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ARTICLE

A guidelines-consistent carrier screening panel that supports equity across diverse populations

Katherine Johansen Taber[1,*], Rotem Ben-Shachar[2], Raul Torres[2], Aishwarya Arjunan[1], Dale Muzzey[3], Kristjan E. Kaseniit[2], James Goldberg[1], Haywood Brown[4]

[1]*Department of Medical Affairs, Myriad Women's Health, Inc, South San Francisco, CA;* [2]*Department of Clinical Development, Myriad Genetics, Inc, Salt Lake City, UT;* [3]*Department of Research and Development, Myriad Genetics, Inc, Salt Lake City, UT;* [4]*Department of Obstetrics & Gynecology, Morsani College of Medicine, University of South Florida, Tampa, FL*

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ABSTRACT

Purpose: The American College of Obstetricians and Gynecologists (ACOG) and the American College of Medical Genetics and Genomics (ACMG) suggest carrier screening panel design criteria intended to ensure meaningful results. This study used a data-driven approach to interpret the criteria to identify guidelines-consistent panels.

Methods: Carrier frequencies in >460,000 individuals across 11 races/ethnicities were used to assess carrier frequency. Other criteria were interpreted on the basis of published data. A total of 176 conditions were then evaluated. Stringency thresholds were set as suggested by ACOG and/or ACMG or by evaluating conditions already recommended by ACOG and ACMG.

Results: Forty and 75 conditions had carrier frequencies of ≥1 in 100 and ≥1 in 200, respectively; 175 had a well-defined phenotype; and 165 met at least 1 severity criterion and had an onset early in life. Thirty-seven conditions met conservative thresholds, including a carrier frequency of ≥1 in 100, and 74 conditions met permissive thresholds, including a carrier frequency of ≥1 in 200; thus, both were identified as guidelines-consistent panels.

Conclusion: Clear panel design criteria are needed to ensure quality and consistency among carrier screening panels. Evidence-based analyses of criteria resulted in the identification of guidelines-consistent panels of 37 and 74 conditions.

Introduction

Serious autosomal recessive and X-linked conditions affect 183 conceptuses per 100,000 United States births.[1] Carrier screening aims to identify couples at risk of having affected pregnancies by testing for disease-causing variants in the same autosomal genes in both members of the couple (for autosomal recessive conditions) or in a gene on the X chromosome (for X-linked conditions). The purpose of carrier screening is to identify these at-risk couples (ARCs)

*Correspondence and requests for materials should be addressed to Katherine Johansen Taber, Department of Medical Affairs, Myriad Women's Health, Inc, 180 Kimball Way, South San Francisco, CA 94080. *E-mail address:* mwh_research@myriad.com

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so that they may maximize their reproductive options.[2,3] In those screened preconceptionally, reproductive options include in vitro fertilization with preimplantation genetic testing for monogenic conditions, the use of a noncarrier donor gamete, adoption, or the avoidance of pregnancy altogether. In those screened during pregnancy, management options include prenatal diagnostic testing, pregnancy termination after a confirmed diagnosis, postnatal diagnostic testing, early preparation for the initiation of medical intervention if and when appropriate, and parental education about postbirth special care needs.[2,3]

The American College of Obstetricians and Gynecologists (ACOG) currently recommends offering carrier screening to all couples, regardless of their race/ethnicity (ie, pan-ethnic carrier screening), for only 2 conditions, namely cystic fibrosis (CF) and spinal muscular atrophy (SMA) (Supplemental Table 1).[4] ACOG additionally recommends screening for 5 conditions, alpha-thalassemia, Hb beta chain-related hemoglobinopathy (including sickle cell disease), hexosaminidase A deficiency (Tay-Sachs disease), Canavan disease, and familial dysautonomia, for those of certain races/ethnicities (Supplemental Table 1).[4] Until recently, the American College of Medical Genetics and Genomics (ACMG) recommended pan-ethnic carrier screening for CF and SMA[5,6] and screening for 8 conditions in individuals of Ashkenazi Jewish (AJ) descent,[7] but in a 2021 Practice Resource, ACMG updated its recommendations to support pan-ethnic carrier screening for 112 conditions.[8]

Pan-ethnic screening for a large number of conditions, traditionally known as "expanded carrier screening" (ECS), but more recently referred to as simply "carrier screening,"[8] has been shown to more effectively identify carriers and ARCs across all races/ethnicities than does screening that is restricted to only certain races/ethnicities.[9-16] However, clearly defined carrier screening panel design criteria are needed to maximize identification of ARCs across all races/ethnicities, a goal that aligns with both ACOG's and ACMG's commitments to work toward the elimination of racial inequities that lead to disparate health outcomes.[17,18] Citing the vast number of conditions that could be screened, ACOG and ACMG have both recommended criteria for carrier screening panel inclusion. ACOG suggests 7 criteria, several of which should be met for a condition to be included on an ECS panel.[2] These criteria include the following: have a carrier frequency of 1 in 100 or greater, have a well-defined phenotype, have a detrimental effect on quality of life, cause cognitive or physical impairment, require surgical or medical intervention, have an onset early in life, and can be diagnosed prenatally (Table 1).[2] ACMG cites similar, although sometimes more permissive, panel design criteria to ACOG's.[8] They address carrier frequency (high prevalence of carriers in the screened population), severity (phenotype severity may impact decision-making), genotype–phenotype relationship (predictable genotype–phenotype correlation), prenatal diagnostic capability (available prenatal diagnosis and reproductive options), and analytical validity (established analytical validity of screening methods) (Table 1).[8]

Several studies have shown challenges in interpreting nonspecific panel design criteria and the resulting impact on panel content.[10,19,20] For example, ACOG's "have a well-defined phenotype" criterion does not offer detail on the mechanism by which it should be evaluated. Furthermore, it is unclear how many criteria should be met by each condition or if certain criteria must always be met. Variable interpretation of panel design criteria may explain why commercially available carrier screening panels have vastly different sizes, with limited overlap in condition inclusion,[21] and differ in their conclusions about whether conditions meet criteria.[10,15,19,20] ACMG acknowledged this problem in its Practice Resource, and for this reason, ACMG suggested specific, quantitative thresholds by which conditions should be evaluated (Table 1).[8]

Using evidence-based interpretations of both ACOG and ACMG criteria[2,8] and leveraging carrier frequency data from >460,000 individuals across 11 ethnicities, we applied a data-driven approach to assess 176 conditions for their adherence to the criteria, resulting in the identification of a panel of conditions that conservatively meet the criteria.

Materials and Methods

Defining and applying the panel design criteria

ACOG and ACMG panel design criteria were categorized into combined criteria 1 to 8 as described in Table 1. Criteria were objectively defined and evaluated as follows, using consensus across published studies when possible. Criterion 1 was defined by carrier frequency thresholds described in ACOG and ACMG criteria and evaluated using carrier rates from 460,608 individuals across 11 races/ethnicities (as seen further on). Criterion 2 was defined as gene–disease association and evaluated by applying the ClinGen clinical validity framework, which quantifies gene–disease association by assessing the strength of available evidence,[22] as recommended by ACMG. Criteria 3 to 5 were defined as factors of severity and were evaluated by mapping criteria to disease traits reported in Arjunan et al.[23] Criterion 6 was evaluated using published age of onset data (Supplemental Table 2). Consistent with professional society consensus,[3] "early in life" was defined as infancy or childhood (birth to age 2 years or age 2 to 12 years, respectively).[24] Criterion 7 was defined as the capability to perform prenatal diagnostic testing for each condition. Criterion 8 was defined as published analytical sensitivity and analytical specificity for each condition.

