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REVIEW

PRENATAL DIAGNOSIS WILEY

Expanded carrier screening: What conditions should we screen for?

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Abstract

Carrier screening tests reproductive couples for their risk of having children affected by serious monogenic conditions. Carrier screening has historically been offered for certain conditions in high-risk populations. However, more recent evidence has shown that offering carrier screening to all patients, regardless of their ethnicity, more effectively and equitably identifies at-risk couples. Coupled with technology that enables screening for a nearly unlimited number of conditions, this expanded carrier screening (ECS) approach is now supported by professional society guidelines. Despite recent recommendations by the American College of Medical Genetics and Genomics to screen all patients who are pregnant or considering pregnancy for 113 conditions, questions remain about what conditions should be included on a core ECS panel. Here, we briefly review the history of carrier screening and guidelines on criteria for panel design. We then suggest which of these criteria are most critical, as well as thresholds to identify which conditions meet these criteria. Based on these interpretations, we recommend a core panel of 64 conditions that would identify the vast majority of at-risk couples. Widespread adoption of a core panel such as this would result in a marked improvement in the number of patients currently receiving comprehensive carrier screening.

Key Points

What's already known about this topic?

- Carrier screening is an essential component of assessing risk prenatally and has been offered for selected conditions for many years, particularly in certain ethnicities.
- Evidence now shows that offering expanded carrier screening (ECS) to all patients, regardless of ethnicity, is a more equitable approach to risk assessment.
- Professional society recommendations have offered criteria for designing ECS panels, and the American College of Medical Genetics and Genomics (ACMG) recommends a panel of 113 conditions.

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What does this review add?

- We briefly review the history and current recommendations for ECS and discuss critical panel design criteria for selecting conditions to screen.
- We then suggest criteria thresholds to identify a core panel of 64 conditions that is appropriate to offer to all patients who are pregnant or considering pregnancy, regardless of ethnicity, and would improve identification of at-risk couples compared to ethnicity-based screening.

1 | INTRODUCTION

Carrier screening aims to identify reproductive couples at risk of having a child with a monogenic condition.[1] Preconceptionally, carrier screening affords couples the ability to reduce the risk of an affected pregnancy by actions such as in vitro fertilization (IVF) with preimplantation genetic testing for monogenic disease (PGT-M), use of donor gametes that do not carry pathogenic variants, adoption, or avoidance of pregnancy altogether. When carrier screening is provided during pregnancy, couples can make informed decisions about prenatal diagnostic testing and pregnancy management.

Carrier screening was originally offered for single conditions and in certain ethnicities, but the advent of large-scale and rapid sequencing has made it possible to screen for many conditions in a single assay. This type of screening is called expanded carrier screening (ECS). Evidence supports the clinical utility of ECS,[2,3] and ECS offered without regard to ethnicity is a more equitable approach than carrier screening restricted to only certain ethnicities.[4–10] But questions persist about which conditions should be included in ECS panels. For example, how high should the population carrier frequency be? How severe should the condition be? Does a treatment for the condition need to exist? Prenatal providers and other stakeholders have studied these questions for several years, making excellent progress on criteria by which conditions can be evaluated for inclusion on ECS panels. Here, we summarize contemporary discussions of panel design and make recommendations for panel size and condition inclusion. We note that this is not intended to be a comprehensive review of carrier screening, but rather a clinical opinion for establishing a standard panel that can be consistently implemented in clinical practice.

