International Scholars Journals

International Journal of Obstetrics and Gynecology ISSN 2736-1594, Vol. 11 (6), pp. 001-027, June, 2023. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Perinatal Genetic Carrier Screening: Could a sequential perinatal carrier screening approach be a better way? (Scoping Review)

R Douglas Wilson MD MSc FRCSC

Professor Emeritus University of Calgary Cumming School of Medicine Department of Obstetrics and Gynecology. Email doug.wilson@ahs.ca. Mobile: +1- 403-470-7229

Accepted 16 May, 2023

Abstract

The gestational time separated genetic carrier screening process with preconception, post conception, and neonatal testing options is complex, poorly provided; poorly implemented; and poorly understood. Methods: scoping review process is used to discuss the opportunity for the development of a sequential perinatal carrier screening process. Results / Discussion: an integrated perinatal genetic carrier screening proposal compared to the separated gestationally timed genetic carrier screening process is introduced using a predelivery informed consent and counselling process to consider the patient or couple personal reproductive carrier plan using 5 possible options: maternal-fetal well-being screening only; fetal aneuploidy / congenital anomalies screening only; expanded fetal genetic screening with next generation sequencing technology; parental-fetal genetic carrier screening prevention (preconception or post conception) using pan-ethnic or focused carrier screening; fetal-neonatal carrier screening treatment (post conception or neonatal screening) based on evidenced-based neonatal treatment score. Conclusion: This sequential perinatal genetic carrier screening proposal has evidence-supported outcomes to determine the access, equity, and validity of a sequential perinatal genetic carrier screening pathway but this proposal may require a clinical trial evaluation for further consideration.

Key Words: genetic carrier screening, preconception carrier screening, post conception carrier screening, neonatal metabolic /lysosomal carrier screening, neonatal therapy, informed consent, ethical carrier evaluation process.

INTRODUCTION

Disease or condition screening is a medical test(s) used to identify a disease and / or a health condition before an individual has any signs or symptoms. Clinical carrier screening opportunities are based on clinical and / or genetic disease being considered (periodical health visit; for personal self-directed population-based screening or directed carrier screening for a targeted condition (case-finding)) [1-6].

A perinatal genetic screening approach can be undertaken at different gestational times but these different times are commonly uncoordinated and redundant. The genetic carrier screening options are not well understood. Complex personal and / or couple counselling, with informed consent, is required but the provider's counselling time is usually limited [1-6].

The clinical objective of this perinatal genetic carrier screening proposal is to consider a more ethical, effective, and equitable carrier genetic screening process for a person, planning to be pregnant or who may already be pregnant. An effective perinatal genetic carrier screening pathway for people and ultimately the fetus-neonate, needs to be revised from the separate three 'gestational periods' screening models (preconception--post conception -neonatal) into an effective 'continuum'

using a practical, educational, and counselling-informed consent process.

MATERIAL AND METHODS

A scoping review methodology was used to analysis the extent and characteristics of the research literature regarding parental-fetal-neonatal genetic carrier screening. [7, 8] Heterogeneous literature labelling was done with relevance to date, location (country or context), source (peer-reviewed or grey literature), and origin (health care discipline or government policy). A total of 175 data sources were identified and categorized with a final total of 108 being selected for inclusion. A significant proportion of the scoping data sources were from peer-reviewed sources, identified by PubMed (102/108) while the remaining grey literature (6/108) were from national and provincial government controlled-public websites with possible inherent bias. Search terms, report titles, peer-reviewed references, and author names were utilized to identify additional resources. PUBMED was the evidenced based resource, English only, using search terms, genetic carrier screening, preconception carrier screening, post conception carrier screening, neonatal metabolic /lysosomal carrier screening, neonatal therapy, informed consent, ethical carrier evaluation process. This scoping review to support carrier screening innovation has identified limited but adequate data sources. The scoping review checklist score (17/20) summarizes the process and is provided in the appendix.
Gender-neutral language has been considered throughout this manuscript. In this document, the terms of pregnant person / people are used. For reproductive publications, it is important to acknowledge that it is not only people who identify as women, for whom it is necessary to have access to counselling and clinical care. Obstetric - gynecologic services and the delivery of care must therefore be appropriate, inclusive, and sensitive to the needs of those individuals whose gender identity does not align with the sex that they were assigned with at birth (DOI: 10.1111/1471-0528.17206)

RESULT

Perinatal Genetic Carrier Screening: Ethics, Choice, Autonomy

Historically, the criteria for genetic carrier screening have included {1-3, 11-13]:

- a condition with a phenotype severity that impacts ‘quality of life’ decision-making.
- a high prevalence of carriers in the screened / targeted population.
- an established valid analytic screening method.
- an evidenced-based genotype–phenotype correlation.
- available prenatal screening / diagnostic testing.
- an information process to discuss the ethical and available reproductive options.

The ethical understanding and process for a patient’s reproductive education, understanding, and choice, requires a clear and logical process for their informed consent. Pretest counselling is required, as the patient is usually expecting a simple answer from testing but the possibility of unanticipated results with positive and negative impact is common. A pre-screening decision is required for disclosure of the post-test results as well as counselling and the extent of information sharing. The issue of privacy and confidentiality must be clearly determined and understood ascertain test results may have a ‘duty to warn’ if additional family health risks are identified [9, 10].
International perspectives for reproductive carrier screening identifies a large variability as screening utilization is impacted by many factors (geographic variation in carrier frequency and condition prevalence, local health care, financial, cultural, religion)[14-16].

Attitudes of parents with genetically affected children and the use of ECS

Most genetic carrier parents of affected children or young adults believe that there is a benefit for the availability and choice of pan-ethnic ECS despite the concerns regarding personal health and social discrimination and stigmatization outweighing the risk of no genetic carrier screening[17].
Most parents of a Down Syndrome child were reluctant toward the use of pan-ethnic ECS and raised concerns about discrimination, societal acceptance, and societal loss of diversity [17].
Understanding these parental perspectives is essential for the responsible use of pan-ethnic ECS in the general population. The severity of the genetic disorder predominantly shapes the views toward ECS use [17].

Patients with an unknown or positive ECS carrier status

An ECS survey completed by women indicated that 51% had no desire to undergo genetic carrier screening but considered the choice to be beneficial and a personal responsibility. Using a ‘positive genetic carrier’ scenario, 49% of women would have their partners screened, 13% would only have fetal prenatal screening, and 2.6% would continue with the use of IVF technology [18].A better acceptance of their positive carrier status was seen in patients who, understood their potential risk after completing pretest counselling[19].
Although patients expressed a desire for pan-ethnic ECS, the actual uptake and impact was variable[20].Most ‘at risk’ couples choose to prevent the birth of an affected child but the decision for pan-ethnic ECS use was strongly influenced by the clinical severity of the ‘at risk’

condition. There was significant variability in patient decisions, even for the same genetic condition, indicating that these decisions were complex and emotionally charged [21].

Societal attitudes toward pan-ethnic ECS have identified three potential implications: unwanted medicalization; stigmatization and discrimination of carriers and affected people; and the challenges in achieving equitable clinical access. Within these themes, the positive implications were reduction of ethnic stigmatization in ancestry-based offers and increased equity while the negative implications were reinforcement of disability-based stigmatization, less of a possibility for developing clinical healthcare expertise and the social pressure to undergo screening [22]. In Holland, the ECS panel is provided with no financial cost to the patient. A study compared the differences between the acceptors and decliners of the screening test-offer. The groups differed in their planned time to conception, education, and stated barriers to participation. The acceptance was used to prevent the birth of a child with a severe condition while the avoidance was because the ECS result would not affect their reproductive decision [23].

Studies have indicated that for an individual, a positive genetic carrier result does change their reproductive decision-making and planning (IVF / PGT—M technology), but for the general population, the pan-ethnic ECS impact is not clear[20].

The clinical utility and clinical and analytical validity criteria for genetic carrier screening

The clinical utility of a test is determined by the likelihood that, by promoting an intervention, the test will result in an improved health outcome [24-26].

Clinical validity of a test refers to how well the analyzed genetic variant is related to the presence, absence, or risk of a specific disease.

Analytical validity of a test requires a specific connection of the gene to the condition and the ability of the test to predict the presence or absence of the particular gene or genetic change (analytical validity for the CFTR gene has many variants associated with cystic fibrosis; but not all) [27, 28].

It is important for the patient to understand that a negative genetic carrier screening result does not eliminate the carrier risk completely, but the screening process, itself, does reduce their risk. The residual genetic carrier risk, for any condition, is never zero, but it is not practical to generate a precise residual risk estimate for the large group of conditions evaluated through multiplex screening, after a negative screening result has been identified[28].

Gestational timing for perinatal genetic carrier screening options

The three perinatal genetic screening options are ‘time’ separated but for the preconception or post conception options, pre and post-test informed-consent counselling is required while for the neonatal screen, there is an ‘implied’ post-test consent approach considered:

- *preconception or post-conception option with* maternal / paternal blood testing (‘true’ genetic carrier screening) for AR-XL heterozygosity carrier status and risk.(Table 1 - 2 [3, 28-31; 1-3, 32-35])
- *post-conception* fetal screening option requires, first, a condition-based genetic screening process for aneuploidy or other genetic condition via the serum / blood testing of the pregnant person; second if a ‘screen positive’ or increased risk test result is identified, aninvasive fetal diagnostic test should be offered to confirm or exclude the screening ‘prediction’ (aneuploidy, CNVs, AD-AR-XL conditions, congenital anomalies). (Table 3 [36-38])
- *neonatal* genetic-metabolic-lysosomal testing option will have a legally **mandated** multi-condition screening test for a newborn diagnostic result in many North American jurisdictions. A post-delivery neonatal blood (dried blood spot) is used for early identification allowing for either possible treatment or palliative care following the positive diagnostic result (AR homozygosity; XL male heterozygosity) (Table 4 [39-43]).

Genetic carrier screening and counselling tools can be used in either the pre- or post-conception process [28, 44-50]

The pretest patient counselling session should include information re additional screening methods for non-genetic or multifactorial congenital anomalies (malformation, teratogenic disruption, deformation, dysplasia).

Preconception counselling and screening for a person or couple planning to be pregnant

Preconception screening (focused, pan-ethnic) attempts to enhance the patient autonomy. The post-conception genetic carrier screening alternative may bias or influence pregnant people to terminate wanted pregnancies, through the choice of selective abortion. Preconception screening can possibly allow carrier couples to avoid the birth of affected children by using other primary preventive measures (pre-implantation genetic diagnosis, unaffected sperm donor). An additional ethical consideration is related to parental responsibility [51-55].

The pretest counseling information should indicate first, the carrier screening is optional and second, the pretest discussion and counselling should start with the patient’s choice to use pan-ethnic ECS or focused screening (personalized ethnic-religious, personal history, and family history-based) for the informed consent process [1-3, 28].

The ACMG has recommended using the term ‘carrier screening’ along with a cumulated tiered system based on the level of the carrier frequency in the patient’s population (ethnic and population neutral) [28]:

Table 1: ECS Conditions and Screening Number.

