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ACMG PRACTICE RESOURCE

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)

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Carrier screening began 50 years ago with screening for conditions that have a high prevalence in defined racial/ethnic groups (e.g., Tay–Sachs disease in the Ashkenazi Jewish population; sickle cell disease in Black individuals). Cystic fibrosis was the first medical condition for which panethnic screening was recommended, followed by spinal muscular atrophy. Next-generation sequencing allows low cost and high throughput identification of sequence variants across many genes simultaneously. Since the phrase "expanded carrier screening" is nonspecific, there is a need to define carrier screening processes in a way that will allow equitable opportunity for patients to learn their reproductive risks using next-generation sequencing technology. An improved understanding of this risk allows patients to make informed reproductive decisions. Reproductive decision making is the established metric for clinical utility of population-based carrier screening. Furthermore, standardization of the screening approach will facilitate testing consistency. This practice resource reviews the current status of carrier screening, provides answers to some of the emerging questions, and recommends a consistent and equitable approach for offering carrier screening to all individuals during pregnancy or preconception.

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INTRODUCTION

Carrier screening is used to identify individuals or couples that are at risk to have a child with an autosomal recessive or X-linked genetic disorder. Throughout this document, the term "carrier" specifically refers to individuals who are heterozygous for a pathogenic or likely pathogenic variant in an autosomal recessive or X-linked condition. Once identified, carriers of these disorders can become educated about their risks and consider a range of reproductive options. Historically, criteria for screening have included: phenotype severity that may impact decision making,[1,2] high prevalence of carriers in the screened population,[2] established analytic validity of screening methods,[2,3] predictable

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genotype–phenotype correlation,[2] available prenatal diagnosis and reproductive options.[2,4] Although general principles remain similar today these do not speak to the genes that should be included as part of routine carrier screening.

In 2013, the American College of Medical Genetics and Genomics (ACMG) linked the utility of carrier screening to reproductive decision making.[1] Decision making is inherently tied to the severity of any condition being screened. This consensus group recognized that there will be disagreement when defining the severity of various conditions. However, we used published definitions which include (1) profound: shortened lifespan during infancy or childhood, intellectual disability; (2) severe: death in early adulthood, impaired mobility or a [disabling] malformation involving an internal organ; (3) moderate: neurosensory impairment, immune deficiency or cancer, mental illness, dysmorphic features; and (4) mild: not meeting one of those described.[5]

Carrier screening for heritable autosomal recessive conditions, which began 50 years ago,[6] targeted at-risk populations who have been traditionally defined as an ethnic group that is geographically isolated or one with cultural norms and customs that limit random mating (Ashkenazi Jewish [AJ], Amish, Hutterites). The successful implementation of biochemical screening for Tay–Sachs disease (TSD) among the AJ population in the 1970s[7] paved the way to consider carrier screening for other disorders. TSD, a condition meeting the definition for profound severity, has a carrier frequency of approximately 1/30 among AJ and 1/300 among the general population.[8] Similarly, sickle cell disease has a long history of screening.[9] It has a carrier frequency of approximately 1/13 among "African-American[s]" and 1/20 in "Hispanic[s]" resulting in a carrier frequency of about 1/66 in the general population.[10] A wide range in the carrier frequencies of genetic conditions between at-risk groups and the general population raises questions of equity when implementing carrier screening. It raises concerns over how screening policies impact information that leads to reproductive decision making. Restricting carrier screening by using socially defined ethnic constructs or by self-identified ancestry is both inequitable and scientifically flawed. Importantly, those who self-identify with a specific race/ethnicity may be at odds with ancestry defined genetically, which is of relevance to carrier screening.[11,12] A recent report demonstrated that relying on self-identification of AJ ancestry as a criteria to screen for conditions common in the AJ population is imperfect.[13] It is important that carrier screening goes beyond commonly recognized at-risk groups and includes diverse populations.

The goals of carrier screening have not changed over time. However, the technology used in carrier screening has changed dramatically allowing for high throughput with rapid turnaround times.[14] As the cost of sequencing the entire genome has fallen,[15,16] so too have the costs of sequencing panels of genes. The American College of Medical Genetics and Genomics (ACMG)'s last official documents regarding carrier screening for specific conditions were published in 2004 and 2008.[17,18] ACMG adopted an ethnic and population neutral approach to carrier screening for cystic fibrosis and spinal muscular atrophy.[17,18] The American College of Obstetricians and Gynecologists (ACOG) also endorsed universal screening for these two conditions and suggested that one additional screening criterion might be a carrier frequency of ≥1/100.[19] Recommendations by ACMG predate advances in gene sequencing technology. Moreover, there is now a greater societal awareness over equity in care that has evolved since ACOG and ACMG published statements on carrier screening.[20] Whereas in prior years, carrier screening was a scarce resource reserved only for those with the highest risk; a more attainable price point now allows for the opportunity to reach every patient.

In 2015, the ACMG, along with other professional organizations, published a Points to Consider joint statement focused on expanded carrier screening[21] wherein general genetic principles and a historical perspective were discussed. An emphasis was placed on the consent process including elements of pre- and post-test counseling. The principles emphasized in that document remain important today. This current document considers more recent published information and closes gaps in the previously published Points to Consider while acknowledging technological advances in sequencing and the need for equity and distributive justice of genomic technologies. This document replaces the ACMG position statement on prenatal/preconception expanded carrier screening.[1]

Box 1. Consensus questions

1. Are analytical and clinical validity established for carrier screening?
2. Has clinical utility been established for carrier screening?
3. Is "expanded carrier screening" a precise term?
4. What screening approach should be offered to patients considering carrier screening?
5. Which autosomal recessive conditions are appropriate for carrier screening?
6. Which X-linked conditions are appropriate for carrier screening?
7. What should the clinician expect with regard to laboratory reporting of carrier screening results?
8. What should be emphasized during pretest and post-test counseling when performing carrier screening?

METHODS

This consensus group convened to develop and answer a series of questions that are important for clinicians and reproductive age patients to consider as part of the carrier screening process (Box 1).

RESULTS AND DISCUSSION

Consensus question 1: Are analytical and clinical validity established for carrier screening?

Analytical validity refers to how well the test predicts the presence or absence of a particular genetic change, which encompasses sensitivity, specificity, and accuracy among other factors.[22] Carrier screening relies on laboratory methods such as next-generation sequencing (NGS), polymerase chain reaction (PCR), Sanger sequencing, multiplex ligation-dependent probe amplification (MLPA), microarray, and other methods to identify small-scale genetic changes including single-nucleotide variants (SNVs), and large-scale structural variants (SVs), including copy-number variants (CNVs). It is important that laboratories put in place effective quality metrics within the various testing platforms used, to ensure accuracy of variants detected to prevent false negative and/or false positive calls. The ACMG has established guidelines for the development of NGS assays.[23] Each test method optimized for clinical use, should undergo robust validation processes as required by the Clinical Laboratory Improvement Amendments (CLIA) and the College of American Pathologists (CAP) to define the analytical sensitivity, analytical specificity, and analytical accuracy of an assay that establishes confidence in the detection, analysis, and reporting of genetic variants. Analytical validity is in part a function of the number of variants and number of genes interrogated. Interrogations of greater numbers of either variants or variants and genes has the potential for greater error; however, the CLIA validation process mitigates this concern.

Clinical validity relates a test's result to the condition for which the test is designed addressing the issue of how well the genetic variant being analyzed is related to the presence, absence, or risk of a specific disease.[22] In other words, a test has robust clinical validity when both the negative and positive predictive values are high.[24,25] Genetic variants are classified as either pathogenic, likely pathogenic, uncertain significance, likely benign, or benign.[26] Generally, in the setting of screening, laboratories report only

those variants that are classified as pathogenic (>99% certainty) or likely (>90% certainty) pathogenic. However, there are exceptions leading to instances where a variant of uncertain significance (VUS) is reported.[27] For example, when one member of a couple is known to carry a pathogenic or likely pathogenic variant, reporting a VUS after screening the second member of the couple may be considered.[27] The preconception counseling session ideally addresses return of results when a VUS is identified. It is important for patients to understand that changes in the interpretation of clinical genomic test results are possible and recontact may be important. Furthermore, when medical or family history changes this should be communicated with the patient's care provider.[28]

Carrier screening cannot completely eliminate the risk of being a carrier of a heritable condition, because:

- All genes that cause a condition may not be known.
- All genes that cause a condition may not be examined.
- Causative variants may be in a region not included in the test.
- Causative variants may be undetectable by the technology/analysis employed.
- Analysis of gene sequence and its structural variants may be technically difficult.
- Variants may be misclassified with regard to pathogenicity (e.g., laboratory's algorithm for classification of variants).

An individual's residual risk to be a carrier after having a negative screening test can be calculated as follows: Population Carrier frequency × (1 − Detection Rate). However, when carrier screening is implemented by simultaneously interrogating multiple variants within multiple genes for rare conditions, the carrier frequency and detection rate may not be known for each condition being screened. It is impractical to provide a precise residual risk after carrier screening that includes simultaneous analysis of multiple uncommon or rare variants within genes. Instead, patients should be aware that a negative screening test does not eliminate the risk of being a carrier for any condition (i.e., gene variant), although this risk is greatly reduced.

Carrier screening aims to identify pathogenic and likely pathogenic variants within genes known to cause a condition or phenotype of interest as underscored by the relationship between ClinVar and ClinGen. ClinVar[29] is a national registry for the classification of variants within genes. All laboratories that perform genetic testing are expected to report variants identified within their testing cohort using specific submission guidelines to ensure consistency. ClinGen[30,31] hosts a gene-level database (https://www.clinicalgenome.org) that displays results from its gene curation expert panels which score the association of a gene with a condition or phenotype. One of seven classes are used to describe this association: no evidence reported, refuted, disputed, limited, moderate, strong, definitive. Documenting case observations to support these associations relies on clinical information obtained through medical history, pedigree analysis, laboratory data, pathology studies, imaging, and physical examination.[25] It is easy to understand why conditions characterized by variable expressivity or reduced penetrance may produce a lower gene–disease association score. Either of these may make the clinical tools used to define a condition unreliable. For example, reduced penetrance may limit the value of pedigree analysis. Variable expressivity may cause difficulty in linking a physical exam finding to a genetic diagnosis. Sometimes a gene is associated with more than one condition, so within ClinGen a gene may be classified according to more than one clinical condition.

In summary:

- Analytical validity of carrier screening is to be established by a laboratory in compliance with CLIA/CAP regulations and adhering to ACMG Laboratory Standards and Guidelines.
- Establishing clinical validity is gene and condition specific. For example, *CFTR* and many (but not all) of its variants are associated with cystic fibrosis.[27]
- As evidence evolves, ClinVar and ClinGen continually update pathogenicity of variants and the association between genes and conditions, respectively.
- A negative screening result does *not* eliminate the risk of being a carrier for the conditions screened but does reduce that risk. The residual risk to be a carrier for any condition is never zero.
- It is not practical to generate a precise residual risk estimate for the group of conditions interrogated through multiplex screening after a negative screening result. This requires a defined carrier frequency and detection rate for all conditions screened.

Consensus question 2: Has clinical utility been established for carrier screening?

Clinical utility in its narrowest sense refers to the ability of a screening or diagnostic test to prevent or ameliorate adverse health outcomes such as mortality, morbidity, or disability through the adoption of efficacious treatments conditioned on test results.[32] The considerations that determine clinical utility are (1) whether the test and any subsequent interventions lead to an improved health outcome among people with a positive test result; and (2) what risks occur as a result of testing.[25] Importantly, the specific metric used to measure clinical utility is context specific. For carrier screening, clinical utility is measured by the fact that individuals or couples are informed and may alter reproductive decision making because of the carrier screening results.[33–35]

The clinical utility of carrier screening is represented by its ability to provide individuals an opportunity to discuss their risks and consider reproductive options that are available prepregnancy, during pregnancy, or after birth. Availability of reproductive options may depend on various socioeconomical, legal, and cultural factors in different regions. Examples of reproductive options include:

- In vitro fertilization with preimplantation genetic testing for monogenic conditions.
- Use of donor gamete/embryo.
- Adoption.
- Prenatal diagnosis using chorionic villus sampling or amniocentesis followed by a decision to either prepare for an affected child including special care after birth or terminate the pregnancy.
- A decision not to have children.

Studies have established that carrier screening of many conditions simultaneously does have an impact on reproductive decision making. Although these studies are few and represent survey data, they include more than 470,000 screened patients.[25,34–37] In the two largest studies (April 2014 through August 2015 and September 2015 through 2017), there were 110 and 176 genes analyzed, respectively. The response rates varied, but of those responding, a majority (~60%) took some action in response to being identified as an at-risk couple. In these studies, reproductive decision making was more common when patients received results before an established pregnancy (62–77%). The most common decisions in the largest study were to pursue in vitro fertilization with preimplantation genetic diagnosis (59%), undergo a diagnostic test during pregnancy (20%), and use of a donor gamete (7.7%). Adoption was being considered by 5.1% at the time survey data were collected.[35] In the two largest studies, an affected fetus was identified in 16% (3/19) to 36% (20/56) of those having a diagnostic procedure and 67% (2/3) and 40% (8/20) respectively discontinued their pregnancy.[34,35]

This workgroup acknowledges that studies listed above may not reflect the clinical utility in an ethnically diverse population of individuals seeking carrier testing. We encourage additional ethnically inclusive studies to address this issue in the future.

In summary:

- Carrier screening enables those screened to consider their reproductive risks, reproductive options, and to make informed decisions.
- Published evidence supports clinical utility for carrier screening of multiple conditions simultaneously.[33]

Consensus question 3: Is "expanded carrier screening" a precise term?

Expanded carrier screening is not well or precisely defined by professional organizations.[1,2,19,21] The term "expanded" might imply an increased number of genes, or a paradigm shift from screening populations with higher carrier frequencies to screening those without regard to ancestry, or both. For some, "expanded" may represent screening many more variants within a gene. It is important for patients and health-care professionals to communicate more precisely when speaking about carrier screening by using a precise and consistent language. Some molecular testing laboratories now offer obstetric care professionals "expanded carrier screening" packages that can include more than a thousand genes;[38] however, other laboratories screen several hundred and the overlap in genes between laboratories is limited. In practical terms, there is no industry standard when it comes to the number of genes interrogated for carrier screening that is used to inform reproductive decision making. Thus far, molecular testing laboratories have determined the genes/conditions on "expanded" carrier screening panels. We propose adopting a tiered definition of carrier screening model (Fig. 1), which will allow patients and health-care professionals to communicate with greater precision.