Thresholds for each criterion were set on the basis of those explicitly cited by ACOG or ACMG[2,8] or, in the absence of an explicitly cited threshold, the degree to which conditions currently recommended by both ACOG and ACMG for screening in 1 or more race/ethnicity[4,8]

(Supplemental Table 1) met the most conservative interpretations of each criterion. Criteria and their thresholds were then applied to 176 conditions on a commercially available ECS panel (Foresight, Myriad Women's Health, Inc).[1,25,26]

Cohort description

We retrospectively analyzed de-identified data of 495,194 individuals who were screened using next-generation sequencing for up to 176 conditions (see Supplemental Methods) during a 7-year period (January 1, 2012-February 2, 2020) and who had consented to research use of their data. To ensure carrier frequencies were representative of the general United States population, we excluded individuals who had a family or personal history of disease or reported consanguinity, resulting in a cohort of 460,608 individuals (Supplemental Table 3). Self-reported race/ethnicity was collected via the test requisition form. The races/ethnicities included in Supplemental Table 3 represent those included on the test requisition.

Carrier rate, ARC rate, and efficiency of ARC detection calculations

Brief descriptions of carrier rate, ARC rate, and efficiency of ARC detection calculations are included in this study but are described in detail in the Supplemental Methods. To calculate race/ethnicity-specific carrier rates, we computed race/ethnicity-specific allele frequencies for each pathogenic or likely pathogenic variant observed in our cohort. To determine ARC rates (Supplemental Table 4), we used modeled fetal disease risk, described in detail in Beauchamp et al[1] and Haque et al[11] and defined as the probability of a disease affecting the conceptus of randomly selected male and female parents. Carrier rates and ARC rates for conditions with complicated inheritance were calculated as described in Ben-Shachar et al.[10] The square root of the carrier rate for X-linked conditions was used to enable direct comparison in carrier frequencies for autosomal recessive and X-linked conditions, except when calculating panel carrier rates and panel ARC rates. Panel carrier rates and panel ARC rates were calculated population-wide by weighting race/ethnicity-specific carrier and ARC rates according to data from the United States Census.[27] Efficiency of ARC detection was determined by calculating the ratio of the panel carrier rate to the panel ARC rate for each panel assessed.

Results

Carrier frequency as a criterion for panel inclusion

Criterion 1 is based on ACOG's statement that conditions selected for inclusion on ECS panels should have a carrier frequency of ≥1 in 100[2] and ACMG's statement that there should be a high prevalence of carriers in the screened population, with a carrier frequency threshold of ≥1 in 200 in any race/ethnicity[8] (Table 1). We therefore analyzed panel composition for both carrier frequency thresholds of ≥1 in 100 and ≥1 in 200.

Consistent with previous interpretations of ACOG's "1 in 100" criterion, we interpreted it to mean a carrier frequency of ≥1 in 100 in any race/ethnicity.[10,19,20] The number of conditions in each race/ethnicity with carrier frequencies of ≥1 in 100 ranged from 10 in individuals of African or African American descent to 32 in individuals of AJ descent (Figure 1A, Supplemental Table 3). This threshold resulted in a panel of 40 conditions that included all 7 conditions currently recommended by both ACOG and ACMG for screening in 1 or more ethnicity[4,8] (Figure 1A, Supplemental Table 5). This 40-condition panel would capture 68.2% of carriers and 92.3% of ARCs compared with a 176-condition panel (Supplemental Table 6). At the more permissive carrier frequency of ≥1 in 200 in any race/ethnicity threshold supported by ACMG, the number of conditions ranged from 16 in individuals of Southeast Asian descent to 52 in individuals of AJ descent. This threshold resulted in a panel of 75 conditions (Figure 1A, Supplemental Table 5), capturing 82.0% of carriers and 96.6% of ARCs compared with a 176-condition panel (Supplemental Table 6).

Genotype–phenotype relationship as a criterion for panel inclusion

Criterion 2 addresses ACOG and ACMG genotype–phenotype relationship criteria (Table 1).[4,8] Although ACOG does not define how to quantify this relationship, ACMG recommends evaluating evidence for gene–disease association using the ClinGen framework that categorizes the strength of such evidence,[22,28] recommending a threshold of at least moderate gene–disease association for panel inclusion.[8] We therefore used ACMG's recommended quantification and threshold for evaluating genotype–phenotype relationship. Of the 176 conditions examined here, 175 (99.4%) met the moderate or higher gene–disease association threshold[22] (Figure 1B). This 175-condition panel would capture 99.8% of carriers and >99.9% of ARCs compared with a 176-condition panel (Supplemental Table 6).

Severity and age of onset as criteria for panel inclusion

Criteria 3 to 5 consist of ACOG and ACMG criteria related to severity (Table 1).[2,8] ACMG suggests that conditions that are at least moderately severe (as defined by Lazarin et al[29]) are appropriate for panel inclusion.[8] Applying this threshold resulted in 175 of 176 conditions (99.4%) having at least

Table 1 ACOG and ACMG ECS panel design criteria

Criteria Category	ACOG Panel Design Criteria[2]	ACMG Panel Design Criteria[8]
1. Carrier frequency	Have a carrier frequency of ≥1 in 100	High prevalence of carriers in the screened population. Carrier frequency threshold is ≥1 in 200 for autosomal recessive conditions and > 1 in 40,000 for X-linked conditions, in at least 1 subpopulation.[a]
2. Genotype–phenotype relationship	Have a well-defined phenotype	Predictable genotype–phenotype correlation. A ClinGen gene–disease association level of at least moderate is recommended. In most cases, only pathogenic or likely pathogenic variants should be reported.
3. Severity (quality of life)	Have a detrimental effect on quality of life	Phenotype severity that may impact decision-making. Condition severity categorizations of moderate, severe, and profound are recommended.
4. Severity (impairment)	Cause cognitive or physical impairment	
5. Severity (intervention)	Require surgical or medical intervention	
6. Age of onset	Have the onset early in life	Not addressed
7. Prenatal diagnostic capability	Can be diagnosed prenatally	Available prenatal diagnosis and reproductive options.
8. Analytical validity	Not addressed	Established analytical validity of screening methods.

ACMG, American College of Medical Genetics and Genomics; *ACOG*, American College of Obstetricians and Gynecologists; *ECS*, expanded carrier screening.
[a]Subpopulations include 1 of 6 ancestral populations (African/African American, Hispanic, Ashkenazi Jewish, East Asian, non-Finnish European, and South Asian) and others that have at least 1% representation in the United States (including United States Territories).

moderate severity (short-chain acyl-CoA dehydrogenase deficiency was categorized as mild) (Figure 1B).[23]

ACOG's 3 severity criteria specifically describe severity-related phenotypes.[2] We therefore also applied ACOG's severity criteria and determined thresholds by examining which of these criteria were met by each of the 7 conditions recommended for screening by both ACOG and ACMG.[4,8] Among these 7 conditions, 6 had a detrimental effect on quality of life, 4 caused cognitive or physical impairment, and 3 required surgical or medical intervention (Figure 1B, Supplemental Table 5). Only 1 of the 7 conditions, SMA, met all 3 severity-related criteria; 4 conditions met 2 criteria; and 2 conditions met 1 criterion. No distinctive pattern could be seen in the severity-related criteria met by these conditions other than meeting at least 1 criterion. We therefore considered a condition to meet the collective severity-related threshold if it met at least 1 of ACOG's 3 severity-related criteria.

Criterion 6 addresses age of onset (Table 1). ACOG specifies that conditions should have an onset early in life,[2] whereas ACMG does not comment specifically on age of onset as a panel design criterion.[8] Therefore, to determine a conservative threshold for age of onset, we examined which of the 7 conditions recommended by both ACMG and ACOG for screening in 1 or more race/ethnicity[4,8] had an onset early in life. All 7 conditions had an onset in infancy or childhood (Figure 1B, Supplemental Table 5). We therefore set an age of onset threshold at infancy or childhood and considered conditions with an onset during adolescence not to meet this threshold.

