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Identification of at-Risk Reproductive Couples via Expanded Carrier Testing at a Commercial Laboratory

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Abstract

Introduction: One of the purposes of genetic carrier testing is to identify individuals and reproductive couples who are at increased risk for having offspring with a heritable genetic disease. Population-based testing is recommended for a handful of disorders, however ethnicity-based and expanded carrier testing approaches are also acceptable strategies. Reproductive couples who are both carriers for an autosomal recessive disease and female patients who are carriers of X-linked diseases are at increased risk for having a child with a heritable genetic disease.

Objective: This research aims to quantify the number of at-risk reproductive couples identified via carrier testing at a commercial laboratory. In addition, this study will report the most commonly identified at-risk diseases.

Materials & Methods: This is a retrospective database review which identified 1,877 known reproductive couples referred for carrier testing at a commercial laboratory. Test results were reviewed, and at-risk couples were quantified. A subset of the cohort was referred from a single practice utilizing a routinely applied expanded carrier testing approach.

Results: Of the 1,877 reproductive couples, 208 (11.1%) were classified as at-risk based on their carrier testing results. Of the 387 reproductive couples referred from a single practice, 75 (19.4%) were at-risk.

Conclusion: As expected, the number of genes examined when pursuing carrier testing affects the chance of identifying at-risk reproductive couples. A protocol routinely applying expanded carrier testing may yield a 19.4% rate of at-risk reproductive couples. Routinely applying expanded carrier testing and partner testing is a best practice for maximizing the identification of at-risk reproductive couples. The quantification of identifying at-risk couples demonstrated by this study may help a referring clinic and potential patients understand the likelihood of identifying reproductive risk via expanded carrier testing.

Keywords: Carrier testing; Expanded carrier testing; Reproductive risk; At-risk reproductive couples

Introduction

The purpose of genetic carrier testing is to detect individuals and reproductive couples who are at increased risk for having offspring with a heritable genetic disease. Every individual is potentially an asymptomatic carrier for approximately 2-3 pathogenic variants associated with autosomal recessive (AR) disease (Bell, 2011) [1]. Reproductive couples who are both carriers for the same AR disease are at increased risk to have offspring affected with the disease, with a 25% chance for every pregnancy initiated (or embryo fertilized). Ideally, at-risk reproductive couples should be identified prior to conception, to maximize reproductive choices (ACOG 690, 2017) [2]. Reproductive counseling explaining options and family planning is essential for at-risk reproductive couples. Preconception identification provides several otherwise unavailable reproductive options, such as in vitro fertilization (IVF) with preimplantation genetic testing for monogenic disease (PGT-M), use of donor gametes, adoption, or forgoing reproduction. Although performing genetic carrier testing in the preconception period allows the couple the widest variety of testing and family planning options, testing may also be incorporated into routine prenatal care during pregnancy (ACOG 690, 2017) [2]. All at-risk pregnancies, regardless of identification pre- or post-conception, have the option of prenatal diagnosis via chorionic villus sampling or amniocentesis. Recent advances in technology also make cell-free DNA screening for inherited monogenic diseases available, depending on the molecular mechanism of the familial variant(s) (Progenity, 2019) [3]. While recommended for all women of childbearing age, carrier testing is optional and voluntary, and some individuals, or their reproductive partners, may decline testing or any intervention after learning of their carrier testing options (ACOG 690, 2017) [3].

It has been well-documented that certain genetic diseases occur more frequently within specific ethnic groups [4-8]. For example, Tay-Sachs disease is more prevalent in the Ashkenazi Jewish population and recognition of this prompted development of the first genetic carrier testing programs (Kabak and Zeiger, 1972) [9]. Since then, an increased prevalence of Tay-Sachs disease has also been recognized in the Irish, French Canadian and Cajun populations (ACOG 442, 2009) [6]. Cystic fibrosis is more common in people with Caucasian and Ashkenazi Jewish ethnicities (ACOG 691, 2017) [7]. Furthermore, hemoglobinopathies (including thalassemias and other alpha/beta globin variants) are more common in the African, Mediterranean, and Asian populations (among other ethnic backgrounds) (ACOG 78, 2007) [8].

Historically, carrier testing has been offered to individuals who fit a high-risk profile. Ethnicity-based guidelines for testing individuals of Ashkenazi Jewish ancestry are published for several diseases common in that lineage [6,10] (ACOG 442, 2009; Gross et al, 2008). Fragile X carrier testing guidelines recommend testing for those with a family history of fragile X-related diseases, autism, and/or intellectual disability (ACOG 691, 2017) [7]. Carrier testing may also be prompted by a positive family history or patient interest. Recommendations for universal carrier testing (irrespective of ethnicity or family history) are currently limited to molecular evaluation for cystic fibrosis and spinal muscular atrophy (SMA), and a complete blood count with red blood cell indices and hemoglobin electrophoresis for hemoglobinopathies and thalassemias (ACOG 691, 2017; ACOG 78, 2007) [7,8].