2 | HISTORY OF CARRIER SCREENING

Carrier screening began several decades ago after the observation that some conditions were more prevalent in certain ethnicities/races. Tay Sachs disease screening was first offered after impacted communities grew to understand that roughly 1 in 30 Ashkenazi Jewish individuals was a carrier for Tay Sachs disease, and that carriers could be detected via a straightforward enzyme assay.[11] Concerned with reducing the risk of affected children in the absence of any effective treatment, Ashkenazi Jewish communities launched education and screening events that helped to drastically reduce the incidence of Tay Sachs disease in the population.[12] A similar community-driven approach was led by the Black Panther Party in the early 1970s to provide sickle cell carrier screening (via sickle prep and hemoglobin electrophoresis) in African-American communities.[13] Shortly after these programs began, Congress passed the National Sickle Cell Disease Control Act in 1972. In contrast to the community-led efforts screening for Tay-Sachs disease, the government-led programs had significant flaws that contributed to misinformation regarding sickle trait and further inflamed an already precarious socio-political relationship between the government and Black communities due to concerns about discrimination based on genetic status.[14]

As Sanger sequencing became available in the 1970's and enabled the first molecular tests, increasing knowledge about the molecular cause of more diseases was uncovered.[15] In part due to the costs associated with Sanger sequencing, the first screening guidelines utilized a targeted genotyping approach and were aimed at populations in which the frequency of carriers was expected to be elevated. Notably, the 1989 discovery of deleterious mutations in the *CFTR* gene as the underlying cause of cystic fibrosis (CF) opened the door for guidelines recommending carrier screening for CF in individuals.[16] In 1997, the National Institutes of Health Consensus Development Conference on Genetic Testing for Cystic Fibrosis recommended that genetic carrier screening for CF be widely offered.[17] Later, the American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG) issued guidelines recommending CF carrier screening to individuals in "high-risk" ethnicities, and eventually, expanded the recommendations to all ethnicities.[18,19] During this timeframe, evidence emerged that spinal muscular atrophy (SMA) was prevalent across several ethnicities. In response, ACMG in 2008 published guidelines for pan-ethnic carrier screening for SMA.[20]

While these earlier genetic screening guidelines were being introduced, the technology and processes of DNA analysis continued to evolve with the advent of next generation sequencing (NGS).[21] NGS significantly reduced costs and increased the scale of DNA analysis, making it more feasible to consider carrier screening for more than the targeted populations identified in the earlier guidelines. In 2009, the first "expanded carrier screening" platform was made commercially available that allowed for the option of simultaneous screening of multiple genes via targeted genotyping.[22] Later versions of this innovation were updated to include full exon sequencing and copy number variant (CNV) analysis that increased detection of pathogenic mutations across panels.[23]

Several studies have made it clear that ECS offered to all patients is a clinically superior approach for effective identification of at-risk couples compared to past ethnicity-based paradigms.[5–10] In 2016, Haque et al. modeled the risk across more than 340,000 individuals in 15 different self-reported ethnicities in the US population, finding that 1 in 550 US pregnancies would be affected with a severe or profound recessive condition on the assessed panel.[5] Collectively, recessive conditions were shown to be more common than Down Syndrome and neural tube defects, conditions that are routinely screened during the course of routine prenatal care.[5] The study also found that utilization of an ECS approach would improve detection of affected pregnancies across all ethnicities. A more recent study was consistent with Haque et al. and also reported that carrier rates across ethnicities were higher than previously thought.[6]

3 | CURRENT PROFESSIONAL ORGANIZATION RECOMMENDATIONS

Professional organization recommendations are helpful in providing guidance to practitioners, patients, and payers who are considering carrier screening. Traditionally guidelines tend to lag behind scientific advances but strive to provide a standardized approach for most patients. While still evolving, the following provides a summary of current guidelines from the United States and emerging recommendations from Europe.