ACMG recommends:

- The phrase "expanded carrier screening" be replaced by "carrier screening".
- Adopting a more precise tiered system based on carrier frequency (Fig. 1).

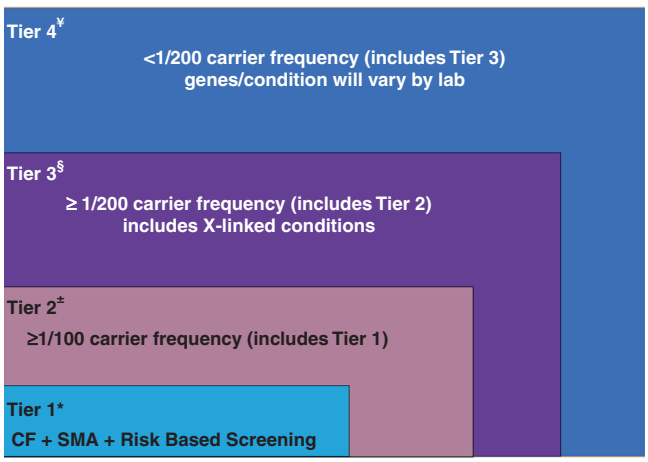

Fig. 1 The Euler diagram shows an overlapping tiered approach to carrier screening. *Recommended by the American College of Medical Genetics and Genomics (ACMG)[17,18] and American College of Obstetricians and Gynecologists (ACOG).[19] ±Recommended by ACOG.[2] §Supported by literature.[49,50] ¥Offered by molecular testing laboratories; the list of genes/conditions may vary by the laboratory. *CF* cystic fibrosis, *SMA* spinal muscular atrophy.

When patients are asked to report their ancestry, they respond with their learned/self-identified ancestry or report their ethnicity and race. The manner in which patients ascribe their ancestry is impacted by ethnic admixture, awareness and preservation of knowledge about ancestral origins, prevailing ideologies about race and racial divisions, and the number of generations removed from the arrival of immigrant ancestors.[39] Ethnic groups are defined by characteristics that include cultural traditions and norms.[40] There is increasing evidence that self-described ethnicity has inherent and unpredictable inaccuracies,[12,13,41–44] and genetically determined ancestry using single-nucleotide polymorphisms helps identify population/geographic origin, which is of particular importance for carrier screening. A risk-based strategy of carrier screening, which relied on self-described ethnicity, was first adopted for Tay–Sachs disease screening[7] and for the most part continues today.[19,21] In many cases reproductive partners are not chosen randomly.[45] Instead partners are chosen based on societal pressures, norms, and expectations. However, data show that population intermixing in the United States has increased dramatically over the last several centuries.[39] This requires that carrier screening be useful for all of those living in the United States regardless of their ancestry.

ACMG recommends:

- Carrier screening paradigms should be ethnic and population neutral and more inclusive of diverse populations to promote equity and inclusion.

Consensus question 4: What screening approach should be offered to patients considering carrier screening?

This consensus group recommends establishing a tier-based system of carrier screening, which will enhance communication and precision while advancing equity in carrier screening.

Tier 1 screening conveys the recommendations previously adopted by ACMG[17,18] and ACOG.[19] Tier 1 screening adopts an ethnic and population neutral approach when screening for cystic fibrosis and spinal muscular atrophy. Beyond these two conditions, additional carrier screening is determined after risk assessment, which incorporates personal medical and family history as well as laboratory and imaging information where appropriate.

Tier 2 carrier screening stems from an ACOG recommendation for conditions that have a severe or moderate phenotype and a carrier frequency of at least 1/100.[2] A carrier frequency of at least 1/100 would encompass screening all patients for spinal muscular atrophy (SMA) since SMA carrier frequency was thought to be 1/60 without regard to the population screened.[18] Studies have shown that the carrier frequency of SMA in the United States is not uniform across populations. In "Caucasian[s]" (This term is no longer used by the journal but is used in the original article to which these studies refer. We have therefore not changed the term but recognize it does not accurately describe the ancestry of the populations originally studied.[46]) this has been shown to be 1/46 and in "Hispanic[s]" 1/125.[47] For cystic fibrosis when 32 pathogenic variants were examined among a US population, carrier frequency ranged from 1/28 ("Caucasian") (This term is no longer used by the journal but is used in the original article to which these studies refer. We have therefore not changed the term but recognize it does not accurately describe the ancestry of the populations originally studied.[46]) to 1/105 ("African American") and 1/261 ("Asian").[48] These data demonstrate that carrier screening for two common conditions using a carrier frequency threshold of 1/100 may not be equitable across diverse populations. Others have shown that limiting the carrier frequency to ≥1/100 creates missed opportunities to identify couples at risk for serious conditions.[49,50]

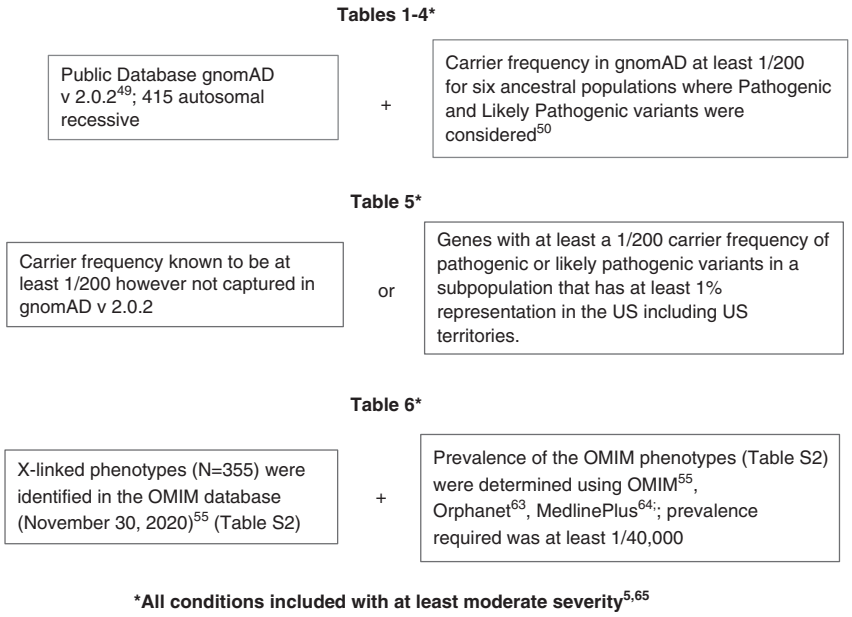

Fig. 2 The criterion used to generate the list of genes recommended for screening in Tables 1-6 are shown. Criterion for genes listed in Tables 1-4 were identical and derive from gnomAD. Those genes listed in Table 5 do not derive from gnomAD data. The X-linked conditions derive from the OMIM database.[55] The prevalence data for X-linked conditions derives from either OMIM,[55] Orphanet,[63] or MedlinePlus.[64] All conditions were at least moderately severe.[5,65] *OMIM* Online Mendelian Inheritance in Man.[55].

We define Tier 3 screening as carrier screening for conditions with a carrier frequency ≥1/200. The reader is directed to the Supplemental material ("Rationale for Tier 3 Screening" and Figure S1) for a detailed description of the derivation of ≥1/200 as a criterion for autosomal recessive genes. Tier 2 and Tier 3 screening prioritize carrier frequency as a way to think about conditions most appropriate for screening in the general population. However, when ACOG proposed this level, they did not specify whether it was thinking about carrier frequency in terms of the global population or subpopulations. We use "carrier frequency" to mean in any ethnic group with reasonable representation in the United States.

Tier 4 includes genes less common than those in Tier 3 and can identify additional at-risk couples.[49,50] Tier 4 has no lower limit carrier screening frequency and can greatly extend the number of conditions screened. Although there are many serious conditions at a carrier frequency below 1/200,[49] there may be less information about the natural history of many of these conditions. Additionally, pleiotropy, locus heterogeneity, variant interpretation and poor genotype–phenotype correlation may disproportionately impact the ability to provide accurate prognostic information for these rarer conditions. For these reasons, the clinical validity at this level of carrier screening may be less compelling, therefore we suggest reserving this level of screening for consanguineous pregnancies (second cousins or closer) and in couples where family or medical history suggests Tier 4 screening might be beneficial. Some patients want maximum information and will ultimately choose to have Tier 4 screening either due to convenience (a diagnostic laboratory might make their test the most accessible and hassle-free) or simply because it tests for the most conditions. Importantly, patients should understand that their chance of being a carrier for one or more conditions increases as the number of conditions screened is increased. Also, laboratories may not offer screening for the same genes within the Tier 4 option. Independent of whether laboratories offer conditions that satisfy the carrier frequencies of Tier 2, Tier 3, or Tier 4, all conditions screened should adhere to the same criteria (e.g., at least moderate severity).

ACMG recommends:

- All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening.
- Tier 4 screening should be considered:
  - When a pregnancy stems from a known or possible consanguineous relationship (second cousins or closer);
  - When a family or personal medical history warrants.

ACMG does not recommend:

- Offering Tier 1 and/or Tier 2 screening, because these do not provide equitable evaluation of all racial/ethnic groups.
- Routine offering of Tier 4 panels.

Consensus question 5: Which autosomal recessive conditions are appropriate for carrier screening?

Professional organizations have an obligation to define the conditions appropriate for carrier screening. Until now, molecular testing laboratories have assumed this responsibility with the consequence that conditions screened for are not uniform across laboratories.[38] We applied several criteria (Fig. 2) to determine the autosomal recessive genes listed in Tables 1–5.

There were 86 genes that satisfied the aforementioned criteria (Tables 1–4). After reviewing this list of genes, we evaluated genes that previously have been recommended for carrier screening by ACOG or ACMG.[44,51] We identified three genes (*SMN1*: spinal muscular atrophy, *ELP1*: familial dysautonomia, and *BLM*: Bloom syndrome) and included these in Table 5. All three of these genes are associated with conditions that have a carrier frequency that is highly represented in one or more patient populations and have the potential to be underrepresented in gnomAD. Detection of *SMN1* copy number by NGS is impeded by the presence of a highly homologous pseudogene (*SMN2*), and could artifactually lower allele frequencies in gnomAD. Like *SMN1*, the *HBA* locus is technically complex to assess and most cases of α-thalassemia result from deletions of one or more of the alpha globin genes (*HBA1* and *HBA2*) and thus, could create an artifactually lower

Table 1. Autosomal recessive genes for screening with carrier frequency ≥1/50.

OMIM gene	OMIM gene name	Maximum carrier frequency[a]	OMIM phenotype	Conditions
141900	*HBB*	0.119837	603903	Sickle cell anemia β-thalassemia
			613985	
613208	*XPC*	0.050885	278720	Xeroderma pigmentosum
606933	*TYR*	0.049337	203100	Oculocutaneous albinism type 1A and 1B
			606952	
613815	*CYP21A2*	0.048459	201910	Congenital adrenal hyperplasia due to 21-hydroxylase deficiency
612349	*PAH*	0.046068	261600	Phenylketonuria
602421	*CFTR*	0.040972	219700	Cystic fibrosis
600985	*TNXB*	0.035134	606408	Ehlers–Danlos-like syndrome due to tenascin-X deficiency
606869	*HEXA*	0.033146	272800	Tay–Sachs disease
121011	*GJB2*	0.026200	220290	Nonsyndromic hearing loss recessive 1A
			601544	Nonsyndromic hearing loss dominant 3A
602858	*DHCR7*	0.023709	270400	Smith–Lemli–Opitz syndrome
277900	*ATP7B*	0.021983	606882	Wilson disease
608034	*ASPA*	0.019856	271900	Canavan disease
607008	*ACADM*	0.016583	201450	Medium-chain acyl-coenzyme A dehydrogenase deficiency
602716	*NPHS1*	0.015994	256300	Finnish congenital nephrotic syndrome
601785	*PMM2*	0.015877	212065	Carbohydrate-deficient glycoprotein syndrome type Ia
607440	*FKTN*	0.015660	611615	Cardiomyopathy, dilated, 1X
			253800	Walker–Warburg congenital muscular dystrophy
605646	*SLC26A4*	0.015422	600791	Deafness autosomal recessive 4
			274600	Pendred syndrome
126340	*ERCC2*	0.015255	610756	Cerebrooculofacioskeletal syndrome 2
			601675	Trichothiodystrophy 1, photosensitive
603297	*DYNC2H1*	0.014817	613091	Short-rib thoracic dysplasia 3 with or without polydactyly

OMIM Online Mendelian Inheritance in Man.[55]
[a]Values round to ≥ 0.02 (two decimal places).

allele frequency in gnomAD. The allele frequencies of sequence variants in gnomAD v2.0.2 for *ELP1* and *BLM* were less common than 1/200, but these genes are known to have an allele frequency of at least 1/200 in AJ. Friedreich ataxia is a recessive trinucleotide repeat disorder that is associated with a GAA expansion located in intron 1 of the *FXN* gene. The condition has its highest carrier frequency in White populations from Northwestern Europe (Spain to Ireland).[52] The remaining genes listed in Table 5 have a carrier frequency ≥1/200 in a US subpopulation. Subpopulations included were the AJ and Puerto Rican, each having at least 1% representation in the United States and US territories combined.

In total, we recommend 97 autosomal recessive genes for carrier screening in Tier 3. We cross-referenced Tier 3 autosomal recessive genes to ClinGen[30] for gene–disease association. One gene was excluded (*BCS1L*) because the curation in ClinGen concluded there was "limited" evidence to support a gene–disease association. A commitment to ongoing curation of the autosomal recessive genes will ensure that new information is reflected in the genes recommended for screening in Tier 3 in future iterations. Curation should include technologies available that will ensure high throughput and accurate screening.

Cross-referencing to ClinGen and the ACMG secondary findings list v3.0[53] allowed for additional observations. Gene–disease association was confirmed as "definitive" in ClinGen for 39 of 97 (40%) (Table S1). Many genes we recommend have not been curated in ClinGen (e.g., *CFTR*, *SMN1*, *HBB*, *ARSA*). Two genes (*MMUT* and *USH3*) we recommend for screening could not be found in ClinGen, likely due to limited curation to date. We also cross-referenced Tier 3 genes to those recommended for universal newborn screening (Table S1). Two genes associated with hearing loss (*GJB2* and *SLC26A4*) are included for screening. We recommend 16 autosomal recessive genes that are screened using metabolic analytes at the time of newborn screening. The potential impact that screening for autosomal recessive conditions will have on families is discussed in the Supplement.