Panel /Author	Number of Conditions	Carrier Frequency ranges	Gene-disease associations	Condition Severity Categorization
ACMG (2021) [28]	**AR genes 19** **AR genes 19** **AR genes 25** **AR genes 23** **AR genes 11*** **X-linked 16** **Gene total =113**	**>/= 1/50** **< 1/50 - >/= 1/100** **< 1/100 - >/= 1/150** **< 1/150 - >/= 1/200** **outside gnomAD criteria** **population prevalence of 1/40,000**	**majority are definite**	**range varies from mild to profound but majority are moderate or greater**
Goldberg (2023) [29]	**64 conditions**	**1/3 – 1/30,000** 1-100 52 100-5000 12	**majority are definite**	**majority are moderate or greater**
Johansen Taber (2022) [30]	**176 conditions** **evidenced-based panels of 37 or 74 conditions were identified**	**40 had >/= 100** **75 had >/= 200**	**175 well defined**	**165 met severity criteria**
Beauchamp (2019) [31]	**176 conditions**	**290 /100,000 predicted to have a condition being screened**	**N/A**	**N/A**
ACOG (2017) [3]	**23 conditions**	**22>/= 1/100** **1 >/= 1/127**	**definite**	**moderate or greater**

(*Genome Aggregation Database (gnomAD) is a resource developed by an international coalition of investigators, with the goal of aggregating and harmonizing both exome and genome sequencing data from a wide variety of large-scale sequencing projects, and making summary data available for the wider scientific community. The gnomAD database is composed of exome and genome sequences from around the world.)

Tier 1: Ethnic based conditions + CF + SMA (population neutral) + Family Risk Based Screening.
Tier 2: ≥ 1/100 carrier frequency (includes Tier 1).
Tier 3: ≥ 1/200 carrier frequency (includes Tier 1-2) including X-linked conditions.
Tier 4: <1/200 carrier frequency (includes Tier 1-3) number of genes / conditions will vary by laboratory who is doing the screening procedure.
The best practice is for both members of the couple to complete the preconception screening process in a timely manner. Despite the clinical recommendations and the impact on clinical utility, only 41.5% of males, with a proven autosomal recessive carrier female partner, elect carrier screening to clarify the couple's reproductive risk. The significant predictors for male completion were female parity and an earlier gestational age at female screening [56].
Consanguineous couples have different attitudes, considerations, and acceptance for ECS. One study evaluated fourteen couples, who were using whole exome screening, with the goal of prevention. Nine couples (64%) had an affected child but understood that the whole exome testing may reveal additional 'at risk' conditions. Patient implications were identified (choice,

Table 2: Diversity identified with International Comparison for Jewish Ancestry.

Location		
Overview of Screening Panels [1-3]	Categories of disorders. Category Diseases 1 ACOG-recommended tests for Ashkenazi Jewish patients: Tay-Sachs disease Cystic fibrosis Familial dysautonomia Canavan syndrome 2 ACOG-recommended additional comprehensive panel: category 1 plus: Bloom Fam hyperinsulinism Fanconi anemia Gaucher Glycogen storage disease type I Joubert Maple syrup urine Mucolipidosis type IV Niemann-Pick Usher 3 Panethnic commercial panel of expanded carrier screening	**Category 1** Canavan Cystic fibrosis Familial dysautonomia Tay-Sachs **Category 2** Fam hyperinsulinism Fanconi anemia C Gaucher Joubert Maple syrup urine Mucolipidosis IV Niemann-Pick Usher syn type 3 Usher syn type 1F **Category 3** Bernard-Soulier Carnitine palmitoyltransferase II def Congenital disorder of glycosylation type Ia Dihydropyrimidine dehydrogenase def Factor XI def Familial Mediterranean fever Medium-chain acyl-CoA dehydrogenase def Nemaline myopathy Smith-Lemli-Opitz syn Spinal muscular atrophy Stargardt Wilson
UK Jewish [32]	Cystic fibrosis 1/35 Tay-Sachs 1/37 Familial dysautonomia 1/48 Canavan 1/45 Glycogen storage type 1a1/95 Mucolipidosis IV 1/95 Fanconi anaemia type C 1/95 Niemann-Pick type A 1/333 Bloom 1/142	

Table 2: Continued

Israel Jewish [33]	The cohort included 1696 individuals (848 couples) tested with the 'MyScreen' multigene panel. The panel covers 1206 variants spanning 385 genes, known in different Jewish ethnicities and local Arab, Druze and Bedouin populations. Out of these, 205 variants in 143 genes are Jewish founder variants.	We identified 859 (50.6%), carriers of at least one variant in 151 genes. Importantly, 569 (66.2%) of carriers could be missed by the current Israeli screening program. In total, 1:40 (2.5%) of carrier couples were identified by the 'MyScreen' panel, compared with 1:144 (0.7%) found by the ethnicity-based screening. Surprisingly, 90 individuals (10.5%) were carriers of variants "unexpected" for their reported origin, and 16 variants were previously unreported in Jewish patients. .
Mexico-Jewish [34]	We recruited 208 participants. The carrier screening results showed that 72.1% were heterozygous for at least 1 severe disease-causing variant in 1 of the genes analyzed. The most common genes with severe disease-causing variants were cystic fibrosis CFTR (16.8% of participants), Familial Mediterranean fever MEFV (11.5%), WNT10A-related disorders WNT10A (6.7%), and Gaucher disease GBA (6.7%). The allele frequencies were compared with those in the gnomAD; 85% of variant frequencies were statistically different from those found in general and Latino gnomAD (P < 05).	Conclusion: The heterozygote frequency of at least 1 severe disease-causing variant in the MJC was 72.1%. Finally, 6% of couples were at risk of having a child with a severe disorder The use of carrier screening in the MJC and other understudied populations could help parents make more informed decisions
USA Jewish [35]	A total of 81 students underwent screening and 36 (44.4%) were ascertained to be carriers of at least one mutation. A total of 45 mutations were identified, as 8 students were carriers for more than one condition. If testing were limited to category 1, 84% of the mutations would not have been identified, and if limited to category 2, 55% of mutations would have gone undetected.	Conclusion(s): Individuals of Ashkenazi Jewish descent are at significant risk for carrying a variety of single-gene mutations and therefore they should be offered pan-ethnic ECS to increase the likelihood of detecting preventable disorders

fear, level of genetic literacy, the time to consider results, effectiveness of testing). Clinical utility for the testing was demonstrated in this population[57, 58].
The ACMG supports [28]:
- a pan-ethnic screening approach
- recommends that all pregnant patients and those patients planning a pregnancy should be offered Tier 3 genetic carrier screening (autosomal recessive and X-linked conditions). The reproductive partners of pregnant patients and those planning a pregnancy, can be offered Tier 3 genetic carrier screening for autosomal recessive conditions only when there productive genetic carrier screening is performed simultaneously for both members of the couple.
- Recommends that X-linked gene testing, in conjunction with the Tier 3 gene screening be offered to all 46, XX patients undergoing ECS.
- Tier 4 carrier screening should be considered for a pregnancy resulting from a known or possible consanguineous relationship (second cousins or closer) or when the family or personal medical history warrants.
- does not recommend the offer of Tier 1 and/or Tier 2 screening(as these tiers do not provide an equitable evaluation of all racial/ethnic populations) or the routine offer of Tier 4 panels.
- informed counselling elements are summarized in the Appendix.

Post-conception counselling and screening opportunity for fetal genetic screening

Fetal 'genetic' screening is routinely offered for aneuploidy, fetal congenital anomalies with both genetic (syndrome / multifactorial) and non-genetic (teratogenic/ infection related) risk.
The fetal genetic screening options using non-invasive screening should be offered, in a timely fashion, to all pregnant persons / couples after obtaining informed consent. Genetically affected fetuses are not uncommon, and may be the result of an inherited maternal / paternal genetic mutations or the possibility of 'new germline' mutations based on parental age, family history, or personal health history. Fetal screening or testing for the common 'at risk' genetic conditions will include either late first or second trimester 'non-invasive' maternal serum aneuploidy screening with / without detailed ultrasound assessment or possibly ultrasound directed placental or amniotic fluid diagnostic testing. Post-conception screening should provide the opportunity for autonomy by a pregnant person but this pathway requires discussion related to either pregnancy termination or birth of an affected child. In-utero therapy for genomic conditions is limited and expensive (evidenced—based, experimental).
Non-invasive prenatal screening (NIPS) for fetal aneuploidy screening was introduced in 2011. The primary aneuploidy screening focus for NIPS is to identify 'at risk' trisomy 21 pregnancies using maternal serum / plasma to compare the chromosomal placental and maternal cell-free DNA. NIPS has a significant aneuploidy screening impact with a high PPV 98.8% (95% CI 97.8-99.3%) (dependent on the population aneuploidy prevalence) and a low FPR 0.04% (95%CI 0.02-0.08%) [1-3, 45, 46, 59-62]. NIPS has a consistently higher screening performance in the detection of fetal T21/18/13 in singleton pregnancies than any of the traditional screening approaches [63, 64].
SRM concluded that NIPS for T21 in twin pregnancies demonstrates equivalent screening characteristics to that of singleton pregnancies, with a sensitivity of 98.2% (95% CI = 88.2%-99.7%) and specificity of 99.9% (95% CI = 99.8%-100%) [64] although fewer published studies exist than the number of studies in singleton gestations.
The clinical utility of noninvasive prenatal screening
The NIPS PPV for T21 ranges from 50% to 95%, thereby requiring 1.1 to 2 amniocentesis procedures to identify a true positive result. The 'traditional placental analyte' screening PPV for T21 is estimated at 2.2% to 3.6%, which requires 28 to 45 diagnostic procedures to identify a true positive result (dependent on the specific placental analyte screening algorithm used) [28].
"No-Call" results
A SRM has reported that approximately 1% of patient NIPS samples were not able to provide a risk prediction and were reported as a 'no-call' result. The optimal management for 'no call' result pregnancies is variable and are dependent on the 'no-call' etiology [65-68]. The most frequent etiology reported is insufficient/ low fetal fraction. Repeating the NIPS (at a later gestational age) will provide a screening result in approximately 75% to 80% of cases [65].
A low fetal fraction is associated with various adverse pregnancy outcomes, but definitive rates of pregnancy complications and surveillance protocols have not been established [46, 61, 69].
There are reports of higher rates of NIPS 'no-call' in twin pregnancies than in singleton pregnancies and this issue should be discussed in pretest counselling [70]. The twin etiology is likely due to the placental mass differences between the two gestations and may be associated with aneuploidy in one of the twin-pair.

Other Screening Issues

Another SRM concluded that using NIPS as the primary aneuploidy screening method may be cost-effective in certain screening strategies [71, 72].
The economic impact for this implementation is dependent on multiple considerations, including the patient population, health care system, governmental or third-party payers, the retail or discounted pricing of the test, and downstream healthcare costs for a positive NIPS result [64].