In the United States, the two main organizations providing guidance on carrier screening are ACOG and ACMG. ACOG recommends the following: (1) Information about genetic carrier screening should be provided to every pregnant woman. After counseling, a patient may decline any or all screening. (2) All patients who are considering pregnancy or are already pregnant, regardless of screening strategy and ethnicity, should be offered carrier screening for CF and SMA, as well as a complete blood count and screening for thalassemias and hemoglobinopathies. (3) Ethnic-specific, panethnic, and ECS are acceptable strategies for prepregnancy and prenatal carrier screening.[24,25] ACMG recently published a Practice Resource that supports tier-based carrier screening, recommending that all pregnant patients and those planning a pregnancy, no matter their ethnicity, should be offered "Tier 3" carrier screening, which corresponds to disorders with a carrier frequency of ≥1 in 200 and includes X-linked disorders.[4] This resulted in a suggested panel of 113 conditions. ACOG supports, but has not officially endorsed, ACMG's Practice Resource.[26]

While the European Society of Human Genetics has not specifically published guidelines for ECS, it has published recommendations for implementation of ECS.[27] It states that "ECS allows testing of all individuals regardless of ancestry or geographic origin, which in this respect increases equity and reduces the chance of stigmatization." It also points out that ECS raises many technical, ethical, legal, and social issues and requires responsible implementation. Many other countries have instituted screening protocols that tend to be based on the ethnic mix of their population to achieve high DRs in their communities.[28]

4 | PRINCIPLES OF ECS

Although modern technology has enabled screening for thousands of monogenic conditions, not all are appropriate for inclusion on ECS panels. Criteria for evaluating the appropriateness of panel inclusion provide guidance on the panel design. In 1968, long before the era of modern genetic screening, Wilson and Jungner published criteria to guide the selection of conditions for screening.[29] Remarkably, more than 50 years later, the criteria are still relevant and useful in considering the design of ECS panels. More recently, professional societies have published criteria to guide the ECS panel design, summarized in Table 1.[1,4,24] These criteria include elements of Wilson and Jungner, focusing on carrier frequency, genotype-phenotype association, severity of the condition, the ability to perform prenatal diagnostic testing, and established analytical validity of the test. Below, we explore the criteria that, in our opinion, are the most important to consider in selecting conditions for ECS panel design and identify thresholds that conditions must meet for panel inclusion.

4.1 | Carrier frequency

Carrier frequency refers to the proportion of the individuals in the population carrying a recessive variant. In the context of carrier screening, criteria establishing a carrier frequency threshold are meant to identify individuals who are most likely to be carriers—and as a result, couples who are most likely to have an affected pregnancy—while avoiding the identification of carriers of very rare conditions that are extremely unlikely have a reproductive partner who is also a carrier. ACOG suggests that this threshold be set at 1 in 100, that is, conditions that have a carrier frequency of 1 in 100 or greater are appropriate for carrier screening.[24] ACOG's "1 in 100" threshold has been interpreted to mean a 1 in 100 carrier frequency in any population, as this interpretation supports equity in access to carrier screening across populations.[4,30,31]

ACMG supports a carrier frequency threshold of at least 1 in 200 in any ethnic group with reasonable representation in the US, justifying the threshold by noting the increase in the number of at-risk couples that would be identified.[4] Its analyses showed that when decreasing the threshold from 1 in 100 to 1 in 200, an additional 2400 at-risk couples per year in the US would have the benefit of making informed reproductive decisions.[4] However, this estimate assumes that both members of all reproductive couples receive screening. Unfortunately, current uptake is much lower than this and is unlikely to grow to 100% in the near future.[32]

In our opinion, a carrier frequency threshold of at least 1 in 100 in any ethnicity is currently most appropriate. This threshold would result in the inclusion of conditions that would identify a large majority of at-risk couples,[30,31,33] but would keep the total number of