ACMG recommends:

- All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening for autosomal recessive (Tables 1–5) and X-linked (Table 6) conditions.
- Reproductive partners of pregnant patients and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions (Tables 1–5) when carrier screening is performed simultaneously with their partner.

Table 2. Autosomal recessive genes for screening with carrier frequency <1/50 to ≥1/100.

OMIM gene	OMIM gene name	Maximum carrier frequency[a]	OMIM phenotype	Conditions
610142	*CEP290*	0.014422	610188	Joubert syndrome 5
			611755	Leber congenital amaurosis 10
607839	*GBE1*	0.013799	232500	Glycogen storage disease, type IV
			263570	GBE1-related disorders
606800	*GAA*	0.013565	232300	Glycogen storage disease, type II (Pompe disease)
100725	*CHRNE*	0.013526	100725	Myasthenic syndrome, congenital, 4A, slow-channel
				Myasthenic syndrome, congenital, 4B, fast-channel
613742	*G6PC*	0.013401	232200	Glycogen storage disease type IA
611409	*OCA2*	0.013113	203200	Oculocutaneous albinism brown and type II
120120	*COL7A1*	0.012995	226600	Recessive dystrophic epidermolysis bullosa
600509	*ABCC8*	0.012242	618857	Diabetes mellitus, permanent neonatal 3
612724	*ALDOB*	0.012119	229600	Hereditary fructosuria
613899	*FANCC*	0.011992	227645	Fanconi anemia, complementation group C
604597	*GRIP1*	0.011989	617667	Fraser syndrome
248611	*BCKDHB*	0.011760	245600	Maple syrup urine disease
613726	*ANO10*	0.010781	613728	Spinocerebellar ataxia 10
104170	*NAGA*	0.010637	609241	Schindler disease, type 1
				Schindler disease, type 3
607608	*SMPD1*	0.010259	257200	Niemann–Pick disease, type A
			607616	Niemann–Pick disease, type B
608400	*USH2A*	0.010203	276901	Usher syndrome, type 2A
609058	*MMUT*	0.009999	251000	Methylmalonic aciduria–methylmalonyl–CoA mutase deficiency
600650	*CPT2*	0.009742	600649	Carnitine palmitoyltransferase II deficiency, infantile
			608836	Carnitine palmitoyltransferase II deficiency, lethal neonatal
608894	*AHI1*	0.009740	608629	Joubert syndrome 3

OMIM Online Mendelian Inheritance in Man.[55]
[a]After rounding values are < 0.02 and ≥ 0.01 (two decimal places).

- Ongoing curation of Tier 3 autosomal recessive genes with input from:
  - ACMG Committees and Work Groups;
  - Additional professional organizations and the lay public as appropriate.

Consensus question 6: Which X-linked conditions are appropriate for carrier screening?

Some laboratories offer screening for X-linked conditions as part of their carrier screening package. Like autosomal recessive conditions, the X-linked conditions screened do not overlap across the molecular testing laboratories. In fact, some carrier panels on the market contain genes associated with conditions that have a prevalence of 1 in 3,500 while others a condition with a prevalence less than 1 in 1,000,000. It is important that any designated panel include a transparent description of the process used for including/excluding those genes.

The reader is directed to the Supplemental material ("Rationale for Tier 3 screening" and Figure S1) for a detailed description of the derivation of 1/40,000 disease prevalence as a criterion for X-linked gene inclusion. We applied several criteria (Fig. 2) to determine the X-linked conditions listed in Table 6. Based on the aforementioned criteria, we identified 16 genes that are appropriate for carrier screening (Table 6). Cross-referencing these genes to ClinGen revealed that gene–disease association was definitive for 13/16 (81%). The remaining three have not been curated by ClinGen, including *DMD*, *NR0B1,* and *RPGR*. Among X-linked genes, three are on the ACMG secondary findings list v3.0 (*ABCD1* [adrenoleukodystrophy], *GLA* [Fabry disease], and *OTC* [ornithine transcarbamylase deficiency]).[53] The potential impact that screening for X-linked conditions will have on families is discussed in the Supplement. A commitment to ongoing curation of the X-linked genes will ensure that new information is reflected in the genes recommended for screening in Tier 3 in future iterations. Curation should include technologies available that will ensure high throughput and accurate screening.

ACMG recommends:

- All XX patients should be offered screening for only those X-linked genes listed in Table 6 as part of Tier 3 screening.
- Ongoing curation of Tier 3 X-linked genes with input from:
  - ACMG Committees and Work Groups;
  - Additional professional organizations and the lay public as appropriate.

Table 3. Autosomal recessive genes for screening with carrier frequency <1/100 to ≥1/150.

OMIM gene	OMIM gene name	Maximum carrier frequency[a]	OMIM phenotype	Conditions
608172	*DHDDS*	0.009340	613861	Congenital disorder of glycosylation type 1
				Retinitis pigmentosa 59
606152	*SLC19A3*	0.009163	607483	Basal ganglia disease, biotin-responsive
606999	*GALT*	0.009132	230400	Galactosemia
118485	*CYP11A1*	0.008771	613743	Adrenal insufficiency, congenital, with 46, XY sex reversal, partial or complete
190000	*TF*	0.008615	209300	Atransferrinemia
609831	*MMACHC*	0.008610	277400	Methylmalonic aciduria with homocystinuria cblC type
601615	*ABCA3*	0.008587	610921	Surfactant metabolism dysfunction, pulmonary 3
606463	*GBA*	0.008572	230800	Gaucher disease, type I
			230900	Gaucher disease, type II
605248	*MCOLN1*	0.008531	252650	Mucolipidosis type IV
607840	*GNPTAB*	0.008454	252500	Mucolipidosis type II alpha/beta
			252600	Mucolipidosis type III alpha/beta
613228	*AGA*	0.008364	208400	Aspartylglucosaminuria
605514	*PCDH15*	0.008330	609533	Deafness, autosomal recessive 23
			602083	Usher syndrome, type 1F
613871	*FAH*	0.007716	276700	Tyrosinemia type I
607358	*AIRE*	0.007664	240300	Autoimmune polyendocrinopathy syndrome type I
606151	*BBS2*	0.007501	615981	Bardet–Biedl syndrome 2
			616562	Retinitis pigmentosa 74
606530	*CYP27A1*	0.007399	213700	Cerebrotendinous xanthomatosis
611204	*CCDC88C*	0.007282	236600	Congenital hydrocephalus 1
136132	*FMO3*	0.007190	602079	Trimethylaminuria
613277	*TMEM216*	0.007107	608091	Joubert syndrome 2
			603194	Meckel syndrome 2
605080	*CNGB3*	0.006849	262300	Achromatopsia 3
607117	*MCPH1*	0.006822	651200	Primary microcephaly 1, recessive
602671	*SLC37A4*	0.006748	232220	Glycogen storage disease Ib
			232240	Glycogen storage disease Ic
170280	*PRF1*	0.006734	603553	Hemophagocytic lymphohistiocytosis, familial, 2
604272	*SCO2*	0.006671	604377	Mitochondrial complex IV deficiency, nuclear type 2
604285	*AGXT*	0.006648	259900	Hyperoxaluria, primary type I

OMIM Online Mendelian Inheritance in Man.[55]
[a]After rounding values are < 0.01 and ≥ 0.007 (two decimal places).

Consensus question 7: What should the clinician expect with regard to laboratory reporting of carrier screening results?

The clinical laboratory report represents the final postanalytical step of laboratory testing and is a documented communication to the referring clinician. It should be a structured document with clinically significant findings easily identified and understood by the ordering health-care professional. Information should be provided in a clear, concise, and accurate manner that is adherent to regulatory standards (42 CFR § 493.1291). Several ACMG documents address norms and elements of a clinical laboratory report, including report sections, transparency of methods and limitations, standardized five-category variant classifications, and uniform Human Genome Variation Society (HGVS)–based variant annotations.[23,26] It is important that the report clearly conveys:

- ACMG carrier screening tier number and genetic content of the panel with all tested genes and transcripts listed, or, if the number is large, referenced to an accessible website.
- Whether a targeted (assessment of predefined variants) or comprehensive (assessment of full coding region with splice junctions) approach is carried out with details of the methodology and limitations.
- Detectable types of DNA variation (e.g., SNVs, CNVs, structural rearrangements).
- Variant classification range that is used for reporting.

Table 4. Autosomal recessive genes for screening with carrier frequency <1/150 to ≥1/200.

OMIM gene	OMIM gene name	Maximum carrier frequency[a]	OMIM phenotype	Conditions
609575	*ACADVL*	0.006419	201475	Very long chain acyl-CoA dehydrogenase deficiency
608310	*ASL*	0.006190	207900	Argininosuccinate aciduria
607261	*EVC2*	0.006083	225500	Chondroectodermal dysplasia
607574	*ARSA*	0.005986	250100	Metachromatic leukodystrophy
251170	*MVK*	0.005966	260920	Hyper-IgD syndrome
			610377	Mevalonic aciduria
606702	*PKHD1*	0.005960	263200	Autosomal recessive polycystic kidney disease
609019	*BTD*	0.005953	253260	Biotinidase deficiency
171760	*ALPL*	0.005719	146300	Hypophosphatasia, adult
			241510	Hypophosphatasia, childhood and infantile
209901	*BBS1*	0.005713	209900	Bardet–Biedl syndrome 1
118425	*CLCN1*	0.005688	255700	Congenital myotonia, autosomal recessive form
609506	*CYP27B1*	0.005512	264700	Vitamin D–dependent rickets, type 1
174763	*POLG*	0.005330	203700	Mitochondrial DNA depletion syndrome 4A
			613662	Mitochondrial DNA depletion syndrome 4B
609014	*MCCC2*	0.005184	210210	3-methylcrotonyl CoA carboxylase 2 deficiency
605908	*MLC1*	0.005058	604004	Megalencephalic leukoencephalopathy with subcortical cysts
607809	*ACAT1*	0.005000	203750	α-Methylacetoacetic aciduria
612013	*CC2D2A*	0.004969	612285	Joubert syndrome 9
			612284	Meckel syndrome 6
606718	*SLC26A2*	0.004715	226900	Epiphyseal dysplasia, multiple, 4
			600972	Achondrogenesis Ib
236200	*CBS*	0.004676	236200	Homocystinuria, B6 responsive and nonresponsive
600073	*LRP2*	0.004676	222448	Donnai–Barrow syndrome
252800	*IDUA*	0.004675	607014	Mucopolysaccharidosis, Ih (Hurler S)
			607015	Mucopolysaccharidosis, Ih/s (Hurler–Scheie S)
606596	*FKRP*	0.004668	613153	Muscular dystrophy–dystroglycanopathy, type A, 5
			606612	Muscular dystrophy–dystroglycanopathy, type B, 5
610326	*RNASEH2B*	0.004609	610181	Aicardi Goutieres syndrome 2
611524	*RARS2*	0.004592	611523	Pontocerebellar hypoplasia type 6

OMIM Online Mendelian Inheritance in Man.[55]
[a]After rounding values are < 0.007 and ≥ 0.005 (two decimal places).

Reporting and interpreting results depends on the clinical context and indication for testing. When results are negative, it is often impractical to provide residual risk estimates because (1) for many of the X-linked genes screened, carrier frequencies are imprecise; (2) data sets and populations used to establish carrier frequency can vary; and (3) calculations depend on the patient's self-identified ethnicity. However, whenever possible, the analytical sensitivity of detecting different variant types and the detection rate should be provided. This will help to emphasize that a negative test does not eliminate the possibility of being a carrier for any condition screened, but it does reduce this risk.

All pathogenic and likely pathogenic variants should be reported back to the ordering health-care professional. However, a gene-specific comprehensive sequencing approach with the option of reporting of a VUS should be considered for partners of identified carriers[27] and discussed during pretest counseling. Reports of positive results should include brief clinical information about the disorder, penetrance if known, and variability in expression if understood. Information about genotype–phenotype correlations may be provided with relevant limitations since correlations that are meaningful in a population may not be applicable to an individual. A statement about reproductive risk should be included when a carrier is identified.

The interpretation should consider genes and variants with multiple disease associations, as well as a possibility of mixed modes of inheritance. For example, whereas some pathogenic variants in *ABCC8* gene result in a reduced insulin secretion and hyperglycemia causing permanent neonatal diabetes mellitus, others can cause congenital hyperinsulinism and hypoglycemia. Also, although a number of pathogenic variants

Table 5. Genes that were ascertained for screening outside of the gnomAD criteria[a].

OMIM gene	OMIM gene name	Published carrier frequency[b]	Rationale for inclusion	Ethnic group	OMIM phenotype	Conditions
141800	*HBA1*	U[c]	Carrier frequency	SEA and others	604131	α-Thalassemia
141850	*HBA2*	U[c]	Carrier frequency	SEA and others	604131	α-Thalassemia
600354	*SMN1*	1/60[18]	ACOG/ACMG and carrier frequency	US panethnic	253300	
					253550	Spinal muscular
					253400	atrophy types: I, II, III, IV
					271150	
604982	*HPS1*	1/59[56–58]	Carrier frequency	PR	203300	Hermansky Pudlak S. 1
606118	*HPS3*	1/59[56]	Carrier frequency	PR	614072	Hermansky Pudlak S. 3
603722	*ELP1*	1/32[59]	ACOG/ACMG and carrier frequency	AJ	223900	Familial dysautonomia
606829	*FXN*	1/60–1/100[60]	Carrier frequency	Caucasians[d]	229300	Friedreich ataxia
238331	*DLD*	~1/100[59,61]	Carrier frequency	AJ	246900	Dihydrolipoamide dehydrogenase deficiency
161650	*NEB*	1/168[59]	Carrier frequency	AJ	256030	Nemaline myopathy 2
606397	*CLRN1*	1/120[59]	Carrier frequency	AJ	276902	Usher syndrome 3a
604610	*BLM*	1/100[59]	ACMG and carrier frequency	AJ	210900	Bloom syndrome

ACMG American College of Medical Genetics and Genomics, *ACOG* American College of Obstetricians and Gynecologists, *AJ* Ashkenazi Jewish (≥2% of the US population), *OMIM* Online Mendelian Inheritance in Man,[55] *PR* Puerto Rican, *SEA* South East Asian.
[a]Carrier frequency of a sequence variant is <1/200, if reported in gnomAD.[50]
[b]Diagnostic laboratory data was not used for carrier frequency data.
[c]Specific data for general US population not available; however, recognized as common among many US immigrant populations.[62]
[d]This term is no longer used by the journal but is used in the original article to which these studies refer. We have therefore not changed the term but recognize it does not accurately describe the ancestry of the populations originally studied.[46]

in *ALPL* hypophosphatasia are associated with an autosomal recessive disease, some variants when present in the heterozygous state are associated with an autosomal dominant disease. The possibility of manifesting heterozygotes and their associated clinical features, if such are known, as in cases of carriers of X-linked conditions (for example, cardiomyopathy in *DMD* carriers; primary ovarian failure in *FMR1* premutation carriers) should be discussed as part of pretest counseling. Reports must be specific in designating well-known alleles that are associated with mild symptoms, for example: Asp444His variant in *BTD*, the Duarte allele in *GALT*, *HBA1/HBA2* (-+/++), and the many *CYP21* nonclassic mild variants. Currently, the ACMG list of secondary findings[53] is not validated for reporting in the setting of general population screening.[54] The transition by molecular testing laboratories to the tier-based rubric described is expected to be gradual to accommodate the changes needed to properly implement screening.

