not to answer
15. How did you hear about this project?
- a. CAGC listserv
 - b. NSGC listserv
 - c. Genetics Journal Newsletter
 - d. Social media (e.g. LinkedIn)
 - e. Sponsored Facebook ad
 - f. Forwarded by a colleague
 - g. Other

A.5: Focus Group Case Scenarios

A.5.1 Scenario A: A Risk Distilled

Scenario A: A Risk Distilled

Emma is a 30-year-old female who drank 2-3 standard drinks per week until 11 weeks' gestation. A placental alcohol-exposure methylation test at 13 weeks classifies her fetus as high risk (test sensitivity 66%, specificity 72%). Emma is notably anxious about the potential of fetal alcohol spectrum disorder (FASD) findings.

How might a clinician weigh Emma's personal history of alcohol consumption and the "high-risk" placental methylation score when explaining her risk?



A.5.2 Scenario B: Behind the Haze

Scenario B: Behind the Haze

Part 1: Sofia is a 34-year-old female referred at 28 weeks gestation for isolated intrauterine growth restriction. She denies smoking, yet an epigenetic tobacco-exposure risk score on amniocytes classifies her as high exposure (sensitivity 74%, specificity 58%). She discloses secondhand exposure as a caregiver for her elderly parent, a long-term smoker (3 hrs/day, 4x/week).

Would you be satisfied by this explanation on the basis of this ERS result and late smoking disclosure and close the diagnostic work-up for IUGR?



Scenario B: Behind the Haze

Part 2: The same test produces an incidental "support-needs score" of 75/100, which would predict approximately 9 extra days of early-intervention services per year (e.g., educational support, speech or occupational therapy, behavioral counseling).

How might you address this additional information with your patient and what follow up might you recommend?



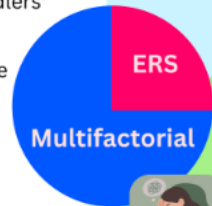
A.5.3 Scenario C: Anxious Beginnings

Scenario C: Anxious Beginnings

Part 1: Maya, a 22-year-old female, presents significant anxiety symptoms during pregnancy. She is referred for prenatal genetic care and offered a cord-blood stress methylation test at delivery. This epigenetic risk score explains approximately 25% of the variability in toddlers' early language skills.

The results predict that the newborn would be in the bottom 20% of their peers for expressive and receptive language development, despite normal newborn exam findings.

How would this knowledge about language delay alter your clinical management or counselling?



Scenario C: Anxious Beginnings

Part 2: The results predict that the newborn would be in the bottom 20% of their peers for expressive and receptive language development, despite normal newborn exam findings.

Update: At 36 months, it's revealed that Maya's child has language delay.

How does this new information influence your interpretation of the score?



A.6: Focus Group Discussion Guide

Timing: 10 min intro, 20 min each scenario, 20 min closing question, 5 end of session

Slide 1: Introduction

- Research Team & Purpose:
 - GC student (R.L.) studying epigenetic risk scores (ERS) for prenatal risk assessment.
 - Goal: Understand clinicians' perspectives on ERS utility and clinical integration.
- Why Participants?
 - Expertise in prenatal genetics is critical for shaping ERS's future clinical use.
- Focus Group Basics:
 - No consensus needed—seeking diverse opinions.
 - In-depth discussion preferred over surveys.
- First 10 mins will be intro – ensure consistency in how I run the focus groups, then will open it up the rest of the time is for discussion

Slide 2: Logistics

- Duration: 90-120 minutes.
- Participation: Encouraged—share different views, expand on others' ideas.
- Confidentiality:
 - Recording for transcription; de-identified data only.
 - Change Zoom names to protect privacy.

Slide 3: Goals for Today

1. Brief overview of ERS (10 mins).
2. Case scenarios to explore ERS in prenatal care.
3. Discuss next steps for clinical integration.

Slides 5-7: Epigenetics & ERS Basics

- Epigenetics:
 - Heritable gene expression changes (e.g., DNA methylation) influenced by environment (e.g., smoking, pollution).
- **ERS vs. PRS:**
 - PRS: Genetic risk (static, lifetime risk).

- ERS: Epigenetic + environmental risk (dynamic, modifiable).
- **ERS Measures:**
 - Exposures (stress, pollutants) or disease risk (autism, FASD).
 - Higher score = higher risk (based on methylation patterns).