Because previous studies have included age of onset as an indicator of severity,[23,29] we evaluated it together with the 3 other ACOG severity criteria, finding that 165 of 176 conditions (93.8%) had an onset in infancy or childhood and met at least 1 ACOG severity criterion, thus meeting the conservative severity threshold that is inclusive of infancy or childhood onset (Figure 1B, Supplemental Table 5). This 165-condition panel would capture 94.2% of carriers and 92.3% of ARCs compared with a 176-condition panel (Supplemental Table 6).

Prenatal diagnosis as a criterion for panel inclusion

Criterion 7 is based on both ACOG's and ACMG's statements that conditions included in ECS panels should have the capability to be diagnosed prenatally (Table 1).[2,8] Single-gene disorders, such as those screened by carrier screening panels, can be diagnosed by targeted genetic testing of amniocytes or chorionic villi if the particular variant carried by parents has been identified.[30] All 176 conditions evaluated here can be diagnosed prenatally (Supplemental Table 5), as confirmed by additional information received from diagnostic testing laboratories[31] and GeneReviews summaries.[32]

Analytical validity as criterion for panel inclusion

Criterion 8 addresses analytical validity and is based on ACMG's statement that analytical validity of the screening method should be established. We interpret this statement to refer to the screening method for each condition. All 176 conditions evaluated here have established and published analytical validity (Supplemental Table 5).[25]

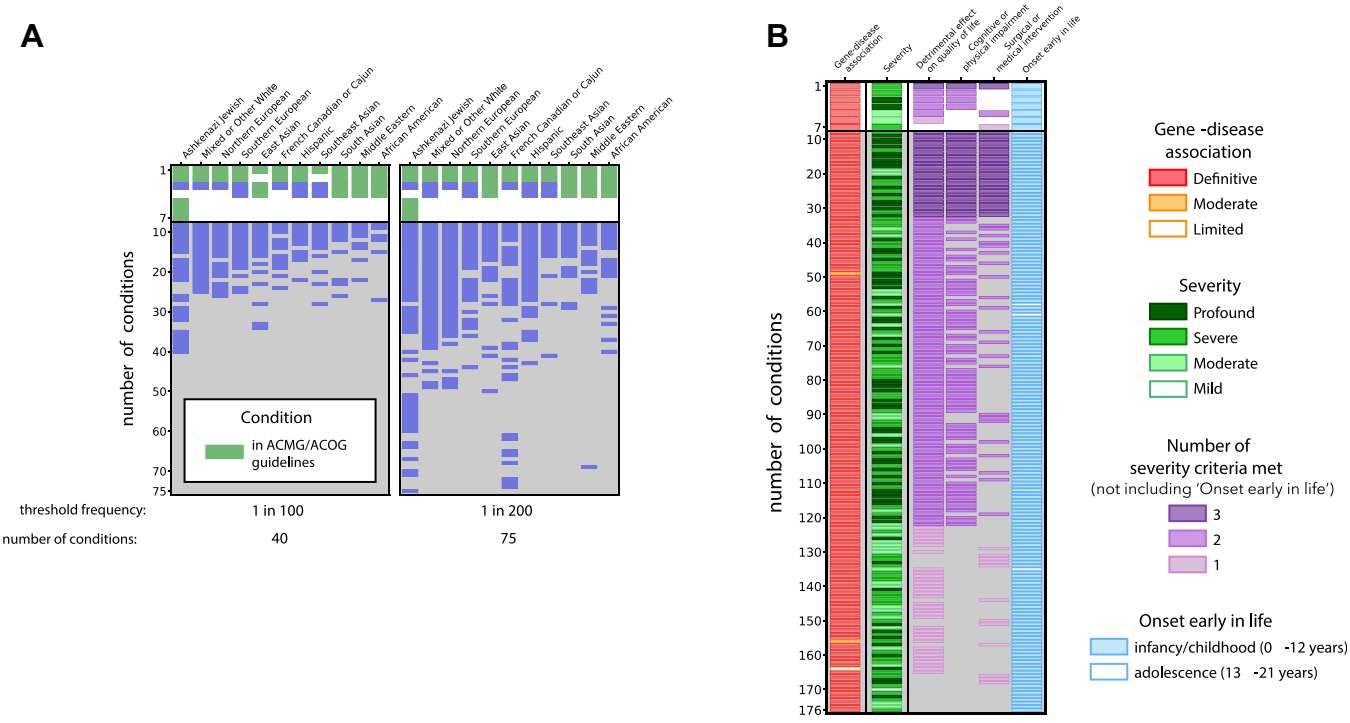

Figure 1 A. Number of conditions in each ethnicity that meet carrier frequency thresholds of ≥1 in 100 or ≥1 in 200. Conditions meeting the given threshold in each ethnicity are represented by boxes (with each box representing 1 condition). Within each ethnicity, conditions are listed vertically in order of decreasing carrier frequency. The conditions in larger boxes above the solid line are those recommended by both ACMG and ACOG for screening in 1 or more ethnicity and that meet the carrier frequency threshold. Green indicates conditions recommended in the corresponding ethnicity. B. Genotype–phenotype relationship and severity criteria met among 176 conditions. The first column represents the genotype–phenotype relationship criterion, indicating the ClinGen gene–disease association categorization of each condition. The next column represents the severity categorization as determined by Arjunan et al.[23] The next 3 columns indicate the 3 ACOG severity criteria related to quality of life, impairment, and intervention. Meeting 3, 2, and 1 criteria are indicated by dark purple, light purple, and pink colors, respectively. The sixth column indicates the "onset early in life" criterion. The conditions in larger boxes above the solid line are those recommended by both ACMG and ACOG for screening in 1 or more ethnicity. ACMG, American College of Medical Genetics and Genomics; ACOG, American College of Obstetricians and Gynecologists.

A guidelines-consistent panel

To determine the composition of a panel consistent with both ACOG and ACMG panel design criteria, we combined the thresholds for each criterion that were applied to all 176 conditions. For criteria that differed between ACOG and ACMG, we applied the more conservative and/or specific of the thresholds. The resulting thresholds were carrier frequency of ≥1 in 100 in any race/ethnicity, moderate or higher gene–disease association evidence level, meeting at least 1 of ACOG's 3 severity criteria, having an onset in infancy or childhood, the ability for the condition to be diagnosed prenatally, and published analytical validity (Figure 2). Taken together, this guidelines-consistent panel would consist of 37 conditions (Figure 2, Table 2), would include all 7 conditions currently recommended by both ACMG and ACOG for screening in at least 1 race/ethnicity, and would capture 63.0% of carriers and 84.6% of ARCs compared with a 176-condition panel (Figure 3A, Supplemental Table 6).

We also examined the composition of a panel meeting more permissive interpretations of certain criteria, including having a carrier frequency threshold of ≥1 in 200 in any race/ethnicity, a moderate or higher gene–disease association, at least moderate severity, age of onset during or before adolescence, the ability for the condition to be diagnosed prenatally, and published analytical validity. This more permissive, but still guidelines-consistent, panel would consist of 74 conditions (Figure 2) and would capture 81.4% of carriers and 96.6% of ARCs compared with a 176-condition panel (Figure 3A, Supplemental Table 6).