ACMG recommends:

- The content of carrier screening panels and the corresponding ACMG tier must be described in the laboratory reports.
- The testing approach and detectable variant types should be clearly stated.
- Not reporting residual risk estimates because carrier frequency and the detection rate of all genes is not established.
- Only pathogenic and likely pathogenic variants should be routinely reported.
- Interpretation should consider genes and variants with multiple disease associations.
- The reporting of a VUS only in the partners of identified carriers and only with consent of the patient.

Consensus question 8: What should be emphasized during pretest and post-test counseling when performing carrier screening?

Education and counseling are critical in carrier screening. Informed decision making with carrier screening is complex and ideally should be a part of preconception care to allow any of the reproductive decision-making options. Health-care professionals should inform patients of the risks, benefits, and consequences of carrier screening. After appropriate counseling that considers the patient's needs and values, patients should be supported to make informed and autonomous decisions including the decision to not undergo carrier screening.

Carrier screening counseling should be provided by knowledgeable and appropriately trained health-care professionals and should be performed pre- and post-test. It should be noted that traditional models of genetic counseling can be both time and labor intensive. Thus, new models need to be developed and instituted for both training nongenetics providers and counseling patients. These models might include videos, chatbots, computer-based learning, or other methods of providing information to patients and assessing their understanding. Carrier screening for autosomal recessive conditions is unique when compared to other medical testing in that test results impact the likelihood of offspring of the patient having a genetic condition, while for the most part, the patient screened is healthy. However, patients with two X chromosomes, who screen positive for X-linked conditions may manifest symptoms of the condition (e.g., OTC deficiency and hemophilia) because of skewed X inactivation. This also explains why some carriers of Duchenne muscular dystrophy (*DMD*) experience cardiomyopathy. A subset of these patients who have a *FMR1* premutation allele are at risk to develop premature ovarian insufficiency, a condition unrelated to that seen in their XY offspring (i.e., fragile X syndrome).

Table 6. X-linked genes recommended for carrier screening.

OMIM gene	OMIM gene name	OMIM phenotype	Phenotype
300371	*ABCD1*	300100	Adrenoleukodystrophy (ALD)
300806	*AFF2*	309548	Mental retardation, X-linked, associated with fragile site FRAXE
300382	*ARX*	308350	Developmental and epileptic encephalopathy 1 (DEE1)
300377	*DMD*	300376	Muscular dystrophy, Becker type (BMD)
		310200	Muscular dystrophy, Duchenne type (DMD)
306700	*F8*	300841	Hemophilia A (HEMA)
300746	*F9*	306900	Hemophilia B (HEMB)
309550	*FMR1*	300624	Fragile X syndrome (FXS)
300644	*GLA*	301500	Fabry disease
308840	*L1CAM*	307000	Hydrocephalus due to congenital stenosis of aqueduct of Sylvius (HSAS)
300552	*MID1*	300000	Opitz GBBB syndrome, type I (GBBB1)
300473	*NR0B1*	300200	Adrenal hypoplasia, congenital (AHC)
300461	*OTC*	311250	Ornithine transcarbamylase deficiency
300401	*PLP1*	312920	Spastic paraplegia 2, X-linked (SPG2)
312610	*RPGR*	300029	Retinitis pigmentosa 3 (RP3; RP)
		300455	Retinitis pigmentosa, X-linked, and sinorespiratory
		300834	Infections, with or without deafness
			Macular degeneration, X-linked atrophic
300839	*RS1*	312700	Retinoschisis 1, X-linked, juvenile (RS1)
300036	*SLC6A8*	300352	Cerebral creatine deficiency syndrome 1 (CCDS1)

OMIM Online Mendelian Inheritance in Man.[55]

Pretest counseling information that all providers should be comfortable discussing:

- Carrier screening is optional and can be performed at any time.
- Preconception screening is recommended over prenatal screening[17,19] since it may be less stressful on patients with positive screening results and it allows for the full complement of reproductive decision making. If done in pregnancy, concurrent partner testing should be offered.
- When a reproductive partner has changed, carrier screening should be readdressed.
- Carrier screening is not a test for all genetic conditions; in fact, considering all genetic conditions, only a minority are screened.
- Genetic variants have likely been in one's family for many generations.
- Carrier screening will not identify de novo variants in the offspring.
- Carrier screening does not replace newborn screening.
- When Tier 1 or Tier 2 carrier screening was performed in a prior pregnancy, Tier 3 screening should be offered.
- A carrier of an autosomal recessive condition will rarely manifest any clinical signs or symptoms of that condition.
- Consanguineous couples have an increased risk to be carriers for the same conditions.
- All genes and variants that cause a condition may not be known and may not be examined as part of Tier 3 or Tier 4 screening. If family history warrants, additional genes may be considered for evaluation and referral to a genetics professional should be considered. A negative test reduces the chance to have an affected child but does not eliminate the risk.
- Laboratories should not report changes in a gene that has no or unclear association with a medical condition.
- A VUS is a change within a gene that may or may not be associated with disease. These are not reported unless one partner is found to be a carrier of a pathogenic or likely pathogenic variant in the same gene. When this occurs the second partner should be asked to decide on whether they want this information. Ideally, this consent to return a VUS result will take place during preconception counseling.
- In some situations, X-linked heterozygous patients will manifest signs and symptoms that are different than the condition seen in offspring (e.g., *DMD*, *FMR1*).

Counseling in specific circumstances

When screening test results are positive after sequential screening. Availability of the partner should not dictate when or if carrier screening is offered; however, the impact on interpretation of the result should be discussed as it may influence the patient's decision making. When carrier screening is performed during an ongoing pregnancy, it is ideal to perform carrier screening on both partners simultaneously, so that screening results can be obtained in a timely manner. Carrier screening can be approached sequentially, meaning that a patient can undergo screening first, obtain results, and then a current or future reproductive partner can be screened later. When sequential screening is performed and one partner is discovered to be a carrier of an autosomal recessive or X-linked condition, that partner should undergo counseling by a knowledgeable and appropriately trained healthcare professional. In specific circumstances, it may be especially appropriate to seek the assistance of a genetics professional, for example (1) when the gene or variant is known to be associated with variable expressivity, (2) when an X-linked carrier is identified, (3) when autosomal recessive carriers of gene variants that have possible phenotypic implications are identified, and (4) when a VUS is disclosed.

ACMG recommends that counseling patients include:

- Education about the condition for which the patient tested positive.
- Offering follow-up screening of the partner with analysis of the same gene that has the pathogenic or likely pathogenic variant as that identified in the partner.
- Laboratory testing of the partner should include sequencing of the full gene identified in the carrier patient and not testing for a limited panel of variants.
- In cases where there is an ongoing pregnancy and the partner declines testing or is unavailable for testing a diagnostic procedure can be offered.[27]
- A plan should be made for results delivery, including whether variants of uncertain significance will be reported.
- A negative test result in the partner does not eliminate the risk of an affected child. The remaining risk cannot be accurately quantified for most conditions, but it is reduced.
- "False positive" results may be due to:
  - Reduced penetrance of known pathogenic and likely pathogenic variants;
  - Conflicting variant interpretation among laboratories;
  - Underreporting of outcomes in patients with same variants;
  - Imperfect in silico modeling of variant expression.
- Patients should be counseled that variability of manifestations of a genetic condition is typical, even in affected individuals within the same family.

When couple is identified as being at risk. When an at-risk couple is identified, counseling by an appropriately trained health-care professional is recommended. In specific circumstances, it may be especially appropriate to seek the assistance of a genetics professional, for example (1) when the gene or variant is known to be associated with variable expressivity, and (2) when a VUS is disclosed. The counseling performed depends on when the carrier couple is identified (i.e., preconceptionally versus prenatally).

ACMG recommends that counseling patients include:
In cases of preconception identification

- A discussion of the risks and benefits of reproductive options.
- A discussion of in vitro fertilization with gamete donation, preimplantation genetic testing, embryo donation, adoption, and prenatal diagnosis (chorionic villi sampling or amniocentesis) followed by a decision to continue or not continue a pregnancy. This discussion includes preparation for medical care after the birth of an affected child.
- Offering educational materials and resources that can facilitate patients in making an informed decision about their reproductive options.
- A plan for disclosure of results.

In cases of identification during an ongoing pregnancy

- Offering a diagnostic procedure (i.e., chorionic villi sampling or amniocentesis) as appropriate to determine whether a fetus is predicted to be affected with the condition(s) identified through carrier screening.
- A discussion of reproductive decisions to carry a pregnancy, including preparation for possible medical care after the birth of an affected child.
- Offering educational materials and resources that can facilitate patients in making an informed decision about their reproductive options.
- A plan should be made for disclosure of results.

When the father cannot be screened and the patient screens positive and there is an ongoing pregnancy

It is acceptable to offer the patient a prenatal diagnostic procedure (CVS or amniocentesis) when the patient screens positive for an autosomal recessive gene and the father cannot be screened for one of the following reasons: (1) partner is unavailable for screening, (2) screening the partner would be cost prohibitive, (3) the results from the partner would not be available in time to allow for reproductive decision making, and (4) a diagnostic procedure is being performed for another reason. This option and these indications have already been established by ACMG for cystic fibrosis,[27] and should be considered an option when a carrier for any other recessive gene(s) is identified. When this situation arises, counseling by an appropriately trained health-care professional is recommended. A laboratory willing to perform the testing must be identified before performing the diagnostic procedure.

ACMG recommends that counseling patients should include the following:

- Education about the condition for which the patient tested positive.
- A plan should be made for results delivery, including whether variants of uncertain significance will be reported.
- Laboratory testing of the partner should include sequencing of the full gene(s) identified in the carrier patient and not testing for a limited panel of variants.
- A diagnostic procedure should be offered when:
  - The partner is unavailable for testing;
  - The partner declines testing;
  - Testing is cost prohibitive;
  - A partner's results would not be available in time for reproductive decision making;
  - A diagnostic procedure is already planned for another indication.
- The patient should be counseled about the limitations of gene analysis in the fetus under these circumstances. The laboratory may be unable to provide definitive diagnosis if one parent's carrier status is unknown.

CONCLUSION

This document establishes a tiered approach to carrier screening and aims to improve the implementation of carrier screening allowing diverse populations to benefit from new and emerging genomic technologies. We have listed the genes that should be offered to all patients who desire carrier screening. We realize that the genes we recommend may not adequately address those seen more frequently in some populations; therefore, family and personal history, including the pedigree and, where appropriate, physical examination, should be used to guide the need to screen selected additional genes. We expect that over time clinicians will become comfortable with the concepts, specific genes, and their associated conditions that are proposed in this document. Importantly, molecular testing laboratories are called on to adapt and innovate to keep carrier screening costs low and throughput high. It will be important that ACMG reevaluate the genes listed for screening and consider the need to modify criteria used to include and exclude genes.

The authors of this practice resource recognize that there are barriers to the implementation of Tier 3 carrier screening in clinical practice. These include the challenges imposed on health-care providers by rapidly changing genetic technologies and information, as well as insurance coverage for carrier screening of patients and partners. Another challenge is for the molecular testing laboratories to adapt new testing strategies since some of the ACMG Tier 3 genes may harbor variants that are not routinely detected by NGS only. We also recognize that the pretest counseling and delivering accurate and timely results to patients is time consuming. The information contained in this document along with that provided by ACMG, ACOG, and other professional

organizations[2,17–19,21] provides much of what needs to be known to feel comfortable offering carrier screening. This workgroup recognizes that offering a comprehensive Tier 3 panel to all is only the first step toward equity in carrier screening and clinical follow up. Working collaboratively genetics professionals are encouraged to innovate by utilizing telemedicine and online tools to overcome challenges to the workforce. Combining these with other ideas will ensure patients receive the highest level of care as genetics and genomics increases its reach into communities that, until now, were unfamiliar with their benefits. We strongly recommend that all payers provide coverage for Tier 3 carrier screening, as well as Tier 4 carrier screening in appropriate clinical circumstances such as personal/medical history or consanguinity, to ensure equitable care to all individuals including those disadvantaged by race and financial hardship.

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COMPETING INTERESTS

M.A., N.T.L., M.T.B. and E.C. are directors of molecular testing laboratories that offer carrier screening. J.S.D. is a member of the Advisory Board for Informed DNA and Medical Co-Director at Insight Medical Genetics in Chicago, which provides genetic laboratory services. The other authors declare no competing interests.

ADDITIONAL INFORMATION

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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)

Supplemental Material

Methods

Rationale for Tier 3 screening

Figure S1. The relationship between Carrier Frequency and identification of an At-Risk couple.

Technology Considerations

Table S1. Autosomal recessive conditions recommended for screening and scored as definitive in ClinGen, listed as a reportable secondary finding, included in newborn screening programs.

Table S2. X-linked conditions listed in OMIM (November 30, 2020) and initially considered for screening

Methods: Literature search of publically available databases

We performed literature searches using the terms "genetic carrier screening and expanded" after examination of the hierarchy of terms in Medical Subjects Headings (MeSH). We searched PubMed multiple times between September 22, 2020 and December 20, 2020 using the year range 2010 through 2020; 262 results were returned. A second strategy performed over the same time-period incorporated the term "utility" and used the same year filter, which returned 67 results. This was further refined to exclude reviews ("not (reviews)"), which yielded 57 results. The abstracts of these search results were reviewed. Snowball sampling of the

articles' reference list identified additional relevant articles that fell outside the date range of 2010 through 2020.