Table 3: NIPS with increased maternal genetic carrier testing.

Technology	Results	Reference
sgNIPS / maternal carrier status and fetal risk from a single maternal blood draw	sgNIPS technology was used to screen carrier status (6) compared to the newborn outcomes Carrier frequency 18.2% heterozygous + 98.7% of pregnancies screened received a result. No-call result rate = 1.3%. **NPV 99.4%** (95% CI = 96.0%-99.9%). **Average positive PPV 48.3%** (95% CI = 36.1%-60.1%). Fetal sgNIPS risk of >9 in 10 (90% PPV) were affected.	[36]
non-biased allelic, target enrichment followed by next NGS for analyses of fetal chromosomal aneuploidies, micro deletion and microduplication syndromes, and monogenic disorders.	1129 qualified pregnancies with the detection of 54 fetal aneuploidies, 8 microdeletions/microduplications, and 8 monogenic variants with **100% sensitivity and 99.3% specificity.** 60.3% of aneuploidy samples had aberrant meiotic recombination providing important insights into the mechanism underlying meiotic non-disjunctions.	[37]
NIPT-Plus technique to detect copy number variation (CNV)	31,260 pregnant people received NIPT-Plus. 31,256 cases received a result. Significant CNV was detected in 221 cases (0.71%). **Overall positive predictive value (PPV) 38.42%** 80% 22q11.22 microduplication 75% Di George deletion 50% Prader-Willi 50% 5p deletion 46.5% CNVs >10 MB 28.6% CNVs <10 MB False positive rate of 0.40%.	[38]

NIPS Genomics testing can be used beyond an Aneuploidy Only Screening process

The additional fetal risk screening use beyond the routine aneuploidy screening, may include additional fetal morbidity related to other chromosomal aneuploidy or copy number variants targets, selected AD-AR-XL syndrome / gene abnormalities, and sex-chromosomes aneuploidy pathology [73-79].

Table 3[36-38] summarizes innovative technology use for additional cell-free placental DNA CNVs and monogenic conditions (CNVs > 10 Mb, CNVs ≤ 10 Mb; CF (CFTR), sickle cell disease and beta-thalassemia (HBB), alpha-thalassemia (HBA1 and HBA2), and SMA (SMN1).

At present, there is insufficient evidence to recommend routine screening for CNV's other than 22q11.2 deletions [46].

A conditional ACMG recommendation indicates that most pregnant persons would request 22q11.2 deletion screening, if offered combined aneuploidy and limited deletion screening, in the pre-screening discussion (benefits and limitations), using a shared decision-making process. A prospective cohort of 18,289 pregnancies with

Table 4: A Total Newborn Screening (NBS) Disease Consensus	**Proposed by: US HHS; Canada (BC; Alberta; Ontario) [39-43]**			
Underlined hemoglobinopathies, endocrine, and otherhave fetal treatment or management consensus.	Underlined metabolic and lysosomal conditions have significant Neonatal Treatment scores > 8.5.			
Hemoglobin, Endocrine and management Other Commonly Screened Conditions	**Primary and Secondary Metabolic Conditions Recommended for NBS**			**Lysosomal Storage Disease / Conditions Recommended for**
	Metabolic	**Metabolic**	**Metabolic**	
Hemoglobin	**Organic Acid Primary**	**Fatty Acid Oxidation Primary**	**Amnio Acid Primary**	**Sphingolipidosis**
Sickle cell anemia *Sickle-Beta thalassemia* *Alpha-Beta thalassemia* *Other Hemoglobinopathies*	Propionic acidemia Methylmalonic acidemia (MMCoA mutase) Methylmalonic acidemia (cobalamin) Isovaleric acidemia	Carnitine uptake defect / carnitine transport defect Medium chain acyl CoA dehydrogenase deficiency Very long chain acyl CoA dehydrogenase deficiency Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency	Argininosuccinic aciduria Citrullinemia type I Maple syrup urine disease Homocystinuria	GM2 gangliosidosis: Type A Tay-Sachs Type O Sandhoff Type AB GM2 activator def Niemann-Pick disease (A, B, C) Gaucherdisease 1, 2, 3 Fabry disease

Table 4: Continued

	3-methylcronoyl-CoA carboxylase deficiency 3-Hydroxy-3-methylglutaric aciduria Holocarboxylase synthase deficiency B-Ketothiolase deficiency Glutaric acidemia type I	Trifunctional protein deficiency	PKU Tyrosinemia type I Guanidinoacetate methyltransferase deficiency	(classic / late-onset) Metachromatic Leukodystrophy Krabbedisease (Globoid leukodystrophy) GM! gangliosidosis 1, 2, 3 Multiple sulfatase deficiency **Oligosaccharidosis** Alfa mannosidosis Schindler Aspartylglucosaminuria Fucosidosis
Endocrine	**Secondary**	**Secondary**	**Secondary**	**Mucopolysaccharidosis**
Primary Hypothyroidism *Congenital Adrenal Hyperplasia*	MMA i homocystinuria Malonic acidemia	Short chain acyl-CoA dehydrogenase deficiency Medium chain L3 hydroxyacyl CoA dehydrogenase deficiency	*Argininaemia* Citrullinemia type II	Hurler (MPS I) Scheie Hurler-Scheie

Table 4: Continued

Other				Hunter (MPS II)
Biliary Atresia	Isobutyrylglycinuria	Glutaric acidemia type II	Hypermethioninemia	Sanfiippo A, B, C, D (MPS III)
Hearing Screen	2-Methyl Butyrylglycinuria	Medium chain ketoacyl CoA thiolase deficiency	Benign hyperphenylalaninemia	Morquio A, B (MPS IV)
Critical Congenital Heart disease	3-Methylglutaconic aciduria	2,4 Dienoyl CoA reductase deficiency	Biopterin defect in cofactor biosynthesis	Maroteaux-Lamy (MPS VI)
Cystic Fibrosis	2-Methyl 3-hydroxybutyric aciduria	*Carnitine palmitoyl transferase type I deficiency*	Biopterin defect in cofactor regeneration	Sly (MPS VII)
Spinal Muscular Atrophy		*Carnitine palmitoyl transferase type II deficiency*	Tyrosinemia type II	
Severe Combined Immuno-Deficiency		*Carnitine acylcarnitine translocase deficiency*	Tyrosinemia type III	
Biotinidase deficiency				
XL-adreno–leukodystrophy				
Classic Galactosemia				
	Other			

Table 4: Continued

	Galactoepimerase deficiency Galactokinase deficiency T-cell related-lymphocyte deficiency			**Neuronal ceroid lipofuscinosis** Lipofuscinosis CLN 1-14 (Batten Disease CLN 2) **Sialic acid disorders** Galactosialidosis Infantile sialic acid Storage Salla Sialuria **Mucolipidosis** Mucolipidosis I-IV
				Miscellaneous
				Lysosomal acid lipase deficiency Pompe disease (Glycogen storage type II) Danon disease Cystinosis

Table 4: Newborn Screening Recommendations for Genetic Screening Conditions (Secretary of the Health and Human Services (USA) and Canadian Provincial Recommendations from BC, Alberta, and Ontario).

complete genetic follow-up, reported a detection of 10 of 12 cases with 22q11.2 deletion. Using a risk cutoff of 1 in 100, there were 19 screen-positive cases giving a FPR of 0.05%. The PPV was 52.6% with 11of 12 subjects having had first trimester testing. The prevalence of 22q11.2 deletion was likely higher in this screened population than the general pregnancy population, as this cohort included pregnancies that were later identified to have structural fetal anomalies [71].

There is insufficient evidence to recommend or not to recommend NIPS technology for the identification of fetal/placental rare autosomal trisomy's (RAT)[46].

Neonate counselling and screening opportunity for newborn genetic screening

Newborn metabolic screening (NBS) is designed to test infants shortly after their birth for disorders, before they become symptomatic, but that cause disability or death [80, 81]. The lack of parental knowledge, prior to birth, about postnatal newborn screening process (mandated or not) is an important issue that needs to be considered during perinatal genetic screening discussion.

New clinical opportunities for NBS, directed to potential neonatal treatment, have been evaluated, using an algorithm with a weight-based score for the inherited metabolic disorders (IDM) inclusion (objectively evaluated; prioritized process) in the European NBS programs. [82].

This innovative NBS consideration has re-purposed the ten Wilson and Junger screening principles related to the genetic metabolic condition for screening, treatment or other [12, 82]. Three of the four categories contained principles that were clinical and measurable: condition, screening, and treatment. The fourth category, other, contained screening principles that were related to economic, societal, or political aspects of screening programs, as these factors were not measurable, this category were removed. Three pillars were considered: **Pillar 1 Condition** (severity / onset / frequency); **Pillar 2 Screening** (availability / performance); **Pillar 3 Treatment** (availability / outcomes).

This novel NBS evaluation algorithm has been used to assess and prioritize inherited metabolic disease (IMDs). Forty-eight IMDs (including 21 lysosomal storage disorders) were identified and assessed using this novel NBS algorithm. Thirty-five disorders were found to strongly support the Wilson - Junger screening principles. An improved communication strategy for parents was required prior to implementation, regarding the results from the NBS dried blood spot testing[6, 82-84]. Table 5 summarizes the IMDs recommendations and their treatment potential {6, 28, 29, 39-45, 57-60, 80].

An Effective Neonatal Therapy is required for NBS Conditions

An better understanding of the expanded IMD screening list used at birth (or following pre- or post-conception screening recognition) may have the potential to reduce the time to diagnosis and to improve the psychological impact on families and patients. This type of NBS approach could increase the neonatal identification and subsequently increase the opportunity for natural history knowledge, disease frequency, and genotype/phenotype correlations for new treatment options [6, 85] (Table 4[39-43]).

It is important to understand the three pillars impact on the NBS evaluation algorithm for the 35 top-ranked disorders (treatment score ≥8.5 points). For the **Condition pillar**, all 35 top-ranked disorders have a rapidly progressing form and all but one disorder, PKU, can be fatal by adolescence. For the **Screening pillar**, 33 /35 have a NBS test available and in use, and for these 33 NBS conditions, 25 have a 'low false-positive rate or a high PPV'. For the **Treatment pillar**, 97% (34/35 disorders) have a treatment strategy available, as14/34 disorders have European Medicines Agency approved treatments and 20/34 disorders have an evidenced-based treatment intervention (diet, hematopoietic stem cell transplantation, bone marrow transplant).

One disorder, Niemann Pick A/B (ASM deficiency), has a treatment for late-stage development. Importantly, 60% (21/35) of the top-ranked disorders have a treatment strategy available that changes the prognosis for all forms of the disorder (mild to severe). Alternatively, none of the 13 lower ranked disorders (treatment score < 8.5) have a treatment strategy available that changes the prognosis for all forms of the disorder.

Considering all three pillars, 54% (19/35 disorders), will meet the following three criteria: (1) "all forms of the disorder are asymptomatic for the first weeks of life"; (2) have a "NBS test available and in use"; and (3) have a treatment strategy where "pre-symptomatic initiation results in better outcomes"[6].