Because the goal of carrier screening is to maximize the number of ARCs identified per individual screened, we evaluated the number of new ARCs identified for different panels. As panels become larger in size because of inclusion of rare conditions, the number of additional ARCs identified decreases (Figure 3B). A panel with conditions that have a population-wide carrier frequency of ≥1 in 100 identifies 100 ARCs per 10,000 patients screened, and a panel with conditions that have a carrier frequency of ≥1 in 200 identifies 108 ARCs per 10,000 patients screened (Figure 3B). We also compared the efficiency of ARC detection, defined as the ratio of the carrier detection rate to the ARC detection rate for different panels; a panel with a

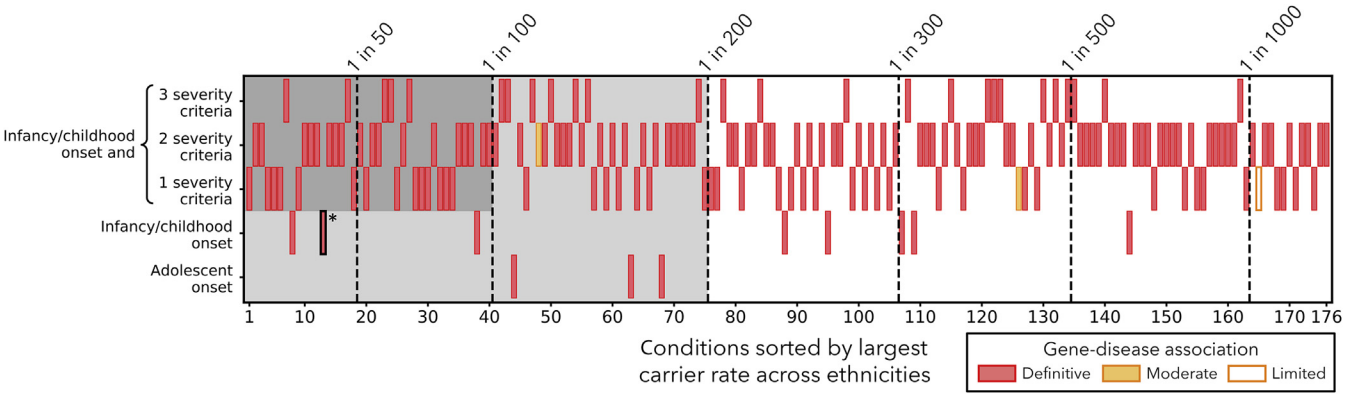

Figure 2 Summary of all panel design criteria met by each of 176 conditions. Conditions are sorted horizontally by carrier frequency of the ethnicity with the highest carrier frequency (shown at top), and the vertical axis indicates age of onset and American College of Obstetricians and Gynecologists (ACOG) severity criteria. The genotype–phenotype criterion is indicated by boxes colored red (definitive), orange (moderate) or clear (limited). As all 176 conditions evaluated can be diagnosed prenatally and have published analytical validity data, those criteria are not shown. Conditions within the dark gray box in the upper left represent the 37-condition conservative guidelines-consistent panel, ie, the conditions that meet carrier frequency of ≥1 in 100 in any ethnicity, moderate or definitive gene–disease association, at least 1 ACOG severity criterion, and onset in infancy or childhood. Conditions in both the dark gray and light gray boxes represent the 74-condition permissive guidelines-consistent panel, ie, conditions that meet carrier frequency of ≥1 in 200 in any ethnicity, moderate or definitive gene–disease association, moderate or higher severity, and an adolescent or earlier age of onset. Only 1 condition (short-chain acyl-CoA dehydrogenase deficiency) in the light gray box did not meet the moderate or higher overall severity criterion; this condition is denoted by a black border and an asterisk and is not included in the 74-condition panel.

lower ratio indicates more efficiency. The efficiency of ARC detection for the 37-condition guidelines-consistent panel was 31:1 (Figure 3C). The efficiency of ARC detection for the 74-condition guidelines-consistent panel was 35:1 (Figure 3C). Both panels were more efficient than the 7-gene ACOG/ACMG panel, for which the efficiency of ARC detection was 36:1.

Discussion

Equitable identification of carriers and ARCs across diverse populations is consistent with the joint statement by ACOG committing to eliminating racial inequities that lead to disparate health outcomes[17] and with the statement of ACMG's president that ACMG is committed to addressing factors that lead to disparities in health care delivery and access.[18] ACMG cited the inequity and scientific flaws associated with race/ethnicity-based screening as justification for its recommendation that carrier screening for 112 conditions be offered to all individuals who are pregnant or considering pregnancy without regard to ethnicity.[8]

Both ACOG and ACMG have published criteria that conditions should meet to be included on carrier screening panels. We considered both conservative and permissive interpretations of criteria to identify 2 guidelines-consistent panels. The conservative panel, identified by applying a carrier frequency threshold of ≥1 in 100 in any race/ethnicity (thus approximating ACMG's tier 2 category[8]), moderate or higher gene–disease association, infancy or childhood onset, and descriptive severity criteria, resulted in the identification of a panel of 37 conditions (Figure 2, Table 1). We also identified a 74-condition permissive panel that met the carrier frequency threshold suggested by ACMG (≥1 in 200 in any race/ethnicity), moderate or higher gene–disease association, moderate or higher severity, and an age of onset during or before adolescence, thus approximating ACMG's tier 3 category.[8] Both the 37-condition conservative panel and the 74-condition permissive panel identify a majority of ARCs in comparison with a 176-condition panel and show similar efficiency of ARC detection and therefore are reasonable clinical options for providers wishing to adhere to guidelines-based panel design criteria.

Previous publications have addressed interpretation of panel design criteria, but these were incomplete because they did not incorporate recent analyses that have used data-driven approaches to quantify each criterion.[20,21,33] For example, Stevens et al[20] evaluated genes from several commercially available panels for their adherence to a combination of ACOG and ACMG panel design criteria but did not include severity because a framework for evaluating severity had only recently been published.[29] In contrast, a 2018 study suggested that severity be used as a primary criterion for condition inclusion but did not provide a recommendation for how to evaluate severity.[21] Kraft et al[33] interpreted both ACOG and ACMG criteria as broad categories addressing scope, impact, age of onset, and actionability but did not propose guidance on how to objectively define the criteria and evaluate conditions for their adherence to the criteria. Our study goes beyond these previous studies because it applies evidence-based definitions of all ACOG criteria and the most recent ACMG criteria to a large number of conditions.

Table 2 Conditions that meet evidence-based thresholds of ACOG and ACMG panel design criteria