Several publicly available databases were used to inform questions 5 and 6. These are shown in **Box S1**. Group consensus informed all ACMG recommendations.

Box S1. Publicly Available Data Bases Utilized	
Name	**URL**
gnomAD v 2.1.1	https://gnomad.broadinstitute.org/
OMIM	https://omim.org/
Orphanet	https://www.orpha.net/consor/cgi-bin/index.php
MedlinePlus	https://medlineplus.gov/
ClinGen	https://www.clinicalgenome.org/

Rationale for ≥ 1/200 autosomal recessive genes included in Tier 3 screening

The rationale for selecting ≥1/200 rests on two studies. One study utilized a diagnostic laboratory's database,[1] the other utilized gnomAD version 2.0.2 a large-scale dataset of unrelated individuals.[2,3] This version of gnomAD consists of 123,136 exome sequencing samples. Variant analysis, within this version, is stratified for seven populations: African/African American, Ashkenazi Jewish, East Asian, Finnish, Hispanic/Admixed American, Non-Finnish European, and South Asian. In this report Finnish were excluded since they represent a very small portion of the US population and a theoretical US population was constructed based on census data. gnomAD allowed investigators to view pathogenic and likely pathogenic allele frequencies within 415 autosomal recessive genes (referenced in ClinVar) by ancestry. Both studies demonstrated a log curve relationship with carrier frequency or total number of screened genes on the X-axis and identified at-risk couples or carriers on the Y-axis (**Figure S1**). At-risk couples (both partners are carrier of a pathogenic or likely pathogenic variant within the same gene) were more common within populations where endogamy was more likely (e.g., Ashkenazi Jewish). When moving from Tier 2 (≥1/100 carrier frequency) to Tier 3 (1/200 carrier frequency) or from point X to Y (**Figure S1**), there were an additional 9/10,000 at-risk couples identified. At a carrier frequency of 1/100 there were 241 per 10,000 at-risk AJ couples identified and this increased to 250/10,000 at 1/200 carrier frequency. This represents a 4% increase in at-risk couples. Additional at-risk couples identified in this interval ranged from 4-9 per 10,000 depending in the endogamous population examined. When the population evaluated was weighted by US census data, at-risk couples identified increased by six per 10,000 couples (45 to 51 per 10,000) when moving from the Tier 2 (≥1/100) carrier frequency to that of Tier 3 (≥1/200). Assuming ~4 million births per year, this translates to an annual increase of 2,400

additional US couples that will have the opportunity to make reproductive decisions following a positive carrier screening result if Tier 3 autosomal recessive conditions are screened rather than Tier 2.

Importantly, for carrier frequency of less than 1/200 the added number of at-risk couples gets diminishingly small (Z-Y in **Figure S1**). In populations where endogamy is common, modeling[2] suggested that screening for conditions with a carrier frequency of 1/1000 would identify only two additional couples per 10,000 couples screened (0.02%) or 252 vs. 250 couples per 10,000). The range of additional at-risk couples identified across the six populations evaluated was 2-5 per 10,000.[2]

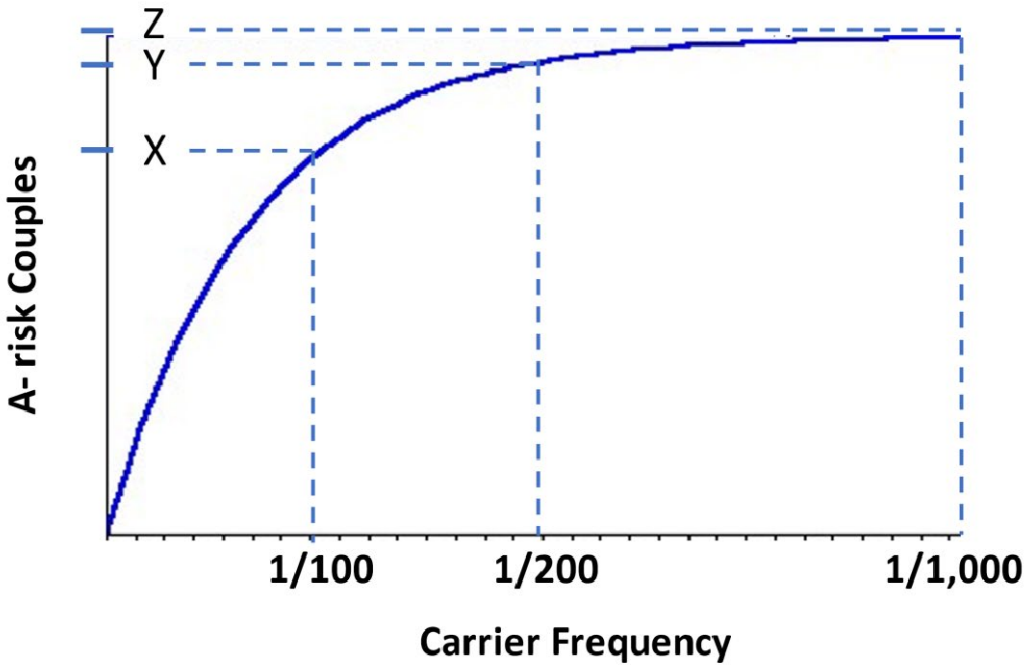

Figure S1. The relationship between Carrier Frequency and identification of an At-Risk couple. The gain in identification of at-risk couples (X-Y) is greatest when moving between conditions with higher frequency (1/100 to 1/200). As we move from higher to lower carrier

frequency (1/200 to 1/1000) the gain in identification of at-risk couples (Y-Z) gets diminishingly small.

Rationale for 1/40,000 disease prevalence of X-linked genes included in Tier 3 screening

It seems logical to apply the risk analysis used for screening autosomal recessive conditions. A 1/200 carrier frequency (Tier 3) results in a 1/160,000 risk of an affected fetus (1/200 carrier frequency threshold x 1/200 carrier frequency threshold x 1/4 risk of an affected fetus = 1/160,000). To reach 1/160,000 for an X-linked condition, the carrier frequency of 1/40,000 is required (1/40,000 X-linked condition carrier frequency x 1/2 chance of inheriting the variant X chromosome x 1/2 chance of inheriting Y = 1/160,000). However, this approach relies on accurate carrier frequency data for the X-linked conditions considered and this is precisely what confounds this approach. Currently there is no gnomAD peer-reviewed study with a comprehensive assessment of variant frequencies in X-linked genes across populations.

Among X-linked genes, variants are often *de novo* and may be high as 25% for some X-linked conditions. In other words, population prevalence for any condition is a function of heritable cases plus *de novo* variants. We chose to include conditions with a disease prevalence of at least 1/40,000 because it approaches the calculated frequency of at-risk couples for autosomal recessive conditions. The conditions we recommend have a prevalence that ranges from 1/3,500 to 1/40,000. With nearly 4 million births each year in the US, a condition with a prevalence as high as of 1/3,500 is expected to result in more than 500 affected XY patients each year; for conditions with a prevalence of 1/40,000, 50 affected XY patients will be born each year. We anticipate that screening for these X-linked conditions has the potential to impact at least 1,000 US families annually.

Technology Considerations

This consensus group recognizes that not all sequence variants and structural rearrangements leading to clinical pathology can be detected using high throughout low-cost laboratory methods. It is beyond the scope of this document to consider the laboratory methods required to make accurate determinations that can reliably classify patients as carriers. The ACMG Laboratory Quality Assurance Committee is assessing the genes proposed for carrier screening to identify appropriate laboratory methods that will result in the greatest sensitivity and specificity while preserving the need for high throughput and low cost.

We also recognize that it will be necessary to reevaluate the genes proposed for screening in this document as there is a continuous growth in accumulation, assessment, and interpretation of the data in human genetic variation. Databases cataloging human sequence accrue new samples leading to a more diverse and representative population composition. Advances in sequencing technology and bioinformatics enlarge the scope of assessed genetic material and improve the number and the type of variants identified. The ClinVar database grows with new submissions and the refinement of variant interpretation is an ongoing process. New genetic etiologies in human disease are being discovered. To address this dynamic nature of available information, a working group of the ACMG Board of Directors is proposed to provide continuing curation of the genes recommended for screening. As ClinGen curates more genes we may find other examples where curation identifies limited gene-disease association as we did for *BCS1L*. Most importantly, new information will be garnered as laboratories use this list of genes for screening across the United States. Using a standardized list of genes that considers many ancestral groups and is built around a transparent process for including and excluding genes will improve our attention to distributive justice. We believe this process recognizes and begins to

address the disparities of genetics and genomics in delivering better health to diverse populations.

Table S1. Autosomal recessive conditions recommended for screening and scored as definitive in ClinGen, listed as a reportable secondary finding, included in newborn screening programs.

Carrier Frequency (Table 1-5) see text	≥1/50 N=19	<1/50 to ≥1/100 N=19	<1/100 to ≥1/150 N=25	< 1/150 to ≥1/200 N=23	≥1/200 del/dup or ≥1/200 US Sub-Population (see text) N=11
ClinGen*	Definitive = 13 genes (68%)	Definitive = 5 genes (26%)	Definitive = 8 genes (32%)	Definitive = 9 genes (39%)	Definitive = 4 genes (36%)
ACMG SF V3.0	*ATP7B*	*GAA*		*BTD*	
Newborn Screening	**N=7 phenotypes** *HBB, CYP21A2, PAH, CFTR, GJB2 (deafness), ACADM, SLC26A4 (deafness)*	**N=3 phenotypes** *GAA, BCKDHB, MMUT*	**N=2 phenotypes** *GALT, FAH,*	**N=6 phenotypes** *ACADVL, ASL, BTD, MCCC2 CBS, IDUA,*	

ACMG, American College of Medical Genetics and Genomics; SF, secondary findings

*sum does not equal N for each carrier frequency because some genes have been curated in ClinGen but there is no statement regarding gene-disease association. One gene demonstrated limited association and was removed from the Tier 3 panel of genes and one gene was not identified in ClinGen.

Table S2: X-linked conditions listed in OMIM (November 30, 2020) and initially considered for screening

OMIM Search - 'prefix:# AND chromosome:X' Downloaded: Nov 30, 2020 Copyright (c) 1966-2020 Johns Hopkins University OMIM, data are provided for research purposes only.			
MIM Number	**Title**[a]	**Included Titles**	**Cytogenetic Location**
#127300	LERI-WEILL DYSCHONDROSTEOSIS; LWD	MADELUNG DEFORMITY, INCLUDED	Xp22.33, Yp11.2
#300009	DENT DISEASE 1		Xp11.23
#300018	46,XY SEX REVERSAL 2; SRXY2		Xp21.2
#300029	RETINITIS PIGMENTOSA 3; RP3		Xp11.4
#300048	INTESTINAL PSEUDOOBSTRUCTION, NEURONAL, CHRONIC IDIOPATHIC, X-LINKED	CONGENITAL SHORT BOWEL SYNDROME, X-LINKED, INCLUDED - FLNA	Xq28
#300049	PERIVENTRICULAR NODULAR HETEROTOPIA 1; PVNH1	HETEROTOPIA, PERIVENTRICULAR NODULAR, WITH FRONTOMETAPHYSEAL DYSPLASIA, INCLUDED	Xq28
#300055	MENTAL RETARDATION, X-LINKED, SYNDROMIC 13; MRXS13		Xq28
#300066	DEAFNESS, X-LINKED 4; DFNX4		Xp22.12
#300067	LISSENCEPHALY, X-LINKED, 1; LISX1	SUBCORTICAL LAMINAR HETEROTOPIA, X-LINKED, INCLUDED; SCLH, INCLUDED	Xq23
#300068	ANDROGEN INSENSITIVITY SYNDROME; AIS		Xq12
#300071	NIGHT BLINDNESS, CONGENITAL STATIONARY, TYPE 2A; CSNB2A		Xp11.23
#300087	X INACTIVATION, FAMILIAL SKEWED, 1; SXI1		Xq13.2
#300088	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 9; DEE9 - PCDH19 gene		Xq22.1
#168600	PARKINSON DISEASE, LATE-ONSET; PD		1q22, 4q23, 6q27, 12q24.12, 13q21.33, 17q21.31, Xq24
#176807	PROSTATE CANCER		7p22.3, 10p15.2, 10q23.31, 10q25.2, 13q13.1, 16q22.1, 16q22.2-q22.3, 22q12.1, Xq12
#194070	WILMS TUMOR 1; WT1		11p13, 13q13.1,

			Xq26.2 (somatic)
#300100	ADRENOLEUKODYSTROPHY; ALD	ADRENOMYELONEUROPATHY, INCLUDED; AMN, INCLUDED	Xq28
#300106	SPONDYLOEPIMETAPHYSEAL DYSPLASIA, X-LINKED; SEMDX - BGN gene		Xq28
#300114	RAYNAUD-CLAES SYNDROME; MRXSRC		Xp22.2
#300123	MENTAL RETARDATION, X-LINKED, WITH PANHYPOPITUITARISM	MENTAL RETARDATION, X-LINKED, WITH ISOLATED GROWTH HORMONE DEFICIENCY, INCLUDED; MRGH, INCLUDED	Xq27.1
#300143	MENTAL RETARDATION, X-LINKED 21; MRX21 - IL1RAPL1 gene		Xp21.3-p21.2
#300148	MEHMO SYNDROME; MEHMO - EIF2S3 gene		Xp22.11
#300166	MICROPHTHALMIA, SYNDROMIC 2; MCOPS2		Xp11.4
#300194	AMME COMPLEX		Xq22.3
#300200	ADRENAL HYPOPLASIA, CONGENITAL; AHC - NR0B1		Xp21.2
#300209	SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 2; SGBS2		Xp22.2
#300210	MENTAL RETARDATION, X-LINKED 58; MRX58 TSPAN7 gene		Xp11.4
#300215	LISSENCEPHALY, X-LINKED, 2; LISX2	HYDRANENCEPHALY AND ABNORMAL GENITALIA, INCLUDED - - ARX gene	Xp21.3
#300219	MYOTUBULAR MYOPATHY WITH ABNORMAL GENITAL DEVELOPMENT - - likely MTM1 contig gene deletion		
#300232	SPONDYLOEPIMETAPHYSEAL DYSPLASIA, X-LINKED, WITH HYPOMYELINATING LEUKODYSTROPHY; SEMDHL; AIFM1 gene		Xq26.1
#300238	MENTAL RETARDATION, X-LINKED, SYNDROMIC 11; MRXS11		Xq26.3
#300243	MENTAL RETARDATION, X-LINKED, SYNDROMIC, CHRISTIANSON TYPE; MRXSCH; SLC9A6 gene		Xq26.3
#300244	TERMINAL OSSEOUS DYSPLASIA; TOD		Xq28
#300257	DANON DISEASE		Xq24
#300260	LUBS X-LINKED MENTAL RETARDATION SYNDROME; MRXSL		Xq28
#300261	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, ARMFIELD TYPE; MRXSA		Xq28
#300263	SIDERIUS X-LINKED MENTAL RETARDATION SYNDROME; MRXSSD		Xp11.22