TABLE 1 ECS panel design criteria by US professional societies

	ACOG[24]	ACMG[4]	Joint Statement[1]
Carrier frequency	Carrier frequency of ≥1 in 100	≥1 in 200 for AR conditions (>1 in 40,000 XL conditions) in at least one subpopulation	
Severity	Detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, early onset in life	Severity that may impact decision-making. Severity categorizations of moderate, severe, and profound	Health problem that encompasses cognitive disability, need for surgical or medical intervention, or effect on quality of life. Adult onset conditions at provider discretion
Genotype-phenotype association	Well-defined phenotype	ClinGen gene-disease association level of at least "moderate"	Well-understood relationship with a phenotype
Prenatal diagnosis	Can be diagnosed prenatally	Prenatal diagnosis and reproductive options should be available	Prenatal diagnosis should result in prenatal intervention, delivery management, parental education
Analytical validity		Established analytical validity of screening methods	

conditions within a range that is acceptable to most stakeholders. For example, a recent analysis found that a 1 in 100 threshold yields a panel of approximately 40 conditions that would identify more than 92% of at-risk couples, relative to a 176-condition panel. However, decreasing the threshold to 1 in 200 nearly doubled the number of conditions on the panel while increasing at-risk couple identification by only 4%.[33] Many providers have stated that they are not prepared or willing to jump from routinely offering screening for only two conditions (SF and SMA) to offering screening for hundreds of conditions, believing that their workload in counseling and arranging for partner screening for the increased number of carriers would be untenable.[32] A carrier frequency threshold of 1 in 100 in any ethnicity represents an impactful step forward in equitably identifying pregnancies at risk for the most common conditions while maintaining a reasonable workload for providers offering such screening.

As providers implement ECS with a 1 in 100 carrier frequency threshold and become comfortable managing patients undergoing such screening, an increase to a 1 in 200 thresholds could be considered. A primary reliance on carrier frequency has been questioned based on the notion that any threshold is arbitrary and will inevitably result in missing the identification of carriers of very rare conditions.[34] We agree with this concern, but maintain that widespread acceptance of ECS and access to it in the United States necessitate an incremental increase in the panel size rather than an increase to many hundreds of conditions.

4.2 | Severity

Panel design criteria addressing severity are directly related to clinical utility. Several studies have found that couples with an affected pregnancy base their reproductive decision-making partly on the severity of the condition.[2,3,35–37] The connection between severity and clinical utility has led to calls for severity to be used as the primary criterion for inclusion of conditions on ECS panels.[38] A framework for classifying the severity of serious monogenic conditions has been developed and validated, which uses an algorithm that takes into account the phenotypic characteristics of the condition, such as the extent to which lifespan is shortened, the involvement of intellectual disability, and the level of impairment to physical mobility.[39] The framework then categorizes conditions into one of four severity categories: profound, severe, moderate, and mild. ACMG states that conditions included on ECS panels should be severe enough to impact reproductive decision-making and references the four severity categories, recommending that included conditions have profound, severe, or moderate classifications.[4] ACOG's severity-related criteria state that conditions included in ECS panels should have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, and have an onset early in life.[24]

We recommend that conditions included in ECS panels have at least moderate severity, according to the four-category scale cited by ACMG and previously applied to many ECS conditions.[4,39,40] This recommendation may seem too permissive to those that interpret "moderate" as not serious enough to impact reproductive decision-making. However, conditions in the "moderate" category include those that cause deafness, visual impairment, mental illness, and/or mobility impairment, and many have treatments that can reduce the severity and psychosocial impacts of the condition itself.

4.3 | Genotype-phenotype association

Genotype-phenotype association, often called gene-disease association, refers to the role of a gene in disease causation. In conditions

with strong gene-disease association, the disease phenotype is caused almost solely by pathogenic variants in a known gene. Because ECS is meant to assess the risk of monogenic disease, it is important that conditions on ECS panels have strong gene-disease association.

The Clinical Genome Resource (ClinGen) has developed an objective, evidence-based method to classify gene-disease association.[41,42] The framework assesses the quality and quantity of evidence supporting genotype-phenotype relationships using a system that categorizes the evidence by strength. Evidence classifications that are supportive of gene-disease association include "Definitive," "Strong," "Moderate," and "Limited." This framework has been applied to many monogenic conditions, including those commonly included on ECS panels, with classifications published on the ClinGen website.[43–48] This provides a valuable resource for considering which conditions are appropriate for inclusion on ECS panels.