Additional non-metabolic/lysosomal genetic conditions, with new and effective therapies, have been added to the NBS 'traditional algorithm' of metabolic and lysosomal NBS conditions (Table 6 [1-3, 28, 29, 39-45, 57-60):

- Spinal Muscular Atrophy (SMA), autosomal recessive diseases; SMN 1 gene deletion; pan-ethnic condition; carrier frequency is close to one in 50 [86, 87].
- Cystic Fibrosis (CF), autosomal recessive; pan-ethnic; carrier frequency is one in 20 [2, 78, 88, 89].
- Duchenne Muscular Dystrophy (DMD), X-linked; pan-ethnic; carrier frequency is one in 813 females.[90-92].
- microdeletion 22q11.2, common human microdeletion syndrome with an incidence of 1/3,000 to 1/6,000; an estimated 10% are inherited [80, 93, 94].
- screening for early identification of pediatric conditions such as hypothyroidism, congenital adrenal hyperplasia, critical congenital heart malformations, genetic hearing loss, and biliary atresia is required.

The 'Pro-Factors' fora Pan-ethnic Genetic Carrier Screening Approach

Johansen Taber et al. evaluated carrier frequencies for 176 conditions (using well-defined phenotype with at least one severity criteria) in > 460,000 individuals across 11 racial / ethnicities [26[. Forty conditions had carrier

Table 5: Fetal-Neonatal Plan.

The Gestational Timing Potential for Neonatal Genetic and Metabolic Treatment Prediction Option **Newborn Diagnostic Screening from Dried Blood Spots** [6, 80]		[28, 29]	[44, 45, 57-60]	[39-43]
NEW INNOVATION IMD NBS Evaluation *Condition / Screening / Treatment Ranking*		*Preconception Condition Screen Panel* *64 113*	*Post Conception Genetic Screen*	*Postnatal Generic Screen*
New Objective Approach with a Condition Treatment Score ***Score: 6 3 4 = 13*** **Pillar 1 Condition Pillar 2 Screening Pillar 3 Treatment** Severity Availability Availability Onset Performance Performance Frequency	**Postnatal Therapy Success Ranking Score (0-13)**	[Table 1]	Genetic carrier screening for conditions (focused or pan-ethnic) [Table 5]	Genetic carrier screening for metabolic and lysosomal conditions [Table 4]
Therapy Scores of >/= 8.5 are considered for screening as the treatment options are considered with best impact / result				Recommended X-primary S-secondary
Carnitine uptake defect/carnitine transport defect (CUD)	12.5	X		X
Severe combined immunodeficiency (SCID)	12			X
Glutaric aciduria type 1 (GA1)	11.5			X
Homocystinuria (HCU)	11.5			X
Phenylketonuria (PKU)	11.5	X		X
Tyrosinemia, type 1 (TYR 1)	11.5	X		X
Classic galactosaemia (GALT)	11	X		X
3-Hydroxy-3-methyglutaric aciduria (HMG)	11			X

Table 5: Continued

Pompe disease (GSD type II)	11	X	X		X
X-linked adrenoleukodystrophy (X-ALD)	10.5	X	X		X
Argininosuccinic aciduria (ASA)	10.5		X		X
Carnitine palmitoyltransferase, type I deficiency (CPT I)	10.5				S
Long-chain 3 hydroxyacyl-CoA dehydrogenase deficiency (LCHAD)	10.5				X
Methylmalonic acidaemia (cobalamin disorders, Cbl A, B)	10.5	X	X		X
Metachromatic leukodystrophy (MLD; lysosomal arylsulfatase A deficiency)	10.5		X		
Mucopolysaccharidosis, type I (MPS I)	10.5				X
Propionic acidaemia (PROP)	10.5				X
Biotinidase deficiency (BIOT)	10.5		X		X
Medium-chain acyl-CoA dehydrogenase deficiency (MCADD)	10		X		X
3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)	10		X		X
Citrullinemia, type I (CIT)	10				X
Holocarboxylase synthetase deficiency (MC**D)**	10				X
Krabbe disease (leukodystrophy galactosylceramidase)	10	X			
Argininaemia (ARG)	9.5				S
Carnitine acylcarnitine translocase deficiency (CACT)	9.5				S
Very long-chain acyl-CoA dehydrogenase deficiency (VLCAD)	9.5		X		X
Maple syrup urine disease (MSUD)	9	X	X		X
Methylmalonic acidaemia (methylmalonyl-CoA mutase) (MUT)	9		X		X
Carnitine palmitoyltransferase type II deficiency (CPT II)	9	X	X		S
Batten disease (CLN2; tripeptidyl peptidase I)	9				
Niemann Pick A/B (acid sphingomyelinase deficiency)	9	X	X		
Isovaleric acidaemia (IVA)	8.5				X

Table 5: Continued

Trifunctional protein deficiency (TFP)	8.5			X
Gaucher disease (lysosomal glucocerebrosidase)	8.5	X X		
Lysosomal acid lipase deficiency (LAL-D/Wolman/CESD)	8.5			
Multiple acyl-CoA dehydrogenase deficiency (MADD)	8			X -short chain
MPS VI (Maroteaux-Lamy syndrome)	8			
Alpha-mannosidosis	7.5			
Fabry disease	7.5	X X		
MPS II (Hunter syndrome)	7	X		X
MPS III (Sanfilippo syndrome)	6.5			
Niemann-Pick type C disease	6.5			
MPS IV (Morquio syndrome)	5.5			
Sandhoff disease (GM2 gangliosidosis, type II)	5.5			
Farber disease	5			
Tay-Sachs disease (GM2 gangliosidosis, type I)	4.5	X X		
MPS VII (Sly syndrome)	3.5			
MPS IX (hyaluronidase deficiency)	1			

frequencies >/= 1/100 and 75 conditions had carrier frequencies of >/= 1/200. Evidence-based analyses of condition 'inclusion' criteria resulted in consistent panels of 37 conditions (conservative carrier thresholds >/= 1 in 100) and 74 conditions (permissive carrier thresholds >/= 1 in 200). A preconception screening modeling tool was used with> 60,000 private insurance patients, who were provided with the informed estimates of the disease incidence, was used to compare a screening model using a minimal number of screened conditions to a 176-condition ESC panel[31]. Although this modelled population is non-generalizable, the preconception ECS approach was predicted to reduce the burden of Mendelian disease in a cost-effective manner compared to the traditional targeted screening approach.

Kauffman et al. [95] evaluated the impact on healthcare utilization following the use of ECS in people who were not found to be at an increased reproductive risk. Specifically, the RCT found no significant differences in outpatient mental health service use between the study arms for the period between randomization and results disclosure or in the year following randomization. Overall, the results provide reassurance that the ECS approach does not result in unnecessary health care utilization, nor does it result in an avoidance of recommended care because of false reassurance.

The 'Con-Factors' for a Pan-ethnic Genetic Carrier Screening Approach

People, who self-identify with a specific race/ ethnicity, may be at odds with their genetically defined ancestry, which would have relevance to genetic carrier screening**.** Studies have demonstrated that relying on self-identification of AJ ancestry, as the criteria to screen for conditions common in the AJ population, was found to be imperfect (Table 2 [1-3, 32-35]).

Reiner et al. [96] reported that possibly 1% of ECS individuals will have findings that require additional clinical evaluation or surveillance (such as female carriers of FMR1 premutation alleles; female heterozygotes with pathogenic DMD variants; heterozygotes with pathogenic somatic malignancies that may confer an increased risk).

Gbur et al. [10] reported on a cohort, using an ECS model for 176 conditions and identified 124 positive carriers with associated personal health implications (only 28 of the carriers were aware of their carrier risk).The other 96 carriers (1.56% of the 6147 screened individuals) had no knowledge of a family history for the identified condition. Additional issues indicated that people were frequently not counseled before or after the screening process regarding their heterozygote carrier status or the associated healthcare risk (cancer, cardiac, renal, myopathy; ophthalmologic; inflammatory; neurologic).

Reproductive care providers have expressed concern in offering pan-ethnic ECS to all patients as they expressed 'time related' obstacles with providing the required pre-test education, ECS results disclosure and then follow-up[20, 29, 97, 98].

There is a societal impact with two potential **positive implications** by reducing ethnic stigmatization in ancestry-based offers and increasing equity. There are three potential **negative implications** by reinforcing the disability-based stigmatization; less expertise in the clinical, research, and healthcare management for the condition; and a greater societal pressure to utilize genetic screening. The empirical evidence, for all these implications, is limited but possible [22].

DISCUSSION

The purpose of this perinatal genetic carrier screening review is to propose an integration of the three separate 'gestational' screening models (pre-post conception - neonatal) into a 'continuum' using a practical, educational, and counselling-informed consent process.

While the 'focused' preconception and pan-ethnic ECS could provide autonomy, more equity for access, an optimization for reproductive decision-making, and knowledge transfer opportunities for the reproductive providers, there are the concerns of patient carrier 'distress', and personal expense. A newly focused approach using the neonatal therapy based weighted-treatment scores (objective; prioritized) could create be a new knowledge transfer and informed consent process for pan-ethnic NBS use (as legally required in many jurisdictions).The clinical utility for pan-ethnic ECS has been evaluated by SRM/MA and reported that the increase in the number of screened conditions (98-176) may lead to a statistically significant decrease in the rates of fetal prenatal diagnosis and termination but not for IVF and PGT use [99].

The routine post conception fetal screening (aneuploidy, CNV, and fetal structural anomalies) would continue with appropriate diagnostic testing as required (cell-free placental DNA or CVS or amniocentesis for specific genetic or 'at risk' etiologies; gametic de-novo mutations; non-genetic infectious or teratogenic screening; additional imaging for specific organ-based anomalies). Additional diagnostic fetal syndromic genomic testing could be initiated for couples with AR or XL reproductive risks that had not utilized post-conception blastocyst PGT-M screening. The use of pan-ethnic ECS post-conception will likely be required but will create ethical and diagnostic stress.

The focused / consensus-based NBS conditions could be better identified by using the pan ethnic or 'targeted' pre or post conception ECS panels.

The genetic-metabolic list of neonatal conditions with high treatment scores (> 8.5 with a max score of 13) identifies 35 conditions from a total of 48 conditions but is incompletely covered by most USA- Canadian Provincial 'generic' NBS panels (28/35 or 30/48 for all treatment scores), ACMG (19/35) or Goldberg (12/35) [28, 29]. These screening gaps are generally related to metabolic /enzyme deficiency conditions with possibly later onset conditions than the usual NBS conditions which are identifiable at birth.

The Proposed Integrated Fetal-Neonatal Genetic Screening Pathway

The routine maternal obstetrical screening elements are is not part of this new genetic screening pathway as these standard obstetrical screening elements would add to the educational complexity for maternal pregnancy-related screening. Consensus from four international preconception and prenatal evidence-based guidance consensus documents would routinely offer 21 specific gestational age reproductive risk screening elements(three preconception; nine first trimester; three second trimester; four third trimester; one intrapartum; and one postpartum) [100].