#300271	MENTAL RETARDATION, X-LINKED 72; MRX72; RAB39B gene		Xq28
#300280	URUGUAY FACIOCARDIOMUSCULOSKELETAL SYNDROME; FCMSU; FHL1 gene		Xq26.3
#300291	ECTODERMAL DYSPLASIA AND IMMUNODEFICIENCY 1; EDAID1		Xq28
#300299	NEUTROPENIA, SEVERE CONGENITAL, X-LINKED; SCNX; allelic with Wiskott Aldrich		Xp11.23
#300310	IMMUNODEFICIENCY 61; IMD61; SH3KBP1 gene; 2 brothers reported		Xp22.12
#300321	FG SYNDROME 2; FGS2; FLNA gene		Xq28
#300322	LESCH-NYHAN SYNDROME; LNS	HPRT DEFICIENCY, NEUROLOGIC VARIANT, INCLUDED	Xq26.2-q26.3
#300323	HYPERURICEMIA, HPRT-RELATED; HRH		Xq26.2-q26.3
#300337	HYPOMELANOSIS OF ITO; HMI; Incontinentia pigmenti Type 1 (not classic type); mosaic translocation		
#300352	CEREBRAL CREATINE DEFICIENCY SYNDROME 1; CCDS1		Xq28
#300354	MENTAL RETARDATION, X-LINKED, SYNDROMIC, CABEZAS TYPE; MRXSC		Xq24
#300367	THROMBOCYTOPENIA, X-LINKED, WITH OR WITHOUT DYSERYTHROPOIETIC ANEMIA; XLTDA; GATA1 gene		Xp11.23
#300373	OSTEOPATHIA STRIATA WITH CRANIAL SCLEROSIS; OSCS; WTX aka AMER1 gene		Xq11.2
#300376	MUSCULAR DYSTROPHY, BECKER TYPE; BMD		Xp21.2-p21.1
#300387	MENTAL RETARDATION, X-LINKED 63; MRX63; ACSL4 gene		Xq23
#300400	SEVERE COMBINED IMMUNODEFICIENCY, X-LINKED; SCIDX1		Xq13.1
#300419	MENTAL RETARDATION, X-LINKED, WITH OR WITHOUT SEIZURES, ARX-RELATED; MRXARX		Xp21.3
#300422	FG SYNDROME 4; FGS4	MENTAL RETARDATION, X-LINKED, WITH OR WITHOUT NYSTAGMUS, INCLUDED; FG4 in OMIM; CASK gene	Xp11.4
#300423	MENTAL RETARDATION, X-LINKED, SYNDROMIC, HEDERA TYPE; MRXSH; ATP6AP2 gene		Xp11.4
#300424	RETINITIS PIGMENTOSA 23; RP23; OFD1 gene		Xp22.2
#300425	AUTISM, SUSCEPTIBILITY TO, X-LINKED 1; AUTSX1; NLGN3 gene		Xq13.1

#300434	STOCCO DOS SANTOS X-LINKED MENTAL RETARDATION SYNDROME; SDSX; SHROOM4 gene		Xp11.22
#300438	HSD10 MITOCHONDRIAL DISEASE; HSD10MD		Xp11.22
#300448	ALPHA-THALASSEMIA MYELODYSPLASIA SYNDROME; ATMDS		Xq21.1
#300455	RETINITIS PIGMENTOSA, X-LINKED, AND SINORESPIRATORY INFECTIONS, WITH OR WITHOUT DEAFNESS		Xp11.4
#300472	CORPUS CALLOSUM, AGENESIS OF, WITH MENTAL RETARDATION, OCULAR COLOBOMA, AND MICROGNATHIA		Xq13.1
#300475	DEAFNESS, DYSTONIA, AND CEREBRAL HYPOMYELINATION; DDCH	CONTIGUOUS ABCD1/DXS1375E DELETION SYNDROME, INCLUDED; CADDS, INCLUDED	Xq28
#300476	CONE-ROD DYSTROPHY, X-LINKED, 3; CORDX3		Xp11.23
#300486	MENTAL RETARDATION, X-LINKED, WITH CEREBELLAR HYPOPLASIA AND DISTINCTIVE FACIAL APPEARANCE		Xq12
#300489	SPINAL MUSCULAR ATROPHY, DISTAL, X-LINKED 3; SMAX3		Xq21.1
#300491	EPILEPSY, X-LINKED, WITH VARIABLE LEARNING DISABILITIES AND BEHAVIOR DISORDERS		Xp11.3-p11.2
#300494	ASPERGER SYNDROME, X-LINKED, SUSCEPTIBILITY TO, 1; ASPGX1		Xq13.1
#300495	AUTISM, SUSCEPTIBILITY TO, X-LINKED 2; AUTSX2	MENTAL RETARDATION, X-LINKED, INCLUDED	Xp22.32-p22.31
#300496	AUTISM, SUSCEPTIBILITY TO, X-LINKED 3; AUTSX3		Xq28
#300497	ASPERGER SYNDROME, X-LINKED, SUSCEPTIBILITY TO, 2; ASPGX2		Xp22.32-p22.31
#300500	ALBINISM, OCULAR, TYPE I; OA1		Xp22.2
#300510	OVARIAN DYSGENESIS 2; ODG2	PREMATURE OVARIAN FAILURE 4, INCLUDED; POF4, INCLUDED	Xp11.22
#300511	PREMATURE OVARIAN FAILURE 2A; POF2A		Xq21.33
#300514	FANCONI ANEMIA, COMPLEMENTATION GROUP B; FANCB		Xp22.2
#300523	ALLAN-HERNDON-DUDLEY SYNDROME; AHDS		Xq13.2
#300534	MENTAL RETARDATION, X-LINKED, SYNDROMIC, CLAES-JENSEN TYPE; MRXSCJ		Xp11.22

#300539	NEPHROGENIC SYNDROME OF INAPPROPRIATE ANTIDIURESIS; NSIAD		Xq28
#300554	HYPOPHOSPHATEMIC RICKETS, X-LINKED RECESSIVE		Xp11.23
#300555	DENT DISEASE 2		Xq26.1
#300558	MENTAL RETARDATION, X-LINKED 30; MRX30		Xq23
#300559	GLYCOGEN STORAGE DISEASE, TYPE IXd; GSD9D		Xq13.1
#300578	CHROMOSOME Xp11.3 DELETION SYNDROME		Xp11.3
#300582	SHORT STATURE, IDIOPATHIC, X-LINKED; ISS		Xp22.33, Yp11.2
#300590	CORNELIA DE LANGE SYNDROME 2; CDLS2		Xp11.22
#300600	ALAND ISLAND EYE DISEASE; AIED		Xp11.23
#300604	PREMATURE OVARIAN FAILURE 2B; POF2B		Xq21.1
#300607	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 8; DEE8		Xq11.1
#300614	DEAFNESS, X-LINKED 5, WITH PERIPHERAL NEUROPATHY; DFNX5		Xq26.1
#300615	BRUNNER SYNDROME; BRNRS	ANTISOCIAL BEHAVIOR, SUSCEPTIBILITY TO, INCLUDED	Xp11.3
#300622	TN POLYAGGLUTINATION SYNDROME; TNPS		Xq24
#300623	FRAGILE X TREMOR/ATAXIA SYNDROME; FXTAS		Xq27.3
#300624	FRAGILE X SYNDROME; FXS		Xq27.3
#300633	HYPOSPADIAS 1, X-LINKED; HYSP1		Xq12
#300635	LYMPHOPROLIFERATIVE SYNDROME, X-LINKED, 2; XLP2		Xq25
#300636	IMMUNODEFICIENCY 33; IMD33		Xq28
#300643	ROLANDIC EPILEPSY, MENTAL RETARDATION, AND SPEECH DYSPRAXIA, X-LINKED; RESDX		Xq22.1
#300645	IMMUNODEFICIENCY 34; IMD34		Xp21.1-p11.4
#300653	PHOSPHOGLYCERATE KINASE 1 DEFICIENCY		Xq21.1
#300659	MENTAL RETARDATION, X-LINKED 93; MRX93		Xq21.1
#300661	PHOSPHORIBOSYLPYROPHOSPHATE SYNTHETASE SUPERACTIVITY	GOUT, PRPS-RELATED, INCLUDED	Xq22.3
#300672	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 2; DEE2		Xp22.13
#300673	ENCEPHALOPATHY, NEONATAL SEVERE, DUE TO MECP2 MUTATIONS		Xq28
#300676	MENTAL RETARDATION, X-LINKED, SYNDROMIC 14; MRXS14		Xq24
#300679	CHROMOSOME Xp21 DELETION SYNDROME		Xp21
#300695	SCAPULOPERONEAL MYOPATHY, X-LINKED DOMINANT; SPM		Xq26.3

#300696	MYOPATHY, X-LINKED, WITH POSTURAL MUSCLE ATROPHY; XMPMA	EMERY-DREIFUSS MUSCULAR DYSTROPHY 6, X-LINKED, INCLUDED; EDMD6, INCLUDED	Xq26.3
#300699	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, WU TYPE; MRXSW		Xq25
#300705	CHROMOSOME Xp11.22 DUPLICATION SYNDROME		Xp11.22
#300707	TOE SYNDACTYLY, TELECANTHUS, AND ANOGENITAL AND RENAL MALFORMATIONS; STAR		Xq28
#300717	REDUCING BODY MYOPATHY, X-LINKED 1A, SEVERE, WITH INFANTILE OR EARLY CHILDHOOD ONSET; RBMX1A		Xq26.3
#300718	REDUCING BODY MYOPATHY, X-LINKED 1B, WITH LATE CHILDHOOD OR ADULT ONSET; RBMX1B		Xq26.3
#300749	MENTAL RETARDATION AND MICROCEPHALY WITH PONTINE AND CEREBELLAR HYPOPLASIA; MICPCH		Xp11.4
#300751	ANEMIA, SIDEROBLASTIC, 1; SIDBA1		Xp11.21
#300752	PROTOPORPHYRIA, ERYTHROPOIETIC, X-LINKED; XLEPP		Xp11.21
#300755	AGAMMAGLOBULINEMIA, X-LINKED; XLA	HYPOGAMMAGLOBULINEMIA, X-LINKED, INCLUDED	Xq22.1
#300758	HYPOSPADIAS 2, X-LINKED; HYSP2		Xq28
#300770	SURFACTANT METABOLISM DYSFUNCTION, PULMONARY, 4; SMDP4		Xp22.33
#300799	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, RAYMOND TYPE; MRXSR		Xq26.1
#300801	CHROMOSOME Xp11.23-p11.22 DUPLICATION SYNDROME		Xp11.23-p11.22
#300802	MENTAL RETARDATION, X-LINKED 96; MRX96		Xp11.23
#300803	MENTAL RETARDATION, X-LINKED 97; MRX97		Xq21.1
#300804	JOUBERT SYNDROME 10; JBTS10		Xp22.2
#300807	THROMBOPHILIA, X-LINKED, DUE TO FACTOR IX DEFECT; THPH8	DEEP VENOUS THROMBOSIS, PROTECTION AGAINST, INCLUDED	Xq27.1
#300814	NYSTAGMUS 6, CONGENITAL, X-LINKED; NYS6		Xp22.2
#300815	CHROMOSOME Xq28 DUPLICATION SYNDROME		Xq28
#300816	COMBINED OXIDATIVE PHOSPHORYLATION DEFICIENCY 6; COXPD6		Xq26.1
#300818	PAROXYSMAL NOCTURNAL HEMOGLOBINURIA 1; PNH1		Xp22.2
#300830	AUTISM, SUSCEPTIBILITY TO, X-LINKED 4; AUTSX4		Xp22.11
#300831	CK SYNDROME		Xq28

#300833	46,XX SEX REVERSAL 3; SRXX3	CHROMOSOME Xq26 DELETION SYNDROME, INCLUDED	Xq26.3
#300834	MACULAR DEGENERATION, X-LINKED ATROPHIC		Xp11.4
#300835	ANEMIA, X-LINKED, WITH OR WITHOUT NEUTROPENIA AND/OR PLATELET ABNORMALITIES; XLANP		Xp11.23
#300842	MCLEOD SYNDROME; MCLDS	MCLEOD SYNDROME WITH CHRONIC GRANULOMATOUS DISEASE, INCLUDED	Xp21.1
#300844	MENTAL RETARDATION, X-LINKED 19; MRX19		Xp22.12
#300845	MOYAMOYA DISEASE 4 WITH SHORT STATURE, HYPERGONADOTROPIC HYPOGONADISM, AND FACIAL DYSMORPHISM; MYMY4		Xq28
#300847	AUTISM, SUSCEPTIBILITY TO, X-LINKED 5; AUTSX5		Xq28
#300849	MENTAL RETARDATION, X-LINKED 41; MRX41		Xq28
#300850	MENTAL RETARDATION, X-LINKED 90; MRX90		Xq13.1
#300853	IMMUNODEFICIENCY, X-LINKED, WITH MAGNESIUM DEFECT, EPSTEIN-BARR VIRUS INFECTION, AND NEOPLASIA; XMEN		Xq21.1
#300854	RENAL CELL CARCINOMA, Xp11-ASSOCIATED; RCCX1		Xp11.23
#300855	OGDEN SYNDROME; OGDNS		Xq28
#300857	AMYOTROPHIC LATERAL SCLEROSIS 15 WITH OR WITHOUT FRONTOTEMPORAL DEMENTIA; ALS15		Xp11.21
#300860	MENTAL RETARDATION, X-LINKED, SYNDROMIC, NASCIMENTO TYPE; MRXSN		Xq24
#300863	CHONDRODYSPLASIA WITH PLATYSPONDYLY, DISTINCTIVE BRACHYDACTYLY, HYDROCEPHALY, AND MICROPHTHALMIA		Xp11.23
#300867	KABUKI SYNDROME 2; KABUK2		Xp11.3
#300868	MULTIPLE CONGENITAL ANOMALIES-HYPOTONIA-SEIZURES SYNDROME 2; MCAHS2		Xp22.2
#300869	CHROMOSOME Xq27.3-q28 DUPLICATION SYNDROME		Xq27.3-q28
#300872	AUTISM, SUSCEPTIBILITY TO, X-LINKED 6; AUTSX6		Xq28
#300882	CORNELIA DE LANGE SYNDROME 5; CDLS5		Xq13.1
#300884	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 36; DEE36	CONGENITAL DISORDER OF GLYCOSYLATION, TYPE Is, INCLUDED; CDG1S, INCLUDED	Xq23