In its ECS panel design criteria, ACOG states only that included conditions have a well-defined genotype-phenotype relationship, but do not suggest how to determine the strength of the relationship.[24] In contrast, ACMG cites the ClinGen framework, recommending that it is used to evaluate the evidence for gene-disease association and that conditions have at least Moderate gene-disease association.[4] We agree with the Moderate threshold, which is restrictive enough to ensure that included conditions have supportive evidence of gene-disease association, but not so permissive that conditions are included when they have only a few case publications that are not yet convincing.

4.4 | Availability of prenatal diagnosis

Both ACOG and ACMG state that conditions included on ECS panels should be capable of being prenatally diagnosed. Establishing a diagnosis is foundational to the clinical utility of carrier screening, underscoring the importance of this criterion. Due to advances in genetic testing over the last several decades, diagnostic testing with a high positive predictive value (amniocentesis or chorionic villus sampling with single gene follow-up) exists for almost all monogenic conditions. Single gene testing using cell-free fetal DNA is not considered diagnostic by most professional societies, but is gaining traction in research and limited clinical settings. We agree that for conditions to be included on ECS panels, they must be capable of being diagnosed prenatally.

4.5 | Analytical validity

Analytical validity refers to the test's ability to identify the presence or absence of a genetic variation. Sensitivity, specificity, accuracy, and reproducibility are factors that determine analytical validity.[4] Laboratories are required to demonstrate analytical validity of their testing methods in order to offer them clinically. ACMG's panel design criteria include this requirement; ACOG's criteria do not address it.[4,24] We agree that for conditions to be included in ECS, their methods must have demonstrated analytical validity.

5 | CLINICAL OFFERINGS

A variety of different carrier screening panels are currently clinically available in the United States. Panel size ranges from as small as a single condition to over 500 conditions, and various methodologies or combinations of methodologies are used to detect pathogenic mutations including but not limited to: targeted genotyping and gene sequencing and deletion/duplication (CNV) analysis.

A "negative" carrier screening result indicates a reduction in the risk that a given individual is a carrier of the condition assessed. The detection rate (DR) for any given condition represents the proportion of true carriers that will be identified, given the analytical ability of the screening methodology to detect pathogenic variants in the gene. Laboratory standards call for DRs to be made available on reports to help convey to patients and providers what residual risk remains for the screened individual following a negative result on a particular screen.[4,49] The DR achieved via targeted genotyping is limited and is often highest in populations that have very prevalent founder mutations. Outside of these populations, the prevalent mutations may differ, and as a consequence, screening DRs can be significantly lower, presenting a challenge in achieving the goal of identifying at-risk couples.[50]

The use of full exon sequencing to screen for carrier status can increase the DR of an assay, but it also introduces the burden of variant classification for rare and novel sequence variations that may be discovered. ACMG and the Association of Molecular Pathology have described the types of data that should be collected to assess novel variants as well as a tier-based terminology system ("pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign") to describe the pathogenicity of variants.[51] The application of these guidelines and standards, even when applied by different curation teams in the laboratory space, appears to have generated consensus for the majority of variants that are identified; one study found 99% concordance between laboratories assessing variants on ECS panels.[52] This suggests that utilization of a targeted genotyping approach risks missing the identification of more at-risk couples than a sequencing approach coupled with ACMG-consistent novel variant interpretation.