Table 6: Patient Genetic Carrier Pathway Screening Elements				
Maternal-Fetal Well Being Only	***Parental Genetic Carrier Screening[1, 28, 29]*** ***Pan-ethic Expanded Carrier Approach*** ***Parental Pre- or Post Conception***	***ParentalGenetic Carrier Screening [1-3]*** ***Focused-Ethnic Parental Carrier Screening*** ***Parental Pre- or Post Conception***	***Routine Fetal Aneuploidy Screening and Maternal-Fetal Well Being Only*** ***OR*** ***Enhanced Fetal Option*** ***OR*** ***Combined with Parental – Fetal or Fetal-NeonatalPost Conception Options [44-46, 57-60]***	***Newborn Diagnostic Screening combined with Pre- and Post Conception Options[39-43]*** ***Option by Neonatal Treatment Score>/= 8.5 or as recommended NBS by US HHS and Canada (BC; Alberta; Ontario)***
Ultrasound surveillance with pregnancy dating, fetal congenital anomalies screening, and fetal growth surveillance as required	**64-113 Genetic Carrier Conditions**(Table 1) Number of Conditions with the Carrier frequency (CF) for each panel: **Goldberg** 64 (CF) 1-100 52 100-5000 12 **ACMG** 113	**12 conditions** **Ethnic-Religious-Founder Effect Carrier Screening** **SOGC [1]** **X-Linked risk:** Fragile -X FH Hemophilia A (FVIII) Hemophilia B	**Routine Placental analyte Screening +/- NT or Fetal Placental cell-free DNA And Fetal Imaging** **Enhanced option for 10-13 conditions plus malformation identification by ultrasound screening**	**Neonatal Treatment Option** **Full condition name in Table 5** **Condition Treatment Score** **CUD 12.5** **SCID** **GA1 11.5** **PKU** **TYR 1** **GALT 11.0** **HMG**

Table 6. Continued

	(CF) 1-100 38 100-200 48 X-L 16 Required 11 **Expanded AJ Panel:** 13 AR conditions[1] Bloom Fanconi anemia group C Niemann-Pick type A Mucolipidosis type IV Gaucher Glycogen storage disease type 1a Familial hyperinsulinism Maple syrup urine Dihydrolipoamide Dehydrogenase Deficiency Usher Nemaline myopathy Joubert Walker Warburg	(FIX) Duchenne/Becker Muscular Dystrophy **AR risk** *Hemoglobinopathy*: Thalassemia: Alpha / Beta Sickle Cell Cystic Fibrosis ***A J Routine*:** Cystic Fibrosis Tay-Sachs Familial Dysautonomia Canavan ***Canadian Founder populations*:** areas of Quebec; Indigenous Cree; Amish; Mennonite; Hutterite	maternal serum / plasma at >11 weeks gestational age using placental analytes +/- NT or cell-free placental DNA **Aneuploidy** Trisomy 21, 18, 13 **Sex Chromosome** XO, XXX, XXY, XYY **Deletion-Duplication (3]** 22q 2.11 **Other non-recommended ACMG NIPS screening**: Tri-ploidy **Additional microdeletion syndromes**: 1p36 deletion Angelman Prader-Willi Cri-du-Chat	**GSD type II** **X-ALD 10.5** **ASA** **CPT I** **LCHAD** **Cobalamin A, B** **MLD** **MPS I** **PROP** **BIOT** **MCADD 10.0** **3MCC** **CIT** **MCD** **Krabbe** **ARG 9.5** **CACT** **VLCAD** **MSUD 9.0** **MUT** **CPT II** **Batten** **Niemann Pick A/B** **IVA 8.5** **TFP** **Gaucher** **LAL-D**

Table 6. Continued

		ACOG [2, 3]: carrier screening for cystic fibrosis and spinal muscular atrophy, Fragile-X; Tay-Sachs as well as a complete blood count and screening for thalassemia and hemoglobinopathies **Addition Risk Consideration**: Carrier of a balanced chromosomal re-arrangement with risk for fetal 'unbalanced' genomic result.	**Fetal Imaging** **First trimester CRL for dating and early anatomy** **Fetal Diagnostic Etiology Panels** if congenital anomalies / requires amniocentesis or chorionic villus sampling.	**Recommended NBS by US HHS and Canada (BC; Alberta; Ontario)** **Full condition names in Table 4** Non-Metabolic Conditions Metabolic Conditions (Organic Acid; Fatty Acid Oxidation; amnio Acid) Lysosomal StorageConditions(Sphingolipidosis; Mucopolysaccharidosis; Neuronal Ceroid Lipofuscinosis; Miscellaneous)

Tables 6 [1-3, 28, 29, 39-45, 57-60] combines the three 'perinatal' genetic screening pathways (preconception- post conception – neonatal) to propose an evidenced-based sequential/integrated counselling process for persons or couples planning a pregnancy or who present with an unexpected fetal genetic pathology presentation.

A Starting Point – Preferably the preconception period is used to determine the patient or couple's primary clinical care genetic screening plan (or philosophy) related to their reproductive autonomy and with a shared-decision process. The options are summarized as Maternal-Fetal-Neonatal Genetic Screening Pathway 1-5:

1. Pathway 1- Most Limited option with maternal-fetal well-being ultrasounds only (dating 10-11 weeks; fetal anatomy 16-20 weeks of gestation but optional early imaging 11-14 weeks if expertise is available ; fetal growth at 28-34 weeks of gestation).
2. Pathway 2 - Routine Fetal Screening option for fetal aneuploidy (trisomy 21, 18, 13) and congenital anomalies (genetic or non-genetic) only plus Pathway 1.
3. Pathway 3 - Enhanced Fetal Genetic Screening beyond aneuploidy for 4-13 genetic fetal conditions plus Pathway 1-2 (Table 6).
4. Parental -Fetal Plan is to use a preventive genetic carrier screening paradigm approach using screening in either the preconception (preferred) or post-conception period (Table 6).
5. Fetal-Neonatal Plan is to use a neonatal treatment directed paradigm approach regardless of the gestational time of carrier testing (preconception, post conception or neonatal period) (Table 6).

Proposed Enhanced Fetal, Parental- Fetal or Fetal-Neonate Carrier Screening Pathways

Enhanced Fetal Plan(this option removes any IVF pre-implantation options)

Post conception enhanced prenatal screening for

chromosomal (21, 18, 13, sex chromosomes), chromosomal copy number variants, common chromosomal deletion syndromes (22q.2.11, 1p36, Angelman, Prader-Willi, Cri-du-chat), triploidy, and congenital anomaly(ies) can be evaluated by cell free serum DNA screening technology after 10-11 weeks of gestational age with diagnostic testing for screen positive results.

- Within the present **enhanced fetal decision process**, the *common* fetal conditions *screened* for, are generally not 'genetic carrier risk' conditions but are parental sex and age related 'de novo' non-disjunction chromosomal (pregnant person) or autosomal dominant (reproductive sperm donor) outcomes which cannot be accurately predicted but require patient choice for the directed prenatal screening and detection process.
- Another fetal outcome risk results from couples where one member of the couple has a balanced chromosomal re-arrangement that increasing the risk for miscarriage or an unbalanced genome outcome causing congenial anomaly or development concerns. The gamete (egg or sperm) outcome is based on the chromosomes that are involved in the translocation and the meiotic chromosome pairing and segregation.
- Pregnant person / couple plan and access for unplanned or requiring additional urgent obstetrical and / or genetic assessment will need to be available by any healthcare delivery service offering an enhanced perinatal genetic carrier care model or fetal therapy program.

Parental-Fetal Plan Genetic Carrier Identification considerations:

- The new 'genetic carrier screening' collaborative process will require new research, health policy, and healthcare teams / liaisons using shared decision-making communication tools.
- Personal or couple carrier screening should be strongly emphasized or supported for patient ages 20-30 years of age or younger, based on their personal reproductive need and planning.
- A pre-conception genetic carrier screening goal of >75% for persons or couples to understand their genetic carrier risk status, prior to conception, could be a new reproductive KPI measurement (health service recognition; screening test cost inclusion; continuing technology improvement).
- **KEY:** The ethics and options for reproductive autonomy start with the pan-ethnic preconception carrier screening panel option (this 'proof of principle' patient discussion requires that both members of the couple are screened and use panels with > 175 conditions). The number of genetic conditions in the preconception screening panel (primary patient-centered decision) will impact both, the pretest 'choice and number of conditions' for the educational counselling process (provider and health system time impact) and the understanding of the 'residual genetic risk' (couple secondary decision impact) possibly identified during pregnancy and / or during mandated neonatal testing.
- ***KEY:*** *Following the personal / couple preconception risk determination,* patient education can be initiated for the preconception, post conception informed options / reproductive planning, with an additional 'present and regularly updated' neonatal outcome and treatment options communication.
- **KEY:** The availability of health care funding (public or private) for the genetic carrier screening education, screening panel cost, and the use and cost of assisted reproductive technology for PGT-M (if required), would impact the preconception carrier option. The attitudes and comments, from parents with affected children and the 'mutation positive' couple carriers, are both, ethically and clinically important for this primary prevention choice and option implementation.

- A clear, evidenced-based, designated list for the perinatal screened fetal-neonatal conditions with quality neonatal treatment options or without quality / adequate treatment options (creating a palliative option) that could be used through the perinatal screening options for counselling, KT, and decision-making.

Fetal-Neonatal Plan Treatment Paradigm considerations:(this option removes any IVF pre-implantation options)

- **KEY:** The ethics and options for reproductive autonomy start with the preconception carrier screening panel option (this 'proof of principle' patient discussion requires that both members of the couple are screened). The number of genetic conditions in the post conception screening panel (primary patient-centered decision) will impact both, the pretest 'choice and number of conditions' for the educational counselling process (provider and health system time impact) and the understanding of the 'residual genetic risk' (couple secondary decision impact) possibly identified during pregnancy and / or during mandated neonatal testing.

- A clear evidenced-based list for those perinatal diagnosed fetal-neonatal conditions with effective neonatal treatment options or without effective / adequate treatment options (creating a palliative option) is required for use through the perinatal screening choices for counselling, KT, and decision-making.

- **KEY:** The opportunity for patient autonomy in a **secondary decision process** occurs for either a post conception (no PGT-M testing) or post conception (no preconception screening) 'genetic at risk' couple with fetal anomalies (genomic or chromosomal). The requirement for post conception counselling related to undergoing an invasive diagnostic testing (chorionic villus sampling; amniocentesis; cordocentesis; using deep-

- focused NGS) with the small but additional procedure related risk for pregnancy loss.