#300886	MENTAL RETARDATION, X-LINKED, SYNDROMIC 32; MRXS32		Xq28
#300887	LINEAR SKIN DEFECTS WITH MULTIPLE CONGENITAL ANOMALIES 2; LSDMCA2		Xq21.1
#300888	HYPOTHYROIDISM, CENTRAL, WITH TESTICULAR ENLARGEMENT; CHTE		Xq26.1
#300894	NEURODEGENERATION WITH BRAIN IRON ACCUMULATION 5; NBIA5		Xp11.23
#300895	OHDO SYNDROME, X-LINKED; OHDOX		Xq13.1
#300896	CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IIm; CDG2M		Xp11.23
#300905	CHARCOT-MARIE-TOOTH DISEASE, X-LINKED DOMINANT, 6; CMTX6		Xp22.11
#300908	ANEMIA, NONSPHEROCYTIC HEMOLYTIC, DUE TO G6PD DEFICIENCY		Xq28
#300909	ANGIOEDEMA INDUCED BY ACE INHIBITORS, SUSCEPTIBILITY TO; AEACEI		Xq26.1
#300910	BONE MINERAL DENSITY QUANTITATIVE TRAIT LOCUS 18; BMND18		Xq23
#300911	PARKINSONISM WITH SPASTICITY, X-LINKED; XPDS		Xp11.4
#300912	MENTAL RETARDATION, X-LINKED 98; MRX98		Xq13.3
#300914	DEAFNESS, X-LINKED 6; DFNX6		Xq22.3
#300915	MICROPHTHALMIA, SYNDROMIC 13; MCOPS13		Xq28
#300918	PALMOPLANTAR KERATODERMA, MUTILATING, WITH PERIORIFICIAL KERATOTIC PLAQUES, X-LINKED		Xp22.12
#300919	MENTAL RETARDATION, X-LINKED 99; MRX99		Xp11.4
#300923	MENTAL RETARDATION, X-LINKED 100; MRX100		Xq13.1
#300928	MENTAL RETARDATION, X-LINKED 101; MRX101		Xq22.3
#300932	THYROXINE-BINDING GLOBULIN QUANTITATIVE TRAIT LOCUS; TBGQTL		Xq22.3
#300934	CONGENITAL DISORDER OF GLYCOSYLATION, TYPE Iy; CDG1Y		Xq28
#300942	CHROMOSOME Xq26.3 DUPLICATION SYNDROME		Xq26.3
#300943	PITUITARY ADENOMA 2, GROWTH HORMONE-SECRETING; PITA2		Xq26.3
#300946	DIAMOND-BLACKFAN ANEMIA 14 WITH MANDIBULOFACIAL DYSOSTOSIS; DBA14		Xp11.22
#300952	LINEAR SKIN DEFECTS WITH MULTIPLE CONGENITAL ANOMALIES 3; LSDMCA3		Xp11.3

#300953	TRICHOTHIODYSTROPHY 5, NONPHOTOSENSITIVE; TTD5		Xq24
#300957	MENTAL RETARDATION, X-LINKED 12; MRX12		Xq25
#300958	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, SNIJDERS BLOK TYPE; MRXSSB		Xp11.4
#300960	MEND SYNDROME; MEND		Xp11.23
#300963	RITSCHER-SCHINZEL SYNDROME 2; RTSC2		Xp11.23
#300966	MENTAL RETARDATION, X-LINKED, SYNDROMIC 33; MRXS33		Xq13.1
#300967	MENTAL RETARDATION, X-LINKED, SYNDROMIC 34; MRXS34		Xq13.1
#300968	MENTAL RETARDATION, X-LINKED 99, SYNDROMIC, FEMALE-RESTRICTED; MRXS99F		Xp11.4
#300971	BARTTER SYNDROME, TYPE 5, ANTENATAL, TRANSIENT; BARTS5		Xp11.21
#300972	IMMUNODEFICIENCY 47; IMD47		Xq28
#300978	TONNE-KALSCHEUER SYNDROME; TOKAS		Xq13.2
#300979	Xq25 DUPLICATION SYNDROME	Xq25 TRIPLICATION SYNDROME, INCLUDED	Xq25
#300982	MENTAL RETARDATION, X-LINKED 103; MRX103		Xp22.11
#300983	MENTAL RETARDATION, X-LINKED 104; MRX104		Xp22.2
#300984	MENTAL RETARDATION, X-LINKED 105; MRX105		Xp11.23
#300985	VAS DEFERENS, CONGENITAL BILATERAL APLASIA OF, X-LINKED; CBAVDX		Xp22.13
#300986	MENTAL RETARDATION, X-LINKED, SYNDROMIC, BAIN TYPE; MRXSB		Xq22.1
#300988	IMMUNODEFICIENCY 50; IMD50		Xq12
#300989	MEESTER-LOEYS SYNDROME; MRLS		Xq28
#300990	MIDFACE HYPOPLASIA, HEARING IMPAIRMENT, ELLIPTOCYTOSIS, AND NEPHROCALCINOSIS; MFHIEN		Xq23
#300991	CILIARY DYSKINESIA, PRIMARY, 36, X-LINKED; CILD36		Xq22.3
#300997	MENTAL RETARDATION, X-LINKED 106; MRX106		Xq13.1
#300998	MENTAL RETARDATION, X-LINKED, SYNDROMIC, 35; MRXS35		Xq28
#301000	WISKOTT-ALDRICH SYNDROME; WAS		Xp11.23
#301006	GALLOWAY-MOWAT SYNDROME 2, X-LINKED; GAMOS2		Xq28
#301008	MENTAL RETARDATION, X-LINKED, SYNDROMIC, HOUGE TYPE; MRXSHG		Xp22.12
#301010	MYOPIA 26, X-LINKED, FEMALE-RESTRICTED; MYP26		Xq13.1

#301013	MENTAL RETARDATION, X-LINKED 107; MRX107		Xq24
#301014	OSTEOGENESIS IMPERFECTA, TYPE XIX; OI19		Xp22.12
#301015	HEMOLYTIC ANEMIA, CONGENITAL, X-LINKED		Xq27.1
#301018	DEAFNESS, X-LINKED 7; DFNX7		Xq22.1
#301020	MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 12; MC1DN12		Xq24
#301021	MITOCHONDRIAL COMPLEX I DEFICIENCY, NUCLEAR TYPE 30; MC1DN30		Xp11.3
#301022	MULLEGAMA-KLEIN-MARTINEZ SYNDROME; MKMS		Xq25
#301024	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED 108; MRX108		Xp11.3
#301025	PAGANINI-MIOZZO SYNDROME; MRXSPM		Xq26.2
#301026	KEIPERT SYNDROME; KPTS		Xq26.2
#301028	NEPHROTIC SYNDROME, TYPE 20; NPHS20		Xq22.3
#301029	SHUKLA-VERNON SYNDROME; SHUVER		Xq26.1
#301030	VAN ESCH-O'DRISCOLL SYNDROME; VEODS		Xp22.1-p21.3
#301031	CONGENITAL DISORDER OF GLYCOSYLATION, TYPE Icc; CDG1CC		Xq21.1
#301032	BASILICATA-AKHTAR SYNDROME; MRXSBA		Xp22.2
#301033	HYPOTHYROIDISM, CONGENITAL, NONGOITROUS, 8; CHNG8		Xp22.3-p22.2
#301035	HYPOTHYROIDISM, CONGENITAL, NONGOITROUS, 9; CHNG9		Xq22.3
#301039	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, HACKMANN-DI DONATO TYPE; MRXSHD		Xq24
#301040	ALPHA-THALASSEMIA/MENTAL RETARDATION SYNDROME, X-LINKED; ATRX		Xq21.1
#301041	WIEACKER-WOLFF SYNDROME, FEMALE-RESTRICTED; WRWFFR		Xq11.2
#301043	HOLOPROSENCEPHALY 13, X-LINKED; HPE13		Xq25
#301044	EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 85, WITH OR WITHOUT MIDLINE BRAIN DEFECTS; EIEE85		Xp11.22
#301045	CONGENITAL DISORDER OF GLYCOSYLATION, TYPE IIr; CDG2R		Xp11.4
#301050	ALPORT SYNDROME 1, X-LINKED; ATS1		Xq22.3
#301051	IMMUNODEFICIENCY 74, COVID19-RELATED, X-LINKED; IMD74		Xp22.2

#301052	WARFARIN SENSITIVITY, X-LINKED		Xq27.1
#301054	VEXAS SYNDROME; VEXAS		Xp11.3
#301200	AMELOGENESIS IMPERFECTA, TYPE IE; AI1E		Xp22.2
#301220	PIGMENTARY DISORDER, RETICULATE, WITH SYSTEMIC MANIFESTATIONS, X-LINKED; PDR		Xp22.1-p21.3
#301310	ANEMIA, SIDEROBLASTIC, AND SPINOCEREBELLAR ATAXIA; ASAT		Xq13.3
#301500	FABRY DISEASE	FABRY DISEASE, CARDIAC VARIANT, INCLUDED	Xq22.1
#301830	SPINAL MUSCULAR ATROPHY, X-LINKED 2; SMAX2		Xp11.3
#301835	ARTS SYNDROME; ARTS		Xq22.3
#301900	BORJESON-FORSSMAN-LEHMANN SYNDROME; BFLS		Xq26.2
#302045	CARDIOMYOPATHY, DILATED, 3B; CMD3B		Xp21.2-p21.1
#302060	BARTH SYNDROME; BTHS		Xq28
#302200	CATARACT 40; CTRCT40		Xp22.2-p22.1
#302350	NANCE-HORAN SYNDROME; NHS		Xp22.2-p22.1
#302500	SPINOCEREBELLAR ATAXIA, X-LINKED 1; SCAX1		Xq28
#302800	CHARCOT-MARIE-TOOTH DISEASE, X-LINKED DOMINANT, 1; CMTX1		Xq13.1
#302802	CHARCOT-MARIE-TOOTH DISEASE, X-LINKED RECESSIVE, 3; CMTX3		Xq26
#302905	ABRUZZO-ERICKSON SYNDROME; ABERS		Xq21.1
#302950	CHONDRODYSPLASIA PUNCTATA 1, X-LINKED RECESSIVE; CDPX1		Xp22.33
#302960	CHONDRODYSPLASIA PUNCTATA 2, X-LINKED DOMINANT; CDPX2		Xp11.23
#303100	CHOROIDEREMIA; CHM	CHOROIDAL SCLEROSIS, INCLUDED	Xq21.2
#303110	CHOROIDEREMIA, DEAFNESS, AND MENTAL RETARDATION		Xq21
#303350	MASA SYNDROME		Xq28
#303400	CLEFT PALATE WITH OR WITHOUT ANKYLOGLOSSIA, X-LINKED; CPX		Xq21.1
#303600	COFFIN-LOWRY SYNDROME; CLS		Xp22.12
#303700	BLUE CONE MONOCHROMACY; BCM	CONE DYSTROPHY 5, X-LINKED, INCLUDED; COD5, INCLUDED	Xq28, Xq28
#303800	COLORBLINDNESS, PARTIAL, DEUTAN SERIES; CBD	DEUTERANOMALY, INCLUDED	Xq28
#303900	COLORBLINDNESS, PARTIAL, PROTAN SERIES; CBP	PROTANOMALY, INCLUDED	Xq28
#304020	CONE-ROD DYSTROPHY, X-LINKED, 1; CORDX1	CONE DYSTROPHY 1, X-LINKED, INCLUDED; COD1, INCLUDED	Xp11.4
#304100	CORPUS CALLOSUM, PARTIAL AGENESIS OF, X-LINKED		Xq28
#304110	CRANIOFRONTONASAL SYNDROME; CFNS		Xq13.1

#304120	OTOPALATODIGITAL SYNDROME, TYPE II; OPD2		Xq28
#304150	OCCIPITAL HORN SYNDROME; OHS		Xq21.1
#304340	PETTIGREW SYNDROME; PGS		Xp22.2
#304400	DEAFNESS, X-LINKED 2; DFNX2		Xq21.1
#304500	DEAFNESS, X-LINKED 1; DFNX1		Xq22.3
#304700	MOHR-TRANEBJAERG SYNDROME; MTS		Xq22.1
#304790	IMMUNODYSREGULATION, POLYENDOCRINOPATHY, AND ENTEROPATHY, X-LINKED; IPEX	ISLETS OF LANGERHANS, ABSENCE OF, INCLUDED	Xp11.23
#304800	DIABETES INSIPIDUS, NEPHROGENIC, X-LINKED		Xq28
#305000	DYSKERATOSIS CONGENITA, X-LINKED; DKCX	HOYERAAL-HREIDARSSON SYNDROME, INCLUDED; HHS, INCLUDED	Xq28
#305100	ECTODERMAL DYSPLASIA 1, HYPOHIDROTIC, X-LINKED; XHED		Xq13.1
#305390	EXUDATIVE VITREORETINOPATHY 2, X-LINKED; EVR2		Xp11.3
#305400	AARSKOG-SCOTT SYNDROME; AAS	FACIOGENITAL DYSPLASIA WITH ATTENTION DEFICIT-HYPERACTIVITY DISORDER, INCLUDED	Xp11.22
#305450	OPITZ-KAVEGGIA SYNDROME; OKS		Xq13.1
#305600	FOCAL DERMAL HYPOPLASIA; FDH		Xp11.23
#305620	FRONTOMETAPHYSEAL DYSPLASIA 1; FMD1		Xq28
#306000	GLYCOGEN STORAGE DISEASE IXa1; GSD9A1	GLYCOGEN STORAGE DISEASE IXa2, INCLUDED; GSD9A2, INCLUDED	Xp22.13
#306400	GRANULOMATOUS DISEASE, CHRONIC, X-LINKED; CGDX	CYTOCHROME b-POSITIVE GRANULOMATOUS DISEASE, CHRONIC, X-LINKED, INCLUDED	Xp21.1-p11.4
#306700	HEMOPHILIA A; HEMA		Xq28
#306900	HEMOPHILIA B; HEMB	HEMOPHILIA B(M), INCLUDED	Xq27.1
#306955	HETEROTAXY, VISCERAL, 1, X-LINKED; HTX1	CONGENITAL HEART DEFECTS, MULTIPLE TYPES, 1, X-LINKED, INCLUDED; CHTD1, INCLUDED	Xq26.3
#307000	HYDROCEPHALUS DUE TO CONGENITAL STENOSIS OF AQUEDUCT OF SYLVIUS; HSAS	HYDROCEPHALUS, X-LINKED, WITH CONGENITAL IDIOPATHIC INTESTINAL PSEUDOOBSTRUCTION, INCLUDED	Xq28
#307030	GLYCEROL KINASE DEFICIENCY; GKD		Xp21.2
#307150	HYPERTRICHOSIS, CONGENITAL GENERALIZED; HTC2		Xq27.1
#307200	ISOLATED GROWTH HORMONE DEFICIENCY, TYPE III, WITH AGAMMAGLOBULINEMIA; IGHD3		Xq22.1
#307700	HYPOPARATHYROIDISM, X-LINKED; HYPX		Xq27.1