Professional societies call for discussion of residual risk with patients when it is known, regardless of the screening methodology used.[1,4] The reason for this discussion is to help convey to patients who screen negative that false negative results are possible. Residual risk is dependent on the prevalence of the disorder in question as well as the DR of the methodology used to screen. Some of the limitations in calculating a precise residual risk are the significant

TABLE 2 Recommended conditions for a core 64-condition ECS panel

Condition	Gene	Carrier frequency (1 in X)[a]	Gene-disease association[b]	Severity categorization[c]
Alpha thalassemia	*HBA1*, *HBA2*	3	Definitive	Moderate
Hb beta chain-related hemoglobinopathy (including sickle cell disease)	*HBB*	8	Definitive	Profound
Familial Mediterranean fever	*MEFV*	11	Definitive	Moderate
Gaucher disease	*GBA*	18	Definitive	Moderate
Xeroderma pigmentosum C	*XPC*	20	Definitive	Severe
Cystic fibrosis	*CFTR*	20	Definitive	Severe
Oculocutaneous albinism type 1A and 1B	*TYR*	20	Definitive	≥Moderate
Phenylalanine hydroxylase deficiency	*PAH*	21	Definitive	Severe
21-hydroxylase-deficient congenital adrenal hyperplasia	*CYP21A2*	23	Definitive	Severe
GJB2-related DFNB1 nonsyndromic hearing loss and deafness	*GJB2*	24	Definitive	Severe
Ehlers–Danlos-like syndrome due to tenascin-X deficiency	*TNXB*	28	Not curated	≥Moderate
Hexosaminidase A deficiency (Tay-Sachs disease)	*HEXA*	35	Definitive	Profound
Short-chain acyl-CoA dehydrogenase deficiency	*ACADS*	36	Definitive	Mild
Wilson disease	*ATP7B*	39	Definitive	Moderate
Smith-Lemli-Opitz syndrome	*DHCR7*	40	Definitive	Severe
Familial dysautonomia	*ELP1* (*IKBKAP*)	41	Definitive	Profound
Spinal muscular atrophy	*SMN1*	43	Definitive	Severe
Carnitine palmitoyltransferase II deficiency	*CPT2*	47	Definitive	Profound
Pendred syndrome	*SLC26A4*	52	Definitive	Moderate
Congenital disorder of glycosylation type Ia	*PMM2*	53	Definitive	Profound
Canavan disease	*ASPA*	54	Definitive	Profound
Krabbe disease	*GALC*	54	Definitive	Moderate
Medium chain acyl-CoA dehydrogenase deficiency	*ACADM*	57	Definitive	Profound
USH2A-related disorders	*USH2A*	58	Definitive	Moderate
Pompe disease	*GAA*	58	Definitive	Profound
Hermansky Pudlak syndrome 1	*HPS1*	59	Definitive	≥Moderate
Hermansky Pudlak syndrome 3	*HPS3*	59	Definitive	≥Moderate
Friedreich ataxia	*FXN*	60	Definitive	≥Moderate
Primary hyperoxaluria type 3	*HOGA1*	60	Definitive	Profound
Congenital Finnish nephrosis	*NPHS1*	63	Definitive	Profound
Cerebrooculofacioskeletal syndrome 2; Trichothiodystrophy 1, photosensitive	*ERCC2*	66	Definitive	≥Moderate
Short-rib thoracic dysplasia 3 with or without polydactyly	*DYNC2H1*	67	Not curated	≥Moderate
Joubert syndrome 5; Leber congenital amaurosis 10	*CEP290*	69	Definitive	≥Moderate
Hereditary fructose intolerance	*ALDOB*	71	Definitive	Severe
GBE1-related disorders	*GBE1*	72	Not curated	≥Moderate
Autosomal recessive polycystic kidney disease, PKHD1-related	*PKHD1*	73	Definitive	Severe

TABLE 2 (Continued)