Slide 8: Sensitivity vs. Specificity

- Sensitivity: Detects true positives (correctly IDs risk/exposure).
- Specificity: Detects true negatives (correctly IDs no risk/exposure).
- Trade-off: Improving one may reduce the other.

Slide 9: Case Scenario Note

- Hypothetical but realistic examples to spark discussion.
- Focus on broader implications (patient/provider impact) vs. institutional details.
- Open-minded approach encouraged.
- Q&A before diving into scenarios

Slides 10: Scenario A (~20 minutes)

Main question: How might a clinician weigh Emma's personal history of alcohol consumption and the "high-risk" placental methylation score when explaining her risk?

Probing Question 1: Currently, diagnosing FASD at birth relies on clinical examination and exposure history, which can be really challenging to assess. If we consider placental methylation as a potential biomarker, what evidence would you need to trust its reliability for integration into diagnostic criteria? Alternatively, do you see value in using it as a standalone tool?

Probing Question 2: Currently the only way to do this methylation test is at birth (cord blood).

This scenario is looking into the future by assuming that the test can be done early in the pregnancy via CVS. Does this current limitation change how you feel about the utility of this test? When do you think would be the most appropriate or useful time to receive this information for your counselling?

Slide 11: Scenario B Part 1 (~10 minutes):

Main Question: Would you be satisfied by this explanation on the basis of this ERS result and late smoking disclosure and close the diagnostic work-up for IUGR?

Probing Question 1: With a sensitivity of 74% and specificity of 58%, how does your comfort level with this methylation test compare to other tests you use in practice, like NIPT (for example non-invasive prenatal testing for 22q11.2 deletion screen which has a 75% sensitivity and 99.5% specificity)?

Probing Question 2: This test has only been done on placental tissue for research studies, not via amniocentesis. How would this change your counselling?

Slide 12: Scenario B Part 2 (~10 minutes)

Main Question: How might you address this additional information with your patient and what follow up might you recommend?

Probing Question 1: Should early intervention services or closer observation be recommended based solely on a methylation-derived support-needs score before any developmental signs appear?

Probing Question 2: How valuable is a methylation score that doesn't predict a formal diagnosis but does predict greater treatment utilization?

Slide 13: Scenario C Part 1 (~10 minutes)

Main Question: How would this knowledge about language delay alter your clinical management or counselling?

Probing Question 1: The test currently explains 25% of the toddler's early language skills. Is there a different percentage you would feel more comfortable with, higher or lower?

Slide 14: Scenario C Part 2 (~10 minutes)

Main Question: How does this influence your interpretation of the score?

Probing Question 1: You learn Maya's family speaks primarily Mandarin at home. Would this information change your counselling?

Closing Remarks/Final Thoughts: (~20 minutes)

What's missing from these epigenetic risk scores, in your view, for them to be useful in clinical practice? What additional evidence, criteria, or information would you need to evaluate whether or how these tools could be integrated into your work?

What are some technical aspects, clinical utility, ethical considerations, or other aspects of these scores that you feel like need to be addressed that we haven't already discussed?

A.7: Focus Group Consent Form



CONSENT FORM FOR PARTICIPANT

Focus Groups

Study Title: Assessing Genetics Providers' Perceptions of Epigenetic Risk Scores for Prenatal Exposures: A Feasibility and Scenario-Based Study

Student Principal Investigator: Zahra Nasser Moghaddam, Genetic Counselling Trainee
([LINK TO EMAIL](#))

Student Supervisors: Dr. Meaghan Jones ([LINK TO EMAIL](#)) and Jessica Hartley, MS CGC
([LINK TO EMAIL](#))

Funder: MSc in Genetic Counselling Program, Department of Biochemistry and Medical Genetics, University of Manitoba

You are being asked to take part in a research study that will involve a focus group between you, the Student Principal Investigator (PI), Zahra Nasser Moghaddam, and other genetic counsellors or medical geneticists. Please take your time to review this consent form. This consent form will be reviewed with you in detail before the focus group, where you will have the chance to ask any questions you may have before you make your decision. Please ask the study staff to explain any information you do not clearly understand in this form.