Condition[a]	Gene	Ethnicity[b]	Carrier Frequency ("1 in x")	Gene–Disease Association	Onset in Infancy or Childhood	Detrimental Effect on QOL	Cognitive or Physical Impairment	Surgical or Medical Intervention	Severity Category[c]	Prenatal Diagnosis Possible	Analytical Validity Established
Alpha thalassemia[d]	*HBA1 HBA2*	Af/AA	3	Definitive	Yes	Yes	No	No	Moderate	Yes	Yes
Hb beta chain-related hemoglobinopathy (including sickle cell disease)[d]	*HBB*	Af/AA	8	Definitive	Yes	Yes	No	Yes	Moderate	Yes	Yes
Familial Mediterranean fever	*MEFV*	AJ	11	Definitive	Yes	Yes	No	No	Moderate	Yes	Yes
Gaucher disease	*GBA*	AJ	18	Definitive	Yes	Yes	No	No	Severe	Yes	Yes
Cystic fibrosis[d]	*CFTR*	FrCa/Caj	20	Definitive	Yes	No	No	Yes	Severe	Yes	Yes
Phenylalanine hydroxylase deficiency	*PAH*	AJ	21	Definitive	Yes	Yes	Yes	Yes	Severe	Yes	Yes
GJB2-related DFNB1 nonsyndromic hearing loss and deafness	*GJB2*	AJ	24	Definitive	Yes	Yes	No	No	Moderate	Yes	Yes
Hexosaminidase A deficiency (Tay-Sachs disease)[d]	*HEXA*	AJ	35	Definitive	Yes	Yes	Yes	No	Profound	Yes	Yes
Wilson disease	*ATP7B*	EA	39	Definitive	Yes	Yes	No	Yes	Moderate	Yes	Yes
Smith-Lemli-Opitz syndrome	*DHCR7*	AJ	40	Definitive	Yes	Yes	Yes	No	Severe	Yes	Yes
Familial dysautonomia[d]	*ELP1*	AJ	41	Definitive	Yes	Yes	Yes	No		Yes	Yes
Spinal muscular atrophy[d]	*SMN1*	SE	43	Definitive	Yes	Yes	Yes	Yes	Severe	Yes	Yes
Carnitine palmitoyltransferase II deficiency	*CPT2*	AJ	47	Definitive	Yes	Yes	No	No	Profound	Yes	Yes
Pendred syndrome	*SLC26A4*	EA	52	Definitive	Yes	Yes	No	No	Moderate	Yes	Yes
Congenital disorder of glycosylation type Ia	*PMM2*	FrCa/Caj	53	Definitive	Yes	Yes	Yes	No	Profound	Yes	Yes
Canavan disease[d]	*ASPA*	AJ	54	Definitive	Yes	Yes	Yes	No	Profound	Yes	Yes
Krabbe disease	*GALC*	EA	54	Definitive	Yes	Yes	Yes	Yes	Profound	Yes	Yes
Medium chain acyl-CoA dehydrogenase deficiency	*ACADM*	FrCa/Caj	57	Definitive	Yes	Yes	Yes	Yes	Profound	Yes	Yes
USH2A-related disorders	*USH2A*	FrCa/Caj	58	Definitive	Yes	Yes	No	No	Moderate	Yes	Yes
Pompe disease	*GAA*	SE	58	Definitive	Yes	Yes	No	Yes	Severe	Yes	Yes
Primary hyperoxaluria type 3	*HOGA1*	AJ	60	Definitive	Yes	No	No	Yes	Moderate	Yes	Yes
Hereditary fructose intolerance	*ALDOB*	SE	71	Definitive	Yes	No	No	Yes	Severe	Yes	Yes

(continued)

Table 2 Continued

Condition[a]	Gene	Ethnicity[b]	Carrier Frequency ("1 in x")	Gene–Disease Association	Onset in Infancy or Childhood	Detrimental Effect on QOL	Cognitive or Physical Impairment	Surgical or Medical Intervention	Severity Category[c]	Prenatal Diagnosis Possible	Analytical Validity Established
Autosomal recessive polycystic kidney disease, PKHD1-related	*PKHD1*	AJ	73	Definitive	Yes	Yes	No	Yes	Severe	Yes	Yes
Primary carnitine deficiency	*SLC22A5*	EA	78	Definitive	Yes	No	No	Yes	Profound	Yes	Yes
ABCC8-related familial hyperinsulinism	*ABCC8*	AJ	81	Definitive	Yes	No	No	Yes	Severe	Yes	Yes
Dihydrolipoamide dehydrogenase deficiency	*DLD*	AJ	82	Definitive	Yes	Yes	Yes	No	Profound	Yes	Yes
FKTN-related disorders	*FKTN*	AJ	86	Definitive	Yes	Yes	Yes	No	Profound	Yes	Yes
Fanconi anemia, FANCC-related	*FANCC*	AJ	99	Definitive	Yes	Yes	No	Yes	Severe	Yes	Yes
Fragile X syndrome[a]	*FMR1*	AJ	105	Definitive	Yes	Yes	Yes	No	Severe	Yes	Yes
Dystrophinopathy (including Duchenne/Becker muscular dystrophy)[a]	*DMD*	SE	813	Definitive	Yes	Yes	Yes	No	Severe	Yes	Yes
Fabry disease[a]	*GLA*	FrCa/Caj	1050	Definitive	Yes	Yes	No	Yes	Severe	Yes	Yes
X-linked Alport syndrome[a]	*COL4A5*	EA	2427	Definitive	Yes	Yes	No	Yes	Severe	Yes	Yes
X-linked adrenoleukodystrophy[a]	*ABCD1*	AJ	3545	Definitive	Yes	Yes	Yes	Yes	Profound	Yes	Yes
X-linked juvenile retinoschisis[a]	*RS1*	SEA	4516	Definitive	Yes	Yes	No	No	Moderate	Yes	Yes
X-linked congenital adrenal hypoplasia[a]	*NR0B1*	EA	6065	Definitive	Yes	No	No	Yes	Severe	Yes	Yes
mucopolysaccharidosis type II[a]	*IDS*	AJ	7089	Definitive	Yes	Yes	No	Yes	Profound	Yes	Yes
X-linked myotubular myopathy[a]	*MTM1*	AJ	7089	Definitive	Yes	Yes	Yes	No	Severe	Yes	Yes
21-hydroxylase-deficient congenital adrenal hyperplasia	*CYP21A2*	ME	23	Definitive	No	No	No	Yes	Severe	Yes	Yes
Glycogen storage disease type Ia	*G6PC*	AJ	85	Definitive	No	No	No	Yes	Severe	Yes	Yes
NEB-related nemaline myopathy	*NEB*	AJ	104	Definitive	Yes	Yes	No	Yes	Severe	Yes	Yes

(continued)

Table 2 Continued

Condition[a]	Gene	Ethnicity[b]	Carrier Frequency ("1 in x")	Gene–Disease Association	Onset in Infancy or Childhood	Detrimental Effect on QOL	Cognitive or Physical Impairment	Surgical or Medical Intervention	Severity Category[c]	Prenatal Diagnosis Possible	Analytical Validity Established
Methylmalonic aciduria and homocystinuria, cblC type	*MMACHC*	Hisp	104	Definitive	Yes	Yes	Yes	Yes	Profound	Yes	Yes
Homocystinuria caused by cystathionine beta-synthase deficiency	*CBS*	FrCa/Caj	110	Definitive	Yes	Yes	Yes	Yes	Severe	Yes	Yes
Usher syndrome type 3	*CLRN1*	AJ	113	Definitive	Yes	No	No	No	Moderate	Yes	Yes
Mucolipidosis IV	*MCOLN1*	AJ	117	Definitive	Yes	Yes	No	Yes	Severe	Yes	Yes
Galactosemia	*GALT*	NE	120	Definitive	Yes	Yes	Yes	Yes	Profound	Yes	Yes
Joubert syndrome 2	*TMEM216*	AJ	121	Moderate	Yes	Yes	No	Yes	Profound	Yes	Yes
Niemann-Pick disease, SMPD1-associated	*SMPD1*	AJ	124	Definitive	Yes	Yes	No	Yes	Profound	Yes	Yes
PEX1-related Zellweger syndrome spectrum	*PEX1*	FrCa/Caj	127	Definitive	Yes	Yes	No	Yes	Profound	Yes	Yes
Niemann-Pick disease type C	*NPC1*	FrCa/Caj	127	Definitive	Yes	Yes	No	Yes	Profound	Yes	Yes
Argininosuccinic aciduria	*ASL*	FrCa/Caj	129	Definitive	Yes	Yes	Yes	Yes	Profound	Yes	Yes
LAMA2-related muscular dystrophy	*LAMA2*	FrCa/Caj	129	Definitive	Yes	Yes	No	Yes	Moderate	Yes	Yes
Maple syrup urine disease type 1B	*BCKDHB*	AJ	129	Definitive	Yes	Yes	Yes	Yes	Profound	Yes	Yes
Bloom syndrome	*BLM*	AJ	133	Definitive	Yes	No	No	Yes	Severe	Yes	Yes
Sulfate transporter-related osteochondrodysplasia	*SLC26A2*	FrCa/Caj	137	Definitive	Yes	Yes	No	Yes	Moderate	Yes	Yes
Bardet-Biedl syndrome, BBS10-related	*BBS10*	FrCa/Caj	137	Definitive	Yes	No	No	Yes	Severe	Yes	Yes
Tyrosinemia type I	*FAH*	AJ	143	Definitive	Yes	No	Yes	Yes	Profound	Yes	Yes
MYO7A-related disorders	*MYO7A*	FrCa/Caj	145	Definitive	Yes	No	No	Yes	Moderate	Yes	Yes
Bardet-Biedl syndrome, BBS1-related	*BBS1*	NE	148	Definitive	Yes	Yes	No	Yes	Severe	Yes	Yes
GNE myopathy	*GNE*	ME	155	Definitive	Yes	Yes	No	No	Moderate	Yes	Yes
PCDH15-related disorders	*PCDH15*	AJ	158	Definitive	Yes	No	No	Yes	Moderate	Yes	Yes
Biotinidase deficiency	*BTD*	SE	159	Definitive	Yes	No	Yes	Yes	Profound	Yes	Yes
RTEL1-related disorders	*RTEL1*	AJ	159	Definitive	Yes	No	No	Yes	Profound	Yes	Yes
Bardet-Biedl syndrome, BBS2-related	*BBS2*	AJ	159	Definitive	Yes	Yes	No	Yes	Severe	Yes	Yes
Sandhoff disease	*HEXB*	FrCa/Caj	166	Definitive	Yes	Yes	No	Yes	Profound	Yes	Yes
Calpainopathy	*CAPN3*	FrCa/Caj	166	Definitive	Yes	Yes	No	Yes	Moderate	Yes	Yes
ERCC6-related disorders	*ERCC6*	FrCa/Caj	166	Definitive	Yes	Yes	No	Yes	Profound	Yes	Yes
Dysferlinopathy	*DYSF*	FrCa/Caj	166	Definitive	Yes	Yes	No	No	Moderate	Yes	Yes