Condition	Gene	Carrier frequency (1 in X)[a]	Gene-disease association[b]	Severity categorization[c]
Oculocutaneous albinism brown and type II	*OCA2*	73	Definitive	≥Moderate
Myasthenic syndrome, congenital, 4A, slow-channel; Myasthenic syndrome, congenital, 4B, fast-channel	*CHRNE*	74	Not curated	≥Moderate
Recessive dystrophic epidermolysis bullosa	*COL7A1*	77	Definitive	≥Moderate
Primary carnitine deficiency	*SLC22A5*	78	Definitive	Profound
ABCC8-related familial hyperinsulinism	*ABCC8*	81	Definitive	Severe
Dihydrolipoamide dehydrogenase deficiency	*DLD*	82	Definitive	Profound
Fraser syndrome	*GRIP1*	83	Not curated	≥Moderate
Maple syrup urine disease type 1B	*BCKDHB*	85	Definitive	Profound
Glycogen storage disease type Ia	*G6PC*	85	Definitive	Severe
FKTN-related disorders	*FKTN*	86	Definitive	Severe
Spinocerebellar ataxia 10	*ANO10*	93	Not curated	≥Moderate
Schindler disease, type 1; Schindler disease, type 3	*NAGA*	94	Not curated	≥Moderate
Niemann-Pick disease, SMPD1-associated	*SMPD1*	97	Definitive	Profound
Fanconi anemia, FANCC-related	*FANCC*	99	Definitive	Profound
MUT-related methylmalonic acidemia	*MUT*	100	Definitive	Profound
Bloom syndrome	*BLM*	100	Definitive	Severe
Fragile X syndrome[d]	*FMR1*	105	Definitive	Severe
Dystrophinopathy (including Duchenne/Becker muscular dystrophy)[d]	*DMD*	813	Definitive	Severe
Fabry disease[d]	*GLA*	1050	Definitive	Profound
X-linked Alport syndrome[d]	*COL4A5*	2427	Definitive	Moderate
X-linked adrenoleukodystrophy[d]	*ABCD1*	3545	Definitive	Profound
X-linked juvenile retinoschisis[d]	*RS1*	4516	Definitive	Moderate
X-linked congenital adrenal hypoplasia[d]	*NR0B1*	6065	Definitive	Severe
Mucopolysaccharidosis type II[d]	*IDS*	7089	Definitive	Profound
X-linked myotubular myopathy[d]	*MTM1*	7089	Definitive	Severe
Hemophilia A[d]	*F8*	5000–10,000	Definitive	≥Moderate
Hemophilia B[d]	*F9*	30,000	Definitive	≥Moderate
Hydrocephalus due to congenital stenosis of aqueduct of Sylvius (HSAS)[d]	*L1CAM*	30,000	Definitive	≥Moderate

[a]Carrier frequencies listed represent the highest carrier frequency published among ethnicities with substantial representation in the US population.[30,33] A 1 in 10,000 carrier frequency for X-linked conditions is equivalent to a 1 in 100 carrier frequency for autosomal recessive conditions. For Hemophilia A, Hemophilia B, and Hydrocephalus due to congenital stenosis of aqueduct of Sylvius (HSAS), carrier frequencies are unknown; therefore, condition prevalence estimates from GeneReviews are provided instead. A prevalence of 1 in 40,000 is equal to a carrier frequency of 1 in 10,000 for X-linked conditions.

[b]Based on published ClinGen curations.[48] Conditions "Not curated" are assumed to meet at least moderate strength of evidence based on their inclusion in ACMG recommendations.[4]

[c]Based on Arjunan et al.[40] Those with "≥Moderate" severity are assumed to have at least moderate severity based on their inclusion in ACMG recommendations.[4]

[d]X-linked condition.

gaps in global incidence information (due to differences in newborn screening programs in various populations), non-random mating patterns that undermine Hardy-Weinberg assumptions, inaccuracies of self-reported ethnicity, differences in carrier frequencies across ethnic groups, and the increasing number of individuals of admixed ethnicity.[53] While these factors make residual risk calculation

difficult, they do not prohibit discussion of the concept of residual risk with patients, as residual risk is important in determining whether additional clinical intervention is warranted.