The Student PI for this study is Zahra Nasser Moghaddam, an MSc student in the Genetic Counselling Program at the University of Manitoba. This research study is being completed as part of the Student PI's MSc Program. The study is supervised by Meaghan Jones, PhD, a leading researcher in epigenetics and the developmental origins of health and disease, and Jessica Hartley, MS, CGC, Program Director, and prominent researcher in the field of genetic counselling.

PURPOSE OF STUDY

The purpose of this study is to gather perspectives of genetics providers (genetic counsellors and medical geneticists) on the feasibility and clinical utility of epigenetic risk scores for prenatal exposures for neurodevelopmental disorders. These insights will then be combined with and compared to evidence from the published literature to highlight similarities and differences.

PARTICIPANT SELECTION

You are being invited to participate in this study because you meet the criteria based on your responses to the eligibility questionnaire. Specifically, you are a genetic counsellor or medical geneticist with at least one year of experience in the prenatal setting, have practiced in prenatal counselling the prenatal discipline within the last three years and are fluent in English. A maximum of 30 participants will be enrolled in this study.

STUDY PROCEDURES

The focus group will take place over the University of Manitoba Zoom account (UM Zoom) and will be facilitated by the Student Principal Investigator, Zahra Nasser Moghaddam. There may also be another research team member assisting as a notetaker and ensure that Zoom operations run smoothly. You will be in a group of approximately three to four other participants. The focus group will be approximately 90-120 minutes in length.

During the focus group, you will be guided through a series of hypothetical case scenarios depicting the potential use of epigenetic risk scores in genetics, for an in-depth exploration of the ethical challenges, decision-making processes, and limitations of epigenetic risk scores in a “real-world” context. Your responses to the focus group guide and discussions raised in the session will help us better understand how we can translate research findings into clinical practice and potentially improve patient care.

The focus group will be audio recorded. The audio recording will be transcribed word-for-word by the Student Principal Investigator who may use Zoom’s automated transcription feature, or by a confidential transcription service (Transcript Heroes) to ensure accurate reporting of the information that you provide. No personal identifiers will be included in the interview transcript. The transcription service will sign a non-disclosure agreement (NDA) stating that they will not discuss any information included in the audio recordings with anyone other than the study staff.

At the start of the session everyone will be asked to respect the privacy of the other group members. All participants will be asked not to disclose anything said within the context of the discussion, but it is important to understand that other people in the group with you may not keep all information private and confidential.

Upon the completion of the study, we will email you a summary of the study findings, in the form of an executive summary or infographic, using the email address you provided in the eligibility questionnaire.

WHAT ARE MY RESPONSIBILITIES?

By agreeing to participate in this study, you acknowledge that the session will be conducted via Zoom, and it is your responsibility to inform the research team if you require any technical support, such as internet access or Wi-Fi support. There are no correct or incorrect answers, and we value hearing different viewpoints from all participants. We kindly ask that participants respect one another and take turns speaking in the group. Additionally, we request that all participants keep each other's responses confidential.

You will be assigned a participant number which will be used in all transcripts, and in any subsequent analysis or publications. You will be asked to keep your camera on for the duration of the focus group, though you may utilize virtual background or blur features if you prefer additional privacy.

POTENTIAL RISKS

This is a minimal-risk study and there are no anticipated physical risks to participants. You will share your personal opinions and perspectives with other genetic counsellors or genetics providers. Focus group members will be asked to keep the information provided in the groups confidential; however, a potential risk that might exist for some would be that information about you might be discussed outside the group by other participants and be traced back to you. It is also important to acknowledge that due to the small and tightly-knit nature of the genetics counselling community, there remains a possibility that you may recognize other participants despite the use of pseudonyms and others may also recognize you. Should another participant call you by name, the transcriber will remove all names from the transcription. No additional physical risks are associated with this study.

SAFETY

If you require psychological support at any point during the focus group, you may notify the Student Principal Investigator, who can assist in connecting you with appropriate support services or external counselling resources. This may include a referral to the local crisis line (e.g. Klinik 24-hour Crisis Line (1-888-322-3019)) by the Student PI or the study team will help the participant find other counselling help. Please note that confidentiality may be breached if you express intent to harm yourself or others, as required by law.

BENEFITS

There will be no direct benefit to you from participating in this study. However, your contributions will help us better understand how epigenetic risk scores (ERS) can be made more relevant to prenatal genetic care, including genetic counselling and risk assessment for prenatal exposures associated with neurodevelopmental disorders. Your insights will inform future research and clinical practices, potentially improving patient care in this area.