- The neonatal metabolic or lysosomal storage 'treatment' score could be an important factor for a couple's choice when considering the neonatal treatment success or pregnancy termination. Both these choices carry significant 'emotional and medical' cost based on the couple's spontaneous recurrence risks of 25% for autosomal recessive conditions and 50% of males for X-linked conditions.
- A post-conception secondary decision in a genetically positive 'potentially viable live born' fetus will require discussion related to an option for termination of pregnancy or early induction of labor for vaginal birth and very preterm palliative NICU care. These fetal-neonatal reproductive options have significant personal emotional and health system costs.
- **KEY:** The knowledge and understanding of the success of **primary neonatal genetic treatment**/ 'quality of life' outcome (reduced morbidity or cure) for the 'at risk' couple will require complex counselling and decision. The present ECS panels are not adequate for the best risk identification or the minimization of the personal genetic residual risk. More technology, research and knowledge translation is required but must be implemented over the next few years.
- *Neonatal genetic screening* should be offered or considered(regardless of pre or post conception patient screening status), based on the appropriately screened 'early or later onset' genetic conditions with 'scored treatment' options (success; innovation; QOL criteria; ethical standards), with continued innovation, evidenced-based and annual review.

Diagnostic post conception genetic screening and testing

The post conception screening would utilize the results from genetic carrier screening, early 11-14 weeks of gestation ultrasound anatomy imaging, and non-invasive cell-free maternal serum DNA analysis / sequencing > 11 weeks of gestation to determine those pregnancies that would be offered diagnostic fetal testing. Diagnostic fetal testing techniques would include invasive CVS (> 10 weeks of gestation), amniocentesis (> 16 weeks of gestation), cordocentesis (>18 weeks of gestation), and for specific genetic conditions deep- Next Generation Sequencing using non-invasive cell-free maternal serum DNA. The risk-benefit counselling is required for informed consent.

Delivery plan, pregnant person and fetal antenatal care, delivery location and postnatal management determined for a 'known / affected' fetal-neonatal (genetic or congenital anomaly) needs to be discussed and planned, using informed and shared decision-making practices.

The obstetric management and delivery planning for an affected fetus will require more coordinated planning and delivery location in a specific neonatal care center. The 'real' perinatal prevalence and service need for this clinical scenario will need to be determined. These new neonatal services could potentially be supported through the fetal therapy congenital anomaly centers with their collaborative children hospital support services.

Health equity in prenatal diagnosis and therapy requires every person has access to quality prenatal care and utilization of genetic knowledge in support of quality of life and health potential of children and their families. No one should be disadvantaged from achieving this potential because of their identity, geographic location, and social circumstance. As preconception genetic carrier to neonatal genetic testing is becoming more frequently used and accessible, it is the responsibility of healthcare leadership to bring awareness and address factors leading to bias and health inequity [101, 102].

CONCLUSION

1. A new 'genetic carrier screening' process will require collaborative healthcare teams / liaisons to use shared decision-making communication tools.
2. The use of screening panels with > /= 176 conditions and an evidenced-based list for perinatal screened fetal-neonatal conditions with quality neonatal treatment options or without quality / adequate treatment options (creating a palliative option) is available for counselling, KT, and decision-making.
3. Personal or couple carrier screening should be emphasized for ages 20-30 years of age or younger, based on personal reproductive need and plan.
4. A pre-conception genetic carrier screening KPI of >75% for reproductive couples to be aware of their genetic carrier risk status, prior to conception. This KPI could be enhanced with health service recognition and test cost inclusion along.
5. *Prior to preconception (or early post conception)risk determination and* patient education should be initiated to determine a personal genetic carrier screening philosophy and process: maternal-fetal well-being ultrasound only; fetal aneuploidy and congenital anomalies with maternal-fetal well-being; fetal carrier status only added; parental-fetal carrier status (prevention); fetal-neonatal carrier status (neonatal treatment).
6. *Based on the patient's personal reproductive genetic carrier screening plan:*

- *post conception routine prenatal screening and diagnostic* processes for chromosomal CNV variants, AR and X-linked risk screening / diagnosis, and congenital anomaly(ies) can be arranged after 10 weeks of gestational age. Fetal testing can be continued or augmented as necessary for any of the five genetic screening pathways (maternal-fetal well-being only; fetal aneuploidy and congenital anomalies; enhanced fetal genetic screening; parental -fetal screening; fetal-neonatal screening).

- *neonatal genetic screening* could be offered(regardless of pre or post conception patient screening status), based on the appropriately screened 'early or later onset 'genetic conditions with' scored treatment' options(success; innovation; QOL criteria; ethical standards), and will continue to be innovative, evidenced-based and annually reviewed.
7. *Delivery plan, location determined, and postnatal management* for a 'known / affected' fetal-neonatal (genetic or congenital anomaly) should be planned, using informed and shared decision making.
8. Any healthcare service offering an enhanced perinatal genetic carrier care model or fetal therapy program require pregnant person planning and access for unplanned or urgent obstetrical and genetic assessment.

Acknowledgement for Canadian Indigenous reconciliation as this work was undertaken on the traditional, ancestral, and unceded territory of Alberta on Treaty 6-8, the 8 Metis Settlements, and the Metis Nation and for British Columbia the BC Coast Salish, Squamish, and Musqueam Territories.

REFERENCES

1. Wilson RD, De Bie I, Armour CM, Brown RN, et al. Joint SOGC-CCMG Opinion for Reproductive Genetic Carrier Screening: An Update for All Canadian Providers of Maternity and Reproductive Healthcare in the Era of Direct-to-Consumer Testing J Obstet Gynaecol Can 2016; 38:742-762.
2. ACOG Committee Opinion Carrier Screening for Genetic Conditions. Obstet Gynecol 2017; 129: e41-55; (reaffirmed 2020) Committee: Rink B, Romero S, Biggio JR, Saller DN, Giardine R.
3. ACOG Committee Opinion No. 690. Carrier screening in the age of genomic medicine. Obstet. Gynecol. 2017; 129: e35–e40; (reaffirmed 2020) Committee: Romero S, Rink B, Biggio JR, Saller DN.
4. Zhang T, Madeira J, Sun Y, Mertes H, Pennings G, Lindheim SR. Expanded Preconception Carrier Screening in Clinical Practice: Review of Technology, Guidelines, Implementation Challenges, and Ethical Quandaries. Clin Obstet Gynecol 2019; 62: 217-227.
5. Dalatycki MB, Laing N, Kirk E. Expanded reproductive carrier screening – how can we do the most-good and cause the least harm? Euro J Hum Genet.2019; 27: 669-670: https://doi.org/10.1038/s41431-019-0356-y
6. Burlina A, Jones SA, Chakrapani A, Church HJ, Heales S, Wu THY, et al. A New Approach to Objectively Evaluate Inherited Metabolic Diseases for Inclusion on Newborn Screening Programmes. Int. J. Neonatal Screen. 2022; 8: 25: https://doi.org/ 10.3390/ijns8020025
7. Cooper S, Cant R, Kelley M, Levett-Jones T, McKenna L, Seaton P, Bogossian F. An Evidenced-Based Checklist of Improving Scoping Review Quality. Clinical Nursing Research 2021; 30(3): 230-240; DOI 10.1177/1054773819846024
8. Tulandi T, Suarthana E. Narrative Reviews, Systematic Reviews, and Scoping Reviews. J Obstet Gynecol Can 2021; 43(12): 1355- 1356; https://doi.org/10.1016/j.jogc.2021.08.002
9. Braverman G, Shapiro ZE, Bernstein JA. Ethical Issues in Contemporary Clinical Genetics Mayo Clin Proc Inn Qual Out. 2018; 2:81-90; https://doi.org/10.1016/j.mayocpiqo.2018.03.005
10. Gbur S, Mauney L, Gray KJ, Wilkins- Haug L, Guseh S. Counseling for personal health implications identified during reproductive genetic carrier screening. Prenat Diagn. 2021; 41:1460-1466; doi:10.1002/pd.6033.
11. Grody WW, et al. ACMG position statement on prenatal/preconception expanded carrier screening. Genet. Med. 2013;15, 482–483.
12. Wilson JMG, Jungner G. Principles and Practice of Screening for Disease. (World Health Organization, Geneva, 1968).
13. Ram KT, Klugman SD. Best practices: antenatal screening for common genetic conditions other than aneuploidy. Curr. Opin. Obstet. Gynecol. 2010; 22, 139–145.
14. Delatychi MB, Alkuraya F, Archibald A, Castellani C, Cornel M, Grody WW, et al. International perspectives on the implementation of reproductive carrier screening. Prenat Diagn 2019; 1-10; doi: 10.1002/pd.5611.
15. Heather JM, Chain B. The sequence of sequencers: the history of sequencing DNA. Genomics. 2016; 107, 1–8.
16. Gregg AR. Message from ACMG president: overcoming disparities. Genet. Med. 2020: 22, 1758.
17. Woudstra AJ, van den Heuvel LM, van Vliet-Lachotzki EH, Dondorp W, Lakeman P, Haverman L, et al. Views of patients and parents of children with genetic disorders on population-based expanded carrier screening. Prenat Diagn. 2022; 42:1201-1210; https://doi.org/10.1002/pd.6200.
18. Pereira N, Wood M, Luong E, Briggs A, Galloway M, Maxwell R, et al. Expanded genetic carrier screening in clinical practice: A current survey of patient impressions and attitudes. J Assisted Reprod Genet 2019; 36: 709–716; https://doi.org/10.1007/s10815-019-01414-z.
19. Brown EM, Grinzaid KA, Ali N, Mehta N, Hardy MW. Evaluating the experiences of individuals with personal health risks identified through expanded carrier screening. Journal of Genetic Counseling 2022; 31: 598–607; https://doi.org/10.1002/jgc4.1527.
20. Ramdaney A, Lichten L, Propst L, Mann C, Lazarin GA, Jones M, et al. Expanded carrier screening in the United States: A systematic evidence review exploring client and provider experiences. J Genet Couns 2022; 31,937–948; https://doi.org/10.1002/jgc4.1566.
21. Cannon J, Van Steijvoort E, Borry P, Chokoshvili D. How does carrier status for recessive disorders influence