6 | RECOMMENDATION FOR PANEL MAKEUP AND SIZE

A recent study analyzed ACMG and ACOG panel design criteria in detail and suggested conditions that should be included on both a panel that strictly adheres to ACMG and ACOG criteria and a panel that more permissively interprets the criteria.[33] We take a similar approach here using what we believe are the three most critical criteria and associated thresholds for ECS panel design: a carrier frequency of at least 1 in 100 in any ethnicity, a severity of at least moderate, and a gene–disease association of at least moderate strength. The other criteria—established analytical validity and the capability to be prenatally diagnosed—can be considered applicable to all monogenic conditions due to advances in genetic testing technology but should be verified for any conditions under consideration.

Given the above thresholds, we recommend a core ECS panel of 64 conditions that should be offered to all patients who are pregnant or considering pregnancy (Table 2). Routine adoption of this panel would ensure that the vast majority of at-risk couples are identified, while not overwhelming the health care system by identifying carriers that are extremely unlikely to have reproductive partners who are also carriers for the same condition. Importantly, insurers should cover the cost of screening for this core panel, as patients cannot realize any clinical utility if access is limited due to its expense to the patient.

We note two important caveats to the panel recommended in Table 2. First, as stated by ACMG, certain patients would benefit from screening with larger panels, such as its "Tier 4" panel.[4] In particular, those with a consanguineous pregnancy and/or a family history of a rare monogenic condition as well as those undergoing IVF or whose race/ethnicity places them at high risk are appropriate candidates for panels that include conditions with carrier frequencies lower than 1 in 100. Second, as genome sequencing becomes more routine and affordable, data on carrier frequency across ethnicities continues to grow. For example, a study published approximately 1 year after ACMG's current recommendations used gnomAD v 3.1.1 to identify several conditions that now appear to have carrier frequencies of at least 1 in 100[54]; these conditions may be appropriate for inclusion on ECS panels if they also meet severity and gene–disease association thresholds. Additionally, several conditions that ACMG reported in Gregg et al.[4] as not having published gene–disease association are now curated and published on the ClinGen website.[48] Evaluation of conditions that should be included on ECS panels should therefore be a continual activity by professional societies and stakeholders. We urge ACMG and ACOG to form a joint standing committee to regularly review new data so that ECS panel recommendations remain current.

We also underscore the importance of both pre-test education and post-test genetic counseling for patients undergoing ECS. It is not feasible to educate patients about every condition on an ECS panel before they receive screening; however, they should understand the screening process and the severity of the conditions on the panel. Patients should be made aware that newborn screening is not a replacement for ECS, as it usually includes a different set of conditions, and is meant to identify affected children whose conditions should be treated immediately after birth, versus identifying at-risk couples.[1] Post-test counseling should include information on the condition(s) for which a patient tests positive, as well as the need to screen the reproductive partner for carrier status of the condition (unless the condition is X-linked), if partner screening has not already been performed.[1] Heterozygous carriers of a small number or conditions may experience symptoms or increased risk themselves.[11] For example, carriers of a pathogenic variant in ATM have an increased risk of breast cancer, and carriers of a pathogenic variant in GBA have an increased risk for early-onset Parkinson's disease. Carriers of such conditions should be informed about this possibility. Detailed recommendations for the types of educational content to cover pre-test, as well as principles for post-test counseling, have been previously published.[4,11]

7 | CONCLUSIONS

Technological advances now enable ECS, and its clinical utility has been demonstrated. The outstanding question is what conditions should be included on ECS panels. Herein, we offer our recommendations for a panel that would substantially improve identification of at-risk couples compared to ethnicity-based approaches and represent a panel size that we believe would be acceptable to most obstetrics providers. Inconsistent insurance coverage remains as a barrier to patient access to ECS. As payers look to professional societies for evidence-based guidance, we urge professional societies to issue consensus practice guidelines that will improve patient access to ECS.

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CONFLICT OF INTEREST

Summer Pierson and Katherine Johansen Taber are employed by Myriad Genetics, which markets an expanded carrier screening test.

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Not applicable.

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