(continued)

Table 2 Continued

Condition[a]	Gene	Ethnicity[b]	Carrier Frequency ("1 in x")	Gene–Disease Association	Onset in Infancy or Childhood	Detrimental Effect on QOL	Cognitive or Physical Impairment	Surgical or Medical Intervention	Severity Category[c]	Prenatal Diagnosis Possible	Analytical Validity Established
Metachromatic leukodystrophy	*ARSA*	NE	168	Definitive	Yes	Yes	No	Yes	Profound	Yes	Yes
Very-long-chain acyl-CoA dehydrogenase deficiency	*ACADVL*	NE	172	Definitive	Yes	No	Yes	Yes	Severe	Yes	Yes
Mucopolysaccharidosis type I	*IDUA*	NE	172	Definitive	Yes	Yes	Yes	Yes	Profound	Yes	Yes
Cartilage-hair hypoplasia	*RMRP*	AJ	192	Definitive	Yes	No	No	Yes	Severe	Yes	Yes
X-linked severe combined immunodeficiency[a]	*IL2RG*	AJ	14178	Definitive	Yes	No	No	Yes	Severe	Yes	Yes
ATP7A-related disorders[a]	*ATP7A*	Hisp	14803	Definitive	Yes	No	Yes	Yes	Profound	Yes	Yes
ornithine transcarbamylase deficiency[a]	*OTC*	Hisp	14803	Definitive	Yes	Yes	Yes	Yes	Profound	Yes	Yes

Unshaded rows indicate conditions that meet conservative thresholds, shaded rows indicate permissive thresholds.

A carrier frequency of 1 in 10,000 for X-linked conditions is equivalent to a carrier frequency of 1 in 100 for autosomal recessive conditions. A carrier frequency of 1 in 40,000 for X-linked conditions is equivalent to a of carrier frequency 1 in 200 for autosomal recessive conditions.

ACMG, American College of Medical Genetics and Genomics; *ACOG,* American College of Obstetricians and Gynecologists; *Af/AA*, African or African American; *AJ*, Ashkenazi Jewish; *EA*, East Asian; *FrCa/Caj*, French Canadian or Cajun; *Hisp*, Hispanic; *ME*, Middle Eastern; *NE*, Northern European; *SEA*, Southeast Asian; *SE*, Southern European.

[a]X-linked condition. A 1 in 10,000 carrier frequency for X-linked conditions is equivalent to a 1 in 100 carrier frequency for autosomal recessive conditions.

[b]Ethnicity with highest carrier frequency. Does not include Native American, Pacific Islander, Finnish, or Unknown ethnicity.

[c]Based on Arjunan et al.[23]

[d]Recommended by ACOG and/or ACMG for screening in one or more ethnicity.

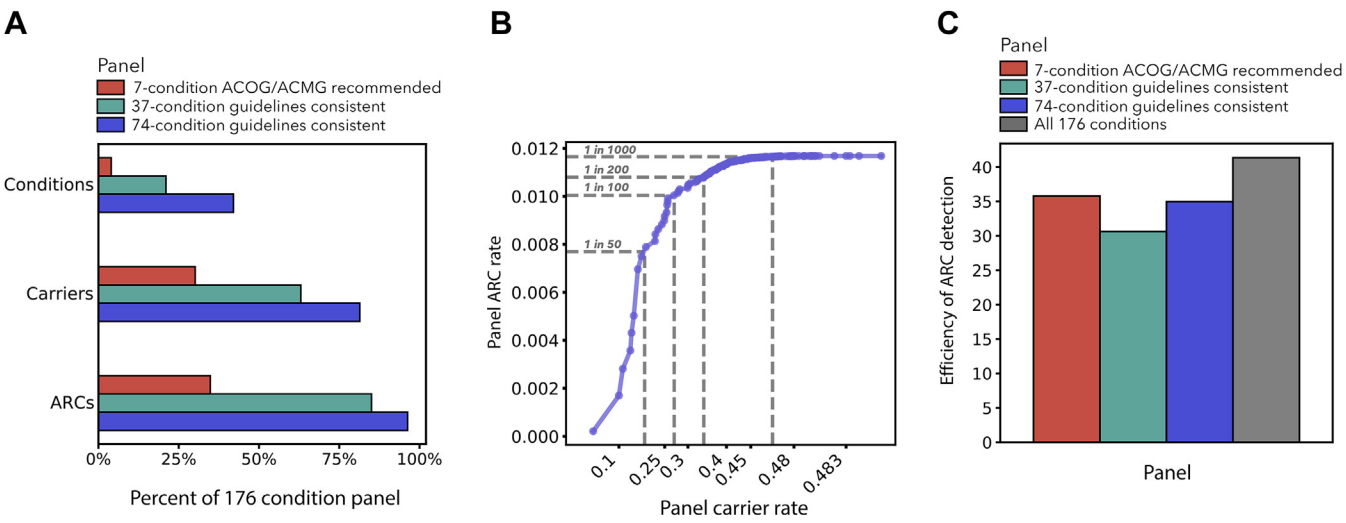

Figure 3 A. Relative proportion of conditions, carriers, and ARCs detected for each of the indicated panels compared with that of a 176-condition panel. Carrier and ARC rates for panels are indicated in Supplemental Table 6 and were calculated population-wide using data from the United States Census to weight ethnicities. B. Panel ARC rate as a function of panel carrier rate. The dotted lines denote respective carrier frequency thresholds. C. Efficiency of ARC detection, which is the ratio of panel carrier rate to panel ARC rate for each of the indicated panels. ACMG, American College of Medical Genetics and Genomics; ACOG, American College of Obstetricians and Gynecologists; ARC, at-risk couple.