reproductive decisions? A systematic review of the literature. Expert Review of Molecular Diagnostics. 2019; 19: 1117–1129; https://doi.org/10.1080/14737159.2020.1690456
22. van den Heuvel LM, van den Berg N, Janssens ACJW, Birnie E, Henneman L, Wybo J, et al. Societal implications of expanded universal carrier screening: a scoping review Euro J Hum Genet. 2023; 31:55–72; https://doi.org/10.1038/s41431-022-01178-8
23. Schuurmans J, Birnie E, Ranchor AV, Abbott KM, Fenwick A, Lucassen A, et al. GP=provided couple-based expanded preconception carrier screening in the Dutch general population: who accepts the test offer and why? Euro J Hum Genet. 2019; https://doi.org/10.1038/s41431-019-0516-0.
24. Blue Cross BlueShield Association. https://app.evidencestreet.com/(2021)
25. Ghossi CE, Goldber JD, Haque LS, Lazarin Ga, Wong KK. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. J Genet Couns. 2018; 27: 616-625.
26. Johansen Taber KA, Beauchamp KA, Kararin GA, Muzzey D, Arjunan A, Goldberg JD. Clinical utility of expanded carrier screening: results-guided actionability and outcomes. Genet Med 2019; 21: 1041-1129.
27. Deignan JL, et al. CFTR variant testing: a technical standard of the American College of Medical Genetics. Genet Med 2020; 22: 1288-1295.
28. Gregg AR, Aarabi M, Klugman S, Leach NT, Bashford MT, Goldwaser T, et al. Screening for autosomal recessive and X-linked conditions during pregnancy and preconception: a practice resource of the American College of Medical Genetics and Genomics (ACMG) Genet Med 2021; 23:1793–1806; https://doi.org/10.1038/s41436-021-01203-z.
29. Goldberg JD, Pierson S, Johansen Taber K. Expanded carrier screening: What conditions should we screen for? Prenat Diagn 2023; doi: 10.1002/pd.6306.
30. Johansen Taber K, Ben-Shachar R, Torres R, Arjunan A, Muzzey D, Kaseniit KE, Goldberg JD, Brown H. A guidelines-consistent carrier screening panel that supports equity across diverse populations. Genet Med 2022; 24, 201–213; doi: https://doi.org/10.1016/j.gim.2021.09.009.
31. Beauchamp KA, Johansen Taber KA, Muzzey D. Clinical impact and cost-effectiveness of a 176-condition expanded carrier screen. Genet Med 2019; 21:1948–1957; https://doi.org/10.1038/s41436- 019-0455-8.
32. Ziff M, Harris J. A collaborative genetic carrier screening model for the British Ashkenazi Jewish community. Journal of Comm Genet 2022; 13:133–135; https://doi.org/10.1007/s12687-021-00568-7.
33. Davidov B, Levon A, Volkov H, Orenstein N, Karo R, Gazit IF, et al. Pathogenic variant-based preconception carrier screening in the Israeli Jewish population. Clin Genet. 2022;101: 517-529; doi:10.1111/cge.14131.
34. Morganstern-Kaplan D, Raijman-Policar J, Majzner-Aronovich S, Aradhya S, Pineeda-Alvarez DE, Aquinaga M, et al. Carrier screening in the Mexican Jewish community using a pan-ethnic expanded carrier screening NGS panel. Genet Med 2022; 24: 821-830; https://doi.org/10.1016/j.gim.2021.11.019.
35. Dolitsky S, Mitra A, Khan S, Ashkinadze E, Sauer MV. Beyond the ‘‘Jewish panel’’: the importance of offering expanded carrier screening to the Ashkenazi Jewish population. Fertil Steril Rep 2020; 1:294–8; https://doi.org/10.1016/j.xfre.2020.08.001.
36. Hoskovec J, Hardisty EE, Talati AN, Carozza JA, Wynn J, Riku S, ten Bosch JR, Vora NL. Maternal carrier screening with single-gene NIPS provides accurate fetal risk assessments for recessive conditions. Genet Med. 2022; https://doi.org/10.1016/j.gim.2022.10.014.
37. Xu C, Li J, Chen S, Cai X, Jing R, Qin X, et al. Genetic deconvolution of fetal and maternal cell-free DNA in maternal plasma enables next-generation non-invasive prenatal screening. Cell Discovery 2022; 8: 109; https://doi.org/10.1038/s41421-022-00457-4.
38. Xue H, Yu A, Lin M, Chen X, Guo Q, Xu L, et al. Efficiency of expanded noninvasive prenatal testing in the detection of fetal subchromosomal microdeletion and microduplication in a cohort of 31,256 single pregnancies. Scientific Reports 2022; 12: 19750; https://doi.org/10.1038/s41598-022-24337-9.
39. Health Resources and Services Administration; Federal Advisory Committee on Heritable Disorders in Newborns and Children; Recommended Uniform Screening Panel (January 2023); Core Conditions (Metabolic, Endocrine, Hemoglobin, Others); https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp. Accessed April 11, 2023
40. Rajkumar V, Dumpa V. Lysosomal Storage Disease – StatPearls - NCBI Bookshelf.html. Last Update July 25, 2022; Accessed April 11, 2023.
41. https://www.newbornscreening.on.ca/en/about-screening/diseases-screened; Accessed April 11, 2023
42. http://www.bcwomens.ca/our-services/labour-birth-post-birth-care/after-the-birth/bc-newborn-screening-program; BC Newborn Screening Program; Accessed April 11, 2023
43. https://www.albertahealthservices.ca/services/Page16749.aspx; Newborn Screening; Accessed April 11, 2023
44. Jelin AC, Sagaser KG, Wilkins-Haug L. Prenatal Genetic Testing Options. Pediatr Clin N Am 2019; 66: 281-293
45. Screening for fetal chromosomal abnormalities. ACOG Practice Bulletin No. 226. Obstet Gynecol 2020;136: e48–69; Committee: Rose NC, Kaimal AJ, Dugoff L, Norton ME.
46. Dungan JS, Klugman S, Darilek S, Malinowski J, Akkari YMN, Monaghan KG, et al. ACMG Practice Guide Noninvasive prenatal screening (NIPS) for fetal chromosome abnormalities in a general-risk population:

An evidence-based clinical guideline of the American College of Medical Genetics and Genomics (ACMG) Genetics in Medicine 2022; 100336; doi: https://doi.org/10.1016/j.gim.2022.11.004.
47. Doan P-C, Nguyen D-A, Le QT, Hoang D-T, Nguyen HD, Nguyen CC, et al. Detection of maternal carriers of common α-thalassemia deletions from cell-free DNA. Scientific Reports 2022; 12:13581; https://doi.org/10.1038/s41598-022-17718-7.
48. Hussein N, Henneman L, Kai J, Qureshi N. Preconception risk assessment for thalassaemia, sickle cell disease, cystic fibrosis, and Tay-Sachs disease. Cochrane Database of Systematic Reviews 2021, 10: Art. No.: CD010849: doi: 10.1002/14651858.CD010849.pub4.
49. Stevens BK, Nunley PB, Wagner C, Murphy L, Wittman T, Ramdaney A, et al. Utility of expanded carrier screening in pregnancies with ultrasound abnormalities. Prenatal Diagnosis. 2022; 42:60–78; https://doi.org/10.1002/pd.6069.
50. Pitt JJ. Newborn Screening. Clin. Biochem. Rev. 2010, 31, 57–68.
51. van der Hout S, Dondorp W, de Wert G. The aims of expanded universal carrier screening: Autonomy, prevention, and responsible parenthood. Bioethics 2019; 33:568–76; doi:10.1111/bioe.12555.
52. Kraft SA, Duenas D, Wilfond BS, Goddard KAB. The evolving landscape of expanded carrier screening: challenges and opportunities. Genet Med. 2019; 21: 790-797; https://doi.org/10.1038/s41436-018-0273-4.
53. Sparks TN. Expanded carrier screening: counseling and considerations. Hum Genet 2019; https://doi.org/10.1007/s00439-019-02080-y.
54. Rowe CA, Wright CF. Expanded universal carrier and its implementation within a publicly funded healthcare service. J Comm Genet 2020; 11: 21-38; https://doi.org/10.1007/s12687-019-00443-6.
55. Sabbagh R, Van den Veyver IB. The current and future impact of genome-wide sequencing on fetal precision medicine. Hum Genet 2019; https://doi.org/10.1007/s00439-019-02088-4
56. Choates NG, Stevens BK, Wagner C, Murphy L, Singletary CN, Wittman AT. It takes two: uptake of carrier screening among male reproductive partners. Prenat Diag 2019; 1-6; doi: 10.1002/pd.5588.
57. Josephi-Taylor S, Barlow-Stewart K, Selvanathan A, Roscioli T, Bittles A, Meiser B, et al. User Acceptability of Whole Exome Reproductive Carrier Testing for Consanguineous Couples in Australia. J Genet Couns 2019; 28: 240-250; https://doi.org/10.1007/s10897-018-0298-5.
58. He Y, Xie R-G, Lou J-W, Li Y-W, Wang C-L, Zhang VW, Li D-Z. Exome -based preconception carrier testing for consanguineous couples in China. Prenat Diagn 2012; 41: 1425-1429; https://doi.org/10.1002/pd.6018.
59. Van Derr Bogaert K, Lannoo L, Brison N, et al. Outcome of publicly funded nationwide first-tier noninvasive prenatal screening. Genet Med 2021; 23: 1137-1142; http://doi.org/10.1038/s41436-021-01101-4 2021.
60. van der Meij KRM, Sistermans EA, Macville MVE, et al. TRIDENT-2: national implementation of genome-wide non-invasive prenatal testing as a first-tier screening test in the Netherlands. Am J Hum Genet. 2019; 105(6):1091-1101; http://doi.org/10.1016/j.ajhg.2019.10.005.
61. Norton ME, Jacobsson B, Swamy GK, et al. Cell-free DNA analysis for noninvasive examination of trisomy. N Engl J Med. 2015; 372:1589-159; http://doi.org/10.1056/NEJMoa1407349.
62. Rousseau F, Langlois S, Johnson JA, Gekas J, Bujold E, Audibert F, et al. Prospective head-to-head comparison of accuracy of two sequencing platforms for screening for fetal aneuploidy by cell-free DNA: the PEGASUS study. Eur J Hum Genet 2019; https://doi.org/10.1038/s41431-019-0443-0.
63. Hamilton BE, Martin JA. Osterman MJK, National Center for Health Statistics (U.S.). Division of Vital Statistics. Births: provisional data for 2020. NVSS vital statistics rapid release; report no. 12. Published May 5, 2021. Accessed March 13, 2022. https://stacks.cdc.gov/view/cdc/1 04993
64. Rose NC, Barrie ES, Malinowski J, et al. Systematic evidenced-based review: the application of noninvasive prenatal screening using cell-free DNA in general -risk pregnancies. Genet Med 2022; 24: 1379-1391; https://doi.org/10.1016/j.gim.2022.03.019.

65. Hopkins MK, Koepler N, Caldwell S, Dyr B, Dugoff L. Obesity and no-call results: optimal timing of cell-free DNA testing and redraw. Am J Obstet Gynecol 2021; 225: 351;
66. Burns W, Koelper N, Barberio A, Deagostino-Kelly M, Mennuti M, Sammel MD, et al. The association between anticoagulation therapy, maternal characteristics, and a failed cfDNA test due to a low fetal fraction. Prenat Diagn. 2017; 37(11):1125-1129. http://doi.org/10.1002/pd.5152.
67. MacKinnon HJ, Kolarova TR, Kdoi: 10.1016/j.ajog.2021.05.027.atz R, Hedge JM, Vinopal E, Lockwood CM, et al. The impact of maternal autoimmune disease on cell-free DNA test characteristics. Am J Obstet Gynecol MFM. 2021; 3:100466; http://doi.org/10.1016/j.ajogmf. 2021.100466.
68. Welker NC, Lee AK, Kjolby RAS, Wan HY, Theilmann MR, Jeon D, et al. High-throughput fetal fraction amplification increases analytical performance of noninvasive prenatal screening. Genet Med. 2021; 23:443-450; http://doi.org/10.1038/ s41436-020-01009-5.
69. Scheffer PG, Wirjosoekarto SAM, Becking EC, Weiss MM, Bax CJ, Oepkes D, et al. Association between low fetal fraction in cell-free DNA testing and adverse pregnancy outcome: a systematic review. Prenat Diagn. 2021; 41(10): 1287-1295; http://doi.org/10.1002/pd.6028.
70. Hedriana H, Martin K, Saltzman D, Billings P, Demko Z, Benn P. Cell free DNA fetal fraction in twin gestations in single-nucleotide polymorphism-based noninvasive prenatal screening. Prenat Diagn. 2020; 40:179-184; http://doi.org/10.1002/pd.5609.
71. Avram CM, Shaffer BL, Sparks TN, Allen AJ, Caughey AB. Cell-free fetal DNA screening for detection of microdeletion syndromes: a cost effectiveness analysis. J Matern Fetal Neonatal Med. 2021; 34: 1732-1740; http://doi.org/10.1080/14767058.2019.1647161.