COSTS

There is no cost to you to attend the focus group discussion.

HONOURARIUM

There will be no payment or reimbursement for taking part in this study.

CONFIDENTIALITY

We will do everything possible to keep your personal information confidential. A list of names and addresses of participants will be kept in a secure file so we can send you a summary of the results of the study. If the results of this study are presented in a meeting, or published, nobody will be able to tell that you were in the study. Please note that although you will not be identified

as the speaker, your words may be used to highlight a specific point. The collection and access to personal information will be in compliance with provincial and federal privacy legislations.

During the focus groups we ask that all participants respect and maintain the confidentiality of the discussion; however, it is not possible for the researchers to guarantee that everyone will do so.

Audio recordings of the group discussion will be transcribed. All identifying information (names, pronouns, clinic name) will be removed during the transcription process of the focus group. All study records, including audio recordings, transcripts, and contact information, will be labelled with a coded ID number, which will be assigned to you upon enrolment into the study. All electronic files (audio recordings, transcripts) will be saved in a secure password-protected computer drive at the University of Manitoba. Only the Student Principal Investigator and study staff will have access to the study records. Study information will be retained for a minimum of seven years after which an evaluation will be conducted on whether data will be destroyed, or a subsequent study will be conducted.

Some people or groups may need to check the study records to make sure all the information is correct. All of these people have a professional responsibility to protect your privacy.

These people are:

- The Health Research Ethics Board of the University of Manitoba which is responsible for the protection of people in research and has reviewed this study for ethical acceptability.
- Quality assurance staff of the University of Manitoba who ensure the study is being conducted properly

Your research information may be shared outside of the University of Manitoba with researchers, other organizations, and/or made publicly available. The information is being shared for further analysis or testing, as part of the research study, and/or because it is required by a funder or journal. It will not include your name or any information that could directly identify you.

Permission to Quote:

We may wish to quote your words directly in reports and publications resulting from this. With regards to being quoted, you acknowledge: “In agreeing to participate in this study, I acknowledge that I could be quoted directly or indirectly but will remain de-identified”.

WHAT IF SOMETHING GOES WRONG?

Signing this form does not remove any of your legal rights or legal claims you may have against the study researchers, participating institutions, or any other people or entities involved in the study.

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Participation in this study is voluntary, and you may choose to skip any questions you do not feel comfortable answering or withdraw from the study at any time. However, once the data has been de-identified, it may not be possible to remove your responses from the dataset.

QUESTIONS

If any questions come up during or after the study, you may contact the Student Principal Investigator, Zahra Nasser Moghaddam, at [LINK TO EMAIL] or [PHONE NUMBER]. You may also contact one of the Student Supervisors, Dr. Meaghan Jones, at [LINK TO EMAIL], or Jessica Hartley, at [LINK TO EMAIL].

If you have questions about your rights as a research participant, you may contact the University of Manitoba Bannatyne Research Ethics Board by phone at [PHONE NUMBER] or by email at [LINK TO EMAIL]. Please feel free to print a copy of this consent page to keep for your records.

CONSENT SIGNATURES

1. I have reviewed all six pages of the consent form with the Student Principal Investigator.
2. I understand what this study entails, and I have had the opportunity to ask questions, all of which have been answered to my satisfaction.
3. I understand that my participation in this study is voluntary, and I do not have to participate in this study if I do not wish to.
4. I understand that any information collected about me during this study may be viewed by the Student Principal Investigator, Zahra Nasser Moghaddam, or a member of the study team, as well as the University of Manitoba Research Ethics Board.
5. I understand that by consenting to participate in this study, I am consenting to be audio recorded for the duration of the focus group.
6. I understand that I may withdraw from the study at any time, and my data can be removed prior to de-identification. Once the data has been de-identified, it will no longer be possible to identify or remove my individual responses.
7. I understand that by providing my consent to participate in this study, I have not waived any of my legal rights.
8. I understand I will be provided with a copy of the consent form for my records.
9. I agree to participate in the study.

Participant name: _____ **Date** _____ (day/month/year)

Participant email address: _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their verbal consent.

Name: _____

Date _____ (day/month/year)

Signature: _____

Role in the study: _____