The process of interpreting panel design criteria revealed the need for important clarifications to make them consistently applicable. For example, ACOG guidelines state that conditions included on carrier screening panels should meet several of 7 criteria,[2] and although ACMG provided specificity by suggesting thresholds by which to evaluate conditions, it too did not specify whether all or only certain criteria must be met.[8] For example, many of the conditions included on the ACMG tier 3 list have not been curated by ClinGen and therefore have unpublished genotype–phenotype association. Analysis of CF, a condition that has been recommended for pan-ethnic screening by both ACOG and ACMG for nearly 2 decades, suggests that it is not necessary for conditions to meet all criteria to be appropriate for panel inclusion because it met only 6 of the 8 collective criteria (Table 2). Explicit language in guidelines stating exactly which of the criteria must be met is needed to provide straightforward guidance on and to promote quality and consistency in panel design to laboratories offering carrier screening. Interpreting guidelines criteria as demonstrated in this study, in addition to carefully understanding how ACMG developed its recommended tier 3 list, provides a roadmap for guidelines-consistent iterations of carrier screening panels. Consistent criteria from both ACMG and ACOG would better facilitate implementation of guidelines by laboratories. Clear guidance is also important for providers who strive to offer guidelines-based care and for payers to ensure that the individuals they insure have access to guidelines-based care.

The ACMG recently applied its updated criteria to identify 112 conditions (113 genes counting *HBA1* and *HBA2* separately) that should be offered to all who are pregnant or considering pregnancy (tier 3 screening).[8] Using similar thresholds, we identified 74 conditions that met all permissive criteria applied in this study. This discrepancy in number of conditions is partially explained by differences in the conditions evaluated in this study versus those by ACMG. ACMG evaluated 415 autosomal recessive conditions, X-linked conditions listed in OMIM, ACMG's secondary findings list,[34] and a subset of conditions included in the recommended universal newborn screening panel. In contrast, our study evaluated only conditions for which data were published and/or available to assess adherence to all panel design criteria. Many of the conditions ACMG evaluated did not have specific severity classifications (291 conditions) or published ClinGen gene–disease associations (186 conditions) and therefore could not be evaluated in this study (Supplemental Table 7). Fifty-three conditions were included in both ACMG's tier 3 panel and our permissive panel (Supplemental Figure 1). Fifty-nine were included on the ACMG tier 3 list but excluded from the permissive panel; of these, 46 did not have severity or ClinGen gene–disease association classifications available. Conversely, of the 21 conditions that were included in the permissive panel but excluded from the ACMG tier 3 list, 10 were not evaluated by ACMG.

The use of different databases—Genome Aggregation Database (gnomAD) v2.0.2 by ACMG[8] and our laboratory's database for this study—to determine race/ethnicity-specific carrier frequencies also contributes to the discrepancy in the number of conditions on ACMG's tier 3 list and our permissive panel. Among the conditions on the ACMG tier 3 list but not on the permissive panel, 13 had carrier frequencies of <1 in 200 in at least 1 ethnicity in

the Myriad database. Eleven conditions on the permissive panel but not on ACMG's tier 3 list had carrier frequencies of <1 in 200 in any ethnicity in the gnomAD database (or <1 in 40,000 prevalence for X-linked conditions). Differences in carrier frequencies may be due to mechanisms used to collect race/ethnicity information. GnomAD uses ancestry-specific single-nucleotide variation (formerly single-nucleotide polymorphisms) to sort individuals into categories,[35] whereas in our database, race/ethnicity is self-reported. The ancestry categories in gnomAD and the race/ethnicity categories in our database are only partially overlapping, resulting in the inability to compare some categories. Furthermore, poor representation of races/ethnicities can artificially increase or decrease carrier frequencies. To account for this possibility, we did not include races/ethnicities for which there were fewer than 1000 individuals; ACMG may have used a different threshold or mechanism to control for poor representation within gnomAD. Methods used to exclude those with known high risk could also result in carrier frequency differences. Our database excludes individuals who have reported high risk for carrier status, such as personal or family history of the condition. It is possible that carrier frequencies in our database could be artificially increased if those with high risk do not report such risk and are therefore inadvertently included in it. GnomAD controls for known high risk by excluding those diagnosed with severe genetic disease and their family members[35]; however, it has been suggested that this method may result in underestimates of carrier frequency.[19] Because panel size is most influenced by carrier frequency threshold, reanalyses and comparisons of carrier frequencies should be undertaken as databases grow and become more racially/ethnically diverse. We encourage laboratories to share carrier frequency data, as we have in this study, to enable robust analyses across diverse populations.

This study has limitations that should be noted. First, conditions other than those evaluated in this study may also meet guidelines criteria, making them appropriate candidates for carrier screening panel inclusion. We urge laboratories to apply the approach presented in this study to provide transparency on their panels' adherence to criteria. Second, it is possible that neither ACOG nor ACMG intended for the criteria to be interpreted as presented in this study. However, thresholds were based on those explicitly cited by ACOG or ACMG or the degree to which conditions recommended for screening met criterion definitions. Finally, the measures previously discussed were taken to ensure that carrier frequencies were accurate and closely representative of the general population; however, we cannot be certain that they are not overestimates or underestimates.

Carrier screening panel design criteria that can be clearly interpreted and applied are needed to ensure quality and consistency of carrier screening offerings. The panels identified here are consistent with evidence-based interpretations of ACOG and ACMG panel design criteria and more effectively identify carriers and ARCs, regardless of their race/ethnicity, than past screening paradigms that relied on race and/or ethnicity to stratify care.

Data Availability

Carrier and at-risk couple frequencies reported in this study are included in Supplemental Tables 3 and 4. All other data included in this study have been previously published and have been appropriately referenced.

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Author Information

Conceptualization: K.J.T., R.B., R.T., A.A., D.M., K.E.K.; Data Curation: K.J.T., R.B., R.T., A.A., D.M., K.E.K.; Formal Analysis: R.B., R.T.; Supervision: J.G., H.B.; Writing-original draft: K.J.T., R.B., R.T., A.A.; Writing-review and editing: K.J.T., R.B., R.T., A.A., J.G., H.B.

Ethics Declaration

This study was reviewed and determined to be exempt by the Advarra Institutional Review Board (Protocol # Pro00041540).

Conflict of Interest

Rotem Ben-Shachar, Katherine Johansen Taber, and Dale Muzzey are current employees and shareholders of Myriad Genetics, Inc. Aishwarya Arjunan, James Goldberg, Kristjan E. Kaseniit, and Raul Torres are former employees of Myriad Genetics, Inc. Haywood Brown is the Executive Medical Director of the Access to Equitable Carrier Screening Coalition, for which he receives compensation. No funding was provided for the purpose of this study. All work was conducted by authors in the course of their respective employment.

Additional Information

The online version of this article (https://doi.org/10.1016/j.gim.2021.09.009) contains supplementary material, which is available to authorized users.