72. Kostenko E, Chautraine F, Vandeweyer K, Schmid M, Lefevre A, Hertz D, et al. Clinical and economic impact of adopting noninvasive prenatal testing as a primary screening method for fetal aneuploidies in the general pregnancy population. Fetal Diagn Ther 2019; 45: 413-423; http://doi.org/10.101159000491750.
73. Hayward J, Chitty LS. Beyond screening for chromosomal abnormalities: Advances in non-invasive diagnosis of single gene disorders and fetal exome sequencing. Semin Fetal Neonat Med 2018; 23: 94-101; https://doi.org/10.1016/j.siny.2017.12.002.
74. Chitty LS, Mason S, Barrett AN, McKay F, Lench N, Daley R, et al. Non-invasive prenatal diagnosis of achondroplasia and thanatophoric dysplasia: next - generation sequencing allows for a safer, more accurate and comprehensive approach. Prenat Diagn 2015; 35: 656-62; doi: 10.1002/pd.4583.
75. Hill M, Twiss P, Verhoef T, Drury S, McKay F, Mason S, et al. Non-invasive prenatal diagnosis for cystic fibrosis: detection of paternal mutations, exploration of patient preferences, and cost analysis. Prenat Diagn 2015; 35: 950-8; doi: 10.1002/pd.4585.
76. New MI, Tong YK, Yuen T, Jang P, Pina C, Chan KCA, et al. Noninvasive prenatal diagnosis of congenital adrenal hyperplasia using cell-free DNA in maternal plasma. J Clin Endocrinol Metab 2014; 99: E1022-30; doi: 10.1210/jc.2014-1118.
77. Papasavva TE, Lederer CW, Traeger-Synodinos J, Mavrou A, Kanavakis E, Ioanna C, et al. A minimal set of SNPs for the noninvasive prenatal diagnosis of B-Thalassemia. Am Hum Genet 2013; 77: 115-24; doi: 10.1111/ahg.12004.
78. Hopkins MK, Dugoff L, Kuller JA. Guidelines for Cystic Fibrosis Carrier Screening in the Prenatal / Preconception Period. Obstet Gynecol Survey 2022; 77: 606-610.
79. Dar P, Jacobsson B, Clifton R, Egbert M, Malone F, Wapner RJ, et al. Cell-free DNA screening for prenatal detection of 22q11.2 deletion syndrome. Am J Obstet Gynecol. 2022; 227: 79.e1-79.e11; http://doi.org/10.1016/j.ajog.2022.01.002.
80. Kelly N, Makarem DC, Wasserstein MP. Screening for Newborns for Disorders with High Benefit-Risk Ratios Should Be Mandatory. J Law Med Ethics 2016; 44: 231-240.
81. Lehotay DC, Hall P, Lepage J, Eichhorst JC, Etter ML, Greenberg CR. LC-MS/MS Progress in Newborn Screening. Clin Biochem. 2011; 44: 21-31
82. Jones, S.A.; Cheillan, D.; Chakrapani, A.; Church, H.J.; Heales, S.; Wu, T.H.Y. et al. Application of a Novel Algorithm for Expanding Newborn Screening for Inherited Metabolic Disorders across Europe. Int. J. Neonatal Screen. 2022; 8:20; https://doi.org/10.3390/ijns8010020.
83. Mutze U, Mengler K, Boy N, Gleich F, Opladen T, Garbade SF, et al. How longitudinal observational studies can guide screening strategy for rare diseases. J Inherit Metab Dis. 2022; 45:889-901; doi:10.1002/jimd.12508.
84. Chudleigh J, Shakespeare L, Holder P, Chinnery H, Hack G, Gill T, et al. Co-designing Improved Communication of Newborn Bloodspot Screening Results to Parents: Mixed Methods Study J Particip Med 2022;14: e33485; https://jopm.jmir.org/2022/1/e33485.
85. Burlina AB, Polo G, Salviati L, Duro G, Zazzo C, Dardis A, et al. Newborn Screening for Lysosomal Storage Disorders by Tandem Mass Spectrometry in North-East Italy. J Inherit Metab Dis. 2018; 41: 209-219.
86. Day JW, Howell K, Place A, Long K, Rossello J, Kertesz N, et al. Advances and limitations for the treatment of spinal muscular atrophy. BMC Pediatrics 2022; 22:632; https://doi.org/10.1186/s12887-022-03671-x.
87. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: diagnosis and management in a new therapeutic era. Muscle Nerve 2015; 51: 157-67.
88. Rock MJ, Baker M, Antos N, Farrell PM. Refinement of newborn screening for cystic fibrosis with next-generation sequencing. Pediatric Pulmonology 2022; doi: 10.1002/ppul.26253.
89. Rafeeq MM, Murad HAS. Cystic Fibrosis: current therapeutic targets and future approaches. Trans. Med 2017; 15: 84; doi: 10.1186/s12967-017-1193-9.
90. Leonard SJ. Reproductive genetic screening for information: evolving paradigms? J Perinat Med 2021; 49: 998-1002; https://doi.org/10.1515/jpm.2021-0353.
91. Elangkovan N, Dickson G. Gene Therapy for Duchenne Muscular Dystrophy. J Neuromuscular Disease 2021; 8: S303-S316; doi:10.3233/JND-210678.
92. Duan D, Goemans N, Takeda S, Mercuri E, Aatsma-Rus A. Duchenne muscular dystrophy. Nature Reviews 2021; 7: 13; https://doi.org/10.1038/s41572-021-002248-3.
93. Olsen L, Sparse L, Wiensheimer SM, Dos Santos MBQ, Mazin W, Rosengren A, et al. Prevalence of rearrangements in the 22q11.2region and population-based risk of neuropsychiatric and developmental disorders in a Danish population: a case-cohort study. Lancet Psychiatry 2018; 5: 573-80; doi: 10.1016/S2215-0366(1)30168-8.
94. McDonald-McGinn DM, Sullivan KE, Marino B, Philip N, Swillen A, Vorstman JAS, et al. 22q11.2 deletion syndrome. Nat Rev Dis Primers. 2015; 1: 15071; doi: 10.1038/nrdp.2015.71.
95. Kauffman TL, Dickerson JF, Lynch FL, Leo MC, Shuster E, Wilfond BS, et al. Impact of Expanded Carrier Screening on Health Care Utilization. Am J Manag Care. 2021; 27:316-321; doi:10.37765/ajmc.2021.88722.
96. Reiner J, Rosenblum LS, Xin W, Zhou Z, Zhu H, Leach N. Incidental molecular diagnoses and heterozygous risk alleles in a carrier screening cohort Genetics in Medicine 2022:100317; doi: https://doi.org/10.1016/j.gim.2022.10.001

97. Dive L, Freeman L, McEwen A. Genetic Counsellors play a key role in supporting ethically responsible expanded universal carrier screening. Eur J Hum Genet 2023; 31:5–6; https://doi.org/10.1038/s41431-022-01218-3.
98. Dive L, Newson AJ. Reproductive carrier screening: responding to the eugenics critique. J Med Ethics 2022; 48:1060–1067; doi:10.1136/medethics-2021-107343.
99. Wang T, Kiss D, McFadden K, Brynes J, Scuffham P, Delatychi MB, et al. Clinical utility of reproductive carrier screening for preconception and pregnant couples for multiple genetic conditions: a systematic review and meta-analysis. Expert Review of Molecular Diagnostics 2023; doi: 10.1080/14737159.2023.2206519
100. Wilson RD. Every mother and every fetus matters: A positive pregnancy test = multiple offerings of reproductive risk screening for personal, family, and specific obstetrical-fetal conditions. Int J Gynecol Obstet. 2022; DOI: 10.1002/ijgo.14074].
101. Adams A, Jumah N, Okun N, Bonham VL. Equitable delivery of expanded genetic technologies: Considerations for prenatal and reproductive care. Prenat Diagn 2023; doi: 10.1002/pd.6338.
102. Matalon DR, Zepeda-Mendoza CJ, Aarabi M, Brown K, Fullerton SM, Kaur S, et al. Clinical, technical, and environmental biases influencing equitable access to clinical genetics / genomic testing: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG). 2023; doi: https://doi.org/10.1016/j.gim.2023.100812

The Scoping Review Checklist: Perinatal Genetic Carrier Screening: Could an innovative sequential perinatal screening approachcould replace the present siloed approaches?

Key criteria	Checklist items	One point for each item
1. Study aim, purpose, and research question	1. The rationale/purpose for the scoping review was stated.	X
	2. Appropriate scoping review methodology was used.	X
	3. At least two reviewers conducted the review.	No
	4. The research question/s was/were used to guide the scope of inquiry (participant, concept, and context included).	X
2. Relevant studies	5. An in-depth literature search was conducted to identify all relevant literature.	X
	6. A comprehensive list of relevant studies that balances breadth with feasibility was identified.	X
3. Study selection	7. The inclusion and exclusion criteria were clearly described and were used to determine eligibility of studies.	X
	8. The study selection involved an iterative process, including searching the literature, refining the search strategy and reviewing articles for inclusion.	X
	9. At least two reviewers independently reviewed the title and abstracts and reached consensus on studies for inclusion.	No
	10. The study selection process was summarized in a flow chart.	No
4. Charting the data	11. The research team collectively developed a data charting format and determined which variables to extract to answer the research question.	X
	12. The data were charted through sifting and sorting; tables include study details based on full texts.	X
	13. A numerical analysis of the extent and nature of included studies was reported.	X
	14. The quality of papers was assessed.	X
5. Collating, summarizing, and reporting the results	15. Results were presented in a logical descriptive or diagrammatic or tabular format.	X
	16. A narrative account of results was presented.	X
	17. The results were aligned with the review aim, purpose/research question/s.	X
	18. Issues associated with bias were discussed.	X
	19. Implications for future research, education, practice, and/or policy were discussed.	X
	20. The conclusion described the current state of the overall literature	X

Key criteria	Checklist items	One point for each item
	in relation to the topic.	
	Total	17/20 points