#307800	HYPOPHOSPHATEMIC RICKETS, X-LINKED DOMINANT; XLHR		Xp22.11
#308050	CONGENITAL HEMIDYSPLASIA WITH ICHTHYOSIFORM ERYTHRODERMA AND LIMB DEFECTS		Xq28
#308100	ICHTHYOSIS, X-LINKED; XLI	ICHTHYOSIS, X-LINKED, COMPLICATED, INCLUDED	Xp22.31
#308205	IFAP SYNDROME 1, WITH OR WITHOUT BRESHECK SYNDROME; IFAP1		Xp22.12
#308230	IMMUNODEFICIENCY WITH HYPER-IgM, TYPE 1; HIGM1		Xq26.3
#308240	LYMPHOPROLIFERATIVE SYNDROME, X-LINKED, 1; XLP1		Xq25
#308300	INCONTINENTIA PIGMENTI; IP		Xq28
#308350	DEVELOPMENTAL AND EPILEPTIC ENCEPHALOPATHY 1; DEE1		Xp21.3
#308700	HYPOGONADOTROPIC HYPOGONADISM 1 WITH OR WITHOUT ANOSMIA; HH1		Xp22.31
#308800	KERATOSIS FOLLICULARIS SPINULOSA DECALVANS, X-LINKED; KFSDX		Xp22.12
#308940	LEIOMYOMATOSIS, DIFFUSE, WITH ALPORT SYNDROME; DL-ATS		
#308990	PROTEINURIA, LOW MOLECULAR WEIGHT, WITH HYPERCALCIURIA AND NEPHROCALCINOSIS		Xp11.23
#309000	LOWE OCULOCEREBRORENAL SYNDROME; OCRL		Xq26.1
#309120	SPERMATOGENIC FAILURE, X-LINKED, 2; SPGFX2		Xq13.1
#309300	MEGALOCORNEA; MGC1		Xq23
#309350	MELNICK-NEEDLES SYNDROME; MNS		Xq28
#309400	MENKES DISEASE; MNK		Xq21.1
#309500	RENPENNING SYNDROME 1; RENS1		Xp11.23
#309510	PARTINGTON X-LINKED MENTAL RETARDATION SYNDROME; PRTS		Xp21.3
#309520	INTELLECTUAL DEVELOPMENTAL DISORDER, X-LINKED, SYNDROMIC, LUJAN-FRYNS TYPE; MRXSLF		Xq13.1
#309530	MENTAL RETARDATION, X-LINKED 1; MRX1		Xp11.22
#309541	METHYLMALONIC ACIDEMIA AND HOMOCYSTEINEMIA, cblX TYPE		Xq28
#309548	MENTAL RETARDATION, X-LINKED, ASSOCIATED WITH FRAGILE SITE FRAXE		Xq28
#309549	MENTAL RETARDATION, X-LINKED 9; MRX9		Xp11.23
#309580	MENTAL RETARDATION-HYPOTONIC FACIES SYNDROME, X-LINKED, 1; MRXHF1		Xq21.1

#309583	MENTAL RETARDATION, X-LINKED, SYNDROMIC, SNYDER-ROBINSON TYPE; MRXSSR		Xp22.11
#309585	WILSON-TURNER X-LINKED MENTAL RETARDATION SYNDROME; WTS		Xq12
#309590	MENTAL RETARDATION, X-LINKED, SYNDROMIC, TURNER TYPE; MRXST		Xp11.22
#309630	METACARPAL 4-5 FUSION; MF4		Xq21.1
#309800	MICROPHTHALMIA, SYNDROMIC 1; MCOPS1		Xq28
#309801	LINEAR SKIN DEFECTS WITH MULTIPLE CONGENITAL ANOMALIES 1; LSDMCA1		Xp22.2
#309900	MUCOPOLYSACCHARIDOSIS, TYPE II; MPS2		Xq28
#310200	MUSCULAR DYSTROPHY, DUCHENNE TYPE; DMD		Xp21.2-p21.1
#310300	EMERY-DREIFUSS MUSCULAR DYSTROPHY 1, X-LINKED; EDMD1		Xq28
#310400	MYOPATHY, CENTRONUCLEAR, X-LINKED; CNMX		Xq28
#310440	MYOPATHY, X-LINKED, WITH EXCESSIVE AUTOPHAGY; MEAX		Xq28
#310468	NEPHROLITHIASIS, X-LINKED RECESSIVE, WITH RENAL FAILURE; XRN		Xp11.23
#310490	CHARCOT-MARIE-TOOTH DISEASE, X-LINKED RECESSIVE, 4, WITH OR WITHOUT CEREBELLAR ATAXIA; CMTX4		Xq26.1
#310500	NIGHT BLINDNESS, CONGENITAL STATIONARY, TYPE 1A; CSNB1A	NYCTALOPIA, INCLUDED	Xp11.4
#310600	NORRIE DISEASE; ND		Xp11.3
#310700	NYSTAGMUS 1, CONGENITAL, X-LINKED; NYS1	NYSTAGMUS, INFANTILE PERIODIC ALTERNATING, X-LINKED, INCLUDED; XIPAN, INCLUDED	Xq26.2
#311070	CHARCOT-MARIE-TOOTH DISEASE, X-LINKED RECESSIVE, 5; CMTX5		Xq22.3
#311200	OROFACIODIGITAL SYNDROME I; OFD1		Xp22.2
#311250	ORNITHINE TRANSCARBAMYLASE DEFICIENCY, HYPERAMMONEMIA DUE TO		Xp11.4
#311300	OTOPALATODIGITAL SYNDROME, TYPE I; OPD1	OTOPALATODIGITAL SPECTRUM DISORDER, INCLUDED	Xq28
#311360	PREMATURE OVARIAN FAILURE 1; POF1		Xq27.3
#311510	WAISMAN SYNDROME; WSMN		Xq28
#311900	TARP SYNDROME; TARPS		Xp11.3
#312000	PANHYPOPITUITARISM, X-LINKED; PHPX		Xq27.1
#312060	PROPERDIN DEFICIENCY, X-LINKED; CFPD	PROPERDIN DEFICIENCY, TYPE II, INCLUDED	Xp11.23

#312080	PELIZAEUS-MERZBACHER DISEASE; PMD		Xq22.2
#312170	PYRUVATE DEHYDROGENASE E1-ALPHA DEFICIENCY; PDHAD	LACTIC ACIDEMIA, THIAMINE-RESPONSIVE, INCLUDED	Xp22.12
#312300	ANDROGEN INSENSITIVITY, PARTIAL; PAIS		Xq12
#312600	RETINITIS PIGMENTOSA 2; RP2		Xp11.3
#312700	RETINOSCHISIS 1, X-LINKED, JUVENILE; RS1		Xp22.13
#312750	RETT SYNDROME; RTT	RETT SYNDROME, ZAPPELLA VARIANT, INCLUDED	Xq28
#312863	COMBINED IMMUNODEFICIENCY, X-LINKED; CIDX		Xq13.1
#312870	SIMPSON-GOLABI-BEHMEL SYNDROME, TYPE 1; SGBS1		Xq26.2
#312920	SPASTIC PARAPLEGIA 2, X-LINKED; SPG2		Xq22.2
#313200	SPINAL AND BULBAR MUSCULAR ATROPHY, X-LINKED 1; SMAX1		Xq12
#313400	SPONDYLOEPIPHYSEAL DYSPLASIA TARDA, X-LINKED; SEDT		Xp22.2
#313500	TOOTH AGENESIS, SELECTIVE, X-LINKED, 1; STHAGX1		Xq13.1
#313900	THROMBOCYTOPENIA 1; THC1	THROMBOCYTOPENIA, X-LINKED, INTERMITTENT, INCLUDED	Xp11.23
#314050	THROMBOCYTOPENIA WITH BETA-THALASSEMIA, X-LINKED; XLTT		Xp11.23
#314250	DYSTONIA 3, TORSION, X-LINKED; DYT3		Xq13.1
#314390	VACTERL ASSOCIATION, X-LINKED, WITH OR WITHOUT HYDROCEPHALUS; VACTERLX		Xq26.3
#314400	CARDIAC VALVULAR DYSPLASIA, X-LINKED; CVD1		Xq28
#314580	WIEACKER-WOLFF SYNDROME; WRWF		Xq11.2
#249700	LANGER MESOMELIC DYSPLASIA; LMD		Xp22.33, Yp11.2
#300000	OPITZ GBBB SYNDROME, TYPE I; GBBB1		Xp22.2
#300004	CORPUS CALLOSUM, AGENESIS OF, WITH ABNORMAL GENITALIA		Xp21.3
#611162	MALARIA, SUSCEPTIBILITY TO	MALARIA, RESISTANCE TO, INCLUDED	1q23.2, 1q23.3, 1q23.3, 1q32.2, 2q14.3, 3p21.2, 4q31.21, 4q31.21, 6p21.33, 7q21.11, 11p15.4, 11q24.2,

			17q11.2, 17q21.31, 19p13.2, Xq28
MIM Number	Title	Included Titles	Cytogenetic Location
#127300	LERI-WEILL DYSCHONDROSTEOSIS; LWD	MADELUNG DEFORMITY, INCLUDED	Xp22.33, Yp11.2
#300009	DENT DISEASE 1		Xp11.23
#300018	46,XY SEX REVERSAL 2; SRXY2		Xp21.2
#300029	RETINITIS PIGMENTOSA 3; RP3		Xp11.4
#300048	INTESTINAL PSEUDOOBSTRUCTION, NEURONAL, CHRONIC IDIOPATHIC, X-LINKED	CONGENITAL SHORT BOWEL SYNDROME, X-LINKED, INCLUDED - FLNA	Xq28

[a]Titles as listed verbatim in OMIM.

References:

1. Ben-Shachar, R., Svenson, A., Goldberg, J. D. & Muzzey, D. A data-driven evaluation of the size and content of expanded carrier screening panels. *Genet. Med.* **21**, 1931-1939 (2019).
2. Guo, M. H. & Gregg, A. R. Estimating yields of prenatal carrier screening and implications for design of expanded carrier screening panels. *Genet. Med.* **21**, 1940-1947 (2019).
3. Lek, M. et al. Analysis of protein-coding genetic variation in 60,706 humans. *Nature*. **536**, 285-291 (2016).

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CORRECTION

Correction to: 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)

Anthony R. Gregg, Mahmoud Aarabi, Susan Klugman, Natalia T. Leach, Michael T. Bashford, Tamar Goldwaser, Emily Chen, Teresa N. Sparks, Honey V. Reddi, Aleksandar Rajkovic, Jeffrey S. Dungan and ACMG Professional Practice and Guidelines Committee*

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Correction to: *Genetics in Medicine* (2021); https://doi.org/10.1038/s41436-021-01203-z; Article published online 20 July 2021

Several instances of non-inclusive language were used in the original version of this paper. The authors regret the errors.

On p. 6:

ACMG recommends:

All pregnant patients and those planning a pregnancy should be offered Tier 3 carrier screening for autosomal recessive (Tables 1–5) and X-linked (Table 6) conditions. Reproductive partners of pregnant patients and those planning a pregnancy may be offered Tier 3 carrier screening for autosomal recessive conditions (Tables 1–5) when carrier screening is performed simultaneously with their partner.

On p. 7:

ACMG recommends:

All XX patients should be offered screening for only those X-linked genes listed in Table 6 as part of Tier 3 screening.

First paragraph on p. 10:

The possibility of manifesting heterozygotes and their associated clinical features, if such are known, as in cases of carriers of X-linked conditions (for example, cardiomyopathy in DMD carriers; primary ovarian failure in *FMR1* premutation carriers) should be discussed as part of pretest counseling.

Last paragraph on p. 10:

Carrier screening counseling should be provided by knowledgeable and appropriately trained health-care professionals and should be performed pre- and post-test. It should be noted that traditional models of genetic counseling can be both time and labor intensive. Thus, new models need to be developed and instituted for both training nongenetics providers and counseling patients. These models might include videos, chatbots, computer-based learning, or other methods of providing information to patients and assessing their understanding. Carrier screening for autosomal recessive conditions is unique when compared to other medical testing in that test results impact the likelihood of offspring of the patient having a genetic condition, while for the most part, the patient screened is healthy. However, patients with two X chromosomes, who screen positive for X-linked conditions may manifest symptoms of the condition (e.g., OTC deficiency and hemophilia) because of skewed X inactivation. This also explains why some carriers of Duchenne muscular dystrophy (DMD) experience cardiomyopathy. A subset of these patients who have a *FMR1* premutation allele are at risk to develop premature ovarian insufficiency, a condition unrelated to that seen in their XY offspring (i.e., fragile X syndrome).

Last paragraph on p. 11:

When sequential screening is performed and one partner is discovered to be a carrier of an autosomal recessive or X-linked condition, that partner should undergo counseling by a knowledgeable and appropriately trained health-care professional. In specific circumstances, it may be especially appropriate to seek the assistance of a genetics professional, for example (1) when the gene or variant is known to be associated with variable expressivity, (2) when an X-linked carrier is identified, (3) when autosomal recessive carriers of gene variants that have possible phenotypic implications are identified, and (4) when a VUS is disclosed.

In addition the ESM was updated.

The original article has been corrected.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41436-021-01300-z.

Correspondence and requests for materials should be addressed to ACMG.

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