References

1. Beauchamp KA, Muzzey D, Wong KK, et al. Systematic design and comparison of expanded carrier screening panels. *Genet Med*. 2018;20(1):55–63. http://doi.org/10.1038/gim.2017.69.
2. Committee opinion no. 690: carrier screening in the age of genomic medicine. *Obstet Gynecol*. 2017;129(3):e35–e40. http://doi.org/10.1097/AOG.0000000000001951.
3. Edwards JG, Feldman G, Goldberg J, et al. Expanded carrier screening in reproductive medicine-points to consider: a joint statement of the American College of Medical Genetics and Genomics, American College of Obstetricians and Gynecologists, National Society of Genetic Counselors, Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine. *Obstet Gynecol*. 2015;125(3):653–662. http://doi.org/10.1097/AOG.0000000000000666.
4. Committee opinion no. 691: carrier screening for genetic conditions. *Obstet Gynecol*. 2017;129(3):e41–e55. http://doi.org/10.1097/AOG.0000000000001952.
5. Prior TW, Professional Practice and Guidelines Committee. Carrier screening for spinal muscular atrophy. *Genet Med*. 2008;10(11):840–842. http://doi.org/10.1097/GIM.0b013e318188d069.
6. Watson MS, Cutting GR, Desnick RJ, et al. Cystic fibrosis population carrier screening: 2004 revision of American College of Medical Genetics mutation panel. *Genet Med*. 2004;6(5):387–391. Published correction appears in *Genet Med*. 2004;6(6):548. Published correction appears in *Genet Med*. 2005;7(4):286. https://doi.org/10.1097/01.gim.0000139506.11694.7c.
7. Gross SJ, Pletcher BA, Monaghan KG, Professional Practice and Guidelines Committee. Carrier screening in individuals of Ashkenazi Jewish descent. *Genet Med*. 2008;10(1):54–56. http://doi.org/10.1097/GIM.0b013e31815f247c.
8. 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*. Published online July 21, 2021. Published correction appears in *Genet Med*. August 27, 2021. https://doi.org/10.1038/s41436-021-01203-z.
9. Akler G, Birch AH, Schreiber-Agus N, et al. Lessons learned from expanded reproductive carrier screening in self-reported Ashkenazi, Sephardi, and Mizrahi Jewish patients. *Mol Genet Genomic Med*. 2020;8(2):e1053. http://doi.org/10.1002/mgg3.1053.
10. Ben-Shachar R, Svenson A, Goldberg JD, Muzzey D. A data-driven evaluation of the size and content of expanded carrier screening panels. *Genet Med*. 2019;21(9):1931–1939. http://doi.org/10.1038/s41436-019-0466-5.
11. Haque IS, Lazarin GA, Kang HP, Evans EA, Goldberg JD, Wapner RJ. Modeled fetal risk of genetic diseases identified by expanded carrier screening. *JAMA*. 2016;316(7):734–742. http://doi.org/10.1001/jama.2016.11139.
12. Kaseniit KE, Haque IS, Goldberg JD, Shulman LP, Muzzey D. Genetic ancestry analysis on >93,000 individuals undergoing expanded carrier screening reveals limitations of ethnicity-based medical guidelines. *Genet Med*. 2020;22(10):1694–1702. http://doi.org/10.1038/s41436-020-0869-3.
13. Lazarin GA, Haque IS, Nazareth S, et al. An empirical estimate of carrier frequencies for 400+ causal Mendelian variants: results from an ethnically diverse clinical sample of 23,453 individuals. *Genet Med*. 2013;15(3):178–186. http://doi.org/10.1038/gim.2012.114.
14. Shraga R, Yarnall S, Elango S, et al. Evaluating genetic ancestry and self-reported ethnicity in the context of carrier screening. *BMC Genet*. 2017;18(1):99. http://doi.org/10.1186/s12863-017-0570-y.
15. Westemeyer M, Saucier J, Wallace J, et al. Clinical experience with carrier screening in a general population: support for a comprehensive pan-ethnic approach. *Genet Med*. 2020;22(8):1320–1328. Published correction appears in *Genet Med*. 2020;22(7):1282. https://doi.org/10.1038/s41436-020-0807-4.
16. Peyser A, Singer T, Mullin C, et al. Comparing ethnicity-based and expanded carrier screening methods at a single fertility center reveals significant differences in carrier rates and carrier couple rates. *Genet Med*. 2019;21(6):1400–1406. http://doi.org/10.1038/s41436-018-0331-y.
17. American Association of Gynecologic Laparoscopists, American Board of Obstetrics and Gynecology, American College of Obstetricians and Gynecologists, et al. Joint statement - obstetrics and gynecology: collective action addressing racism. American College of Obstetricians and Gynecologists Published August 2020. https://www.acog.org/-/media/project/acog/acogorg/files/pdfs/news/commitmentendracism-historyobgyn-082720-v8.pdf. Accessed November 10, 2020.
18. Gregg AR. Message from ACMG President: overcoming disparities. *Genet Med*. 2020;22(11):1758. http://doi.org/10.1038/s41436-020-0882-6.
19. Guo MH, Gregg AR. Estimating yields of prenatal carrier screening and implications for design of expanded carrier screening panels. *Genet Med*. 2019;21(9):1940–1947. http://doi.org/10.1038/s41436-019-0472-7.
20. Stevens B, Krstic N, Jones M, Murphy L, Hoskovec J. Finding middle ground in constructing a clinically useful expanded carrier screening panel. *Obstet Gynecol*. 2017;130(2):279–284. http://doi.org/10.1097/AOG.0000000000002139.
21. Chokoshvili D, Vears D, Borry P. Expanded carrier screening for monogenic disorders: where are we now? *Prenat Diagn*. 2018;38(1):59–66. http://doi.org/10.1002/pd.5109.
22. Balzotti M, Meng L, Muzzey D, et al. Clinical validity of expanded carrier screening: evaluating the gene-disease relationship in more than 200 conditions. *Hum Mutat*. 2020;41(8):1365–1371. http://doi.org/10.1002/humu.24033.
23. Arjunan A, Bellerose H, Torres R, et al. Evaluation and classification of severity for 176 genes on an expanded carrier screening panel. *Prenat Diagn*. 2020;40(10):1246–1257. http://doi.org/10.1002/pd.5762.
24. Hardin AP, Hackell JM, Committee on Practice and Ambulatory Medicine. Age limit of pediatrics. *Pediatrics*. 2017;140(3):e20172151. http://doi.org/10.1542/peds.2017-2151.
25. Hogan GJ, Vysotskaia VS, Beauchamp KA, et al. Validation of an expanded carrier screen that optimizes sensitivity via full-exon sequencing and panel-wide copy number variant identification. *Clin Chem*. 2018;64(7):1063–1073. http://doi.org/10.1373/clinchem.2018.286823.
26. Kaseniit KE, Collins E, Lo C, et al. Inter-lab concordance of variant classifications establishes clinical validity of expanded carrier screening. *Clin Genet*. 2019;96(3):236–245. http://doi.org/10.1111/cge.13582.
27. U.S. Population. United States Census Bureau. https://data.census.gov/cedsci/. Accessed October 10, 2021.
28. Strande NT, Riggs ER, Buchanan AH, et al. Evaluating the clinical validity of gene-disease associations: an evidence-based framework developed by the clinical genome resource. *Am J Hum Genet*. 2017;100(6):895–906. http://doi.org/10.1016/j.ajhg.2017.04.015.
29. Lazarin GA, Hawthorne F, Collins NS, Platt EA, Evans EA, Haque IS. Systematic classification of disease severity for evaluation of expanded carrier screening panels. *PLoS One*. 2014;9(12):e114391. http://doi.org/10.1371/journal.pone.0114391.
30. Practice bulletin no. 162: prenatal diagnostic testing for genetic disorders. *Obstet Gynecol*. 2016;127(5):e108–e122. http://doi.org/10.1097/AOG.0000000000001405.
31. Inheritest gene-specific sequencing. Integrated Genetics. https://www.integratedgenetics.com/providers/tests/carrier-screening/inheritest. Accessed October 10, 2021.
32. Adam MP, Ardinger HH, Pagon RA, et al. *GeneReviews*. University of Washington; 1993-2021 https://www.ncbi.nlm.nih.gov/books/NBK1116/. Accessed October 10, 2021.
33. Kraft SA, Duenas D, Wilfond BS, Goddard KAB. The evolving landscape of expanded carrier screening: challenges and opportunities. *Genet Med*. 2019;21(4):790–797. http://doi.org/10.1038/s41436-018-0273-4.
34. Miller DT, Lee K, Chung WK, et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2021;23(8):1381–1390. Published correction appears in *Genet Med*. 2021;23(8):1582-1584. https://doi.org/10.1038/s41436-021-01172-3.
35. Populations found in gnomAD v2.1 Release data. Genome Aggregation Database. Published 2018. https://gnomad.broadinstitute.org/blog/2018-10-gnomad-v2-1/. Accessed March 12, 2021.