Despite ethnicity-based testing guidelines, risk to have offspring with a genetic disease is neither limited to certain ethnic populations nor to families with a history of genetic disease (Edwards et al, 2015) [11]. Furthermore, a joint statement by multiple medical society stakeholders in 2015 acknowledged that self-reported ethnicity and family history are often not reliable indicators of which individuals are most appropriate to test (Edwards et al, 2015) [11]. More recently, professional societies have highlighted the potential benefits of expanded testing (ACOG 690, 2017) [2]. Benefits of expanded carrier testing may include reduced need for accurate knowledge of ethnicity; unbiased testing for genetic diseases that are observed across multiple

ethnicities; and improved efficiency by testing multiple diseases in a single test (ACOG 690, 2017) [2]. Additionally, advances in technology now allow for rapid and (relatively) inexpensive testing of many genes simultaneously. Carrier testing may evaluate as many as 300 genes or more in a single test. For these reasons, the American College of Obstetricians and Gynecologists (ACOG) acknowledges that ethnicity-based, pan-ethnic, and expanded panels are all acceptable carrier testing strategies, depending on the judgement of the referring health practitioner. Nevertheless, logistical barriers may prevent implementation of expanded testing. These logistical barriers include but are not limited to determining when and how to counsel patients and their partners, and any associated costs for this service; identification of more carriers and associated follow-up; and whether to test couples simultaneously or via stepwise testing [2].

To date, there is limited published data evaluating the impact of expanded carrier testing in clinical practice in order to quantify the at-risk reproductive couples that are identified using different strategies (Capalbo et al., 2019) [12]. Here, we present our clinical experience identifying at-risk reproductive couples following carrier testing as performed at a single clinical laboratory receiving samples from across the United States. The data examined in this study included that from the general referral population (includes referring health providers using various approaches to carrier testing), as well as a subset from the general referral population from a single, high-volume clinic that routinely uses expanded carrier screening. The aim of this study is to quantify at-risk reproductive couples identified in these two cohorts and analyze the diseases for which their offspring are at risk.

Materials and methods

General referral population, representing various carrier testing approaches

The database of the clinical testing laboratory was retrospectively queried for reproductive partners, a provider-reported metric on test requisition forms. This cohort includes referrals by health providers with a variety of approaches to carrier testing. The number of genes tested ranged from 1 to >200 genes. Testing may have also included hemoglobinopathy evaluation (hemoglobin electrophoresis and red blood cell indices), and hexosaminidase A (HexA) enzyme analysis for Tay-Sachs disease. As indicated by the number of genes tested, ordering providers in this cohort may or may not take an expanded carrier testing approach. Timing of testing, including both pre- and post-conception and the logistics of partner testing (concurrent testing vs. stepwise) varied between referring health providers.

A single practice, representing a routinely applied expanded carrier testing approach

This cohort included individuals referred from a single, multi-provider clinic with a well-established protocol where expanded carrier testing is routinely offered to patients. Floating period carrier testing performed for this cohort included molecular evaluation of >200 genes, plus hemoglobinopathy evaluation, and HexA enzyme analysis. Generally, females were offered testing within the first two trimesters of their pregnancies. Testing was offered to the male partner whenever the female tested positive for any autosomal recessive disease. All patients (including male partners) at this practice were offered the same expanded carrier test and male partner testing uptake was tracked.

Analysis of data

Descriptive analysis was performed for ethnicity, test ordered, and results of carrier testing for both cohorts. Of note, the single practice population is a subset of the general referral population, analyzed for the purpose of identifying characteristics unique to a routinely applied expanded testing approach. Reproductive couples were classified as being at risk if both partners were positive for the same autosomal recessive disease or the female partner was positive for an X-linked disease. Results not associated with increased risk for clinically significant disease (intermediate/gray zone results for fragile X syndrome and silent carriers for alpha thalassemia) were excluded.

Ethical consideration

This study was approved by internal review processes in accordance with relevant guidelines and regulations and determined to be exempt from IRB review.

Results

General referral population, representing various carrier testing approaches

Demographics: The distribution of self-reported ethnicity is detailed in Table 1. Caucasian/white was the most commonly reported ethnicity (48.9%) followed by Hispanic (18.5%), other or mixed (14.2%), and African American (9.1%).

At-risk reproductive couples: There were 1,877 cases in which both partners had carrier testing, with a total of 3,754 referrals and test results reviewed. Referrals originated from multiple health providers with varying carrier testing protocols. Thus, this cohort was tested for anywhere from a single disease to more than 220 genetic diseases per

Table 1: Self-reported ethnicity for individuals in this study.

Ethnicity	General referral population Number of individuals (%)	Single practice population Number of individuals (%)
African American	343 (9.1)	32 (4.1)
Ashkenazi Jewish	120 (3.2)	135 (17.4)
Asian	161 (4.3)	46 (5.9)
Caucasian/White	1834 (48.9)	310 (40.1)
Hispanic	693 (18.5)	33 (4.3)
N/A	46 (1.2)	1 (0.1)
Native American	6 (0.2)	0
Other or Mixed	533 (14.2)	199 (25.6)
Sephardic Jewish	18 (0.5)	19 (2.5)
Total	3754	774

sample, depending on the preferences of health practitioner and/or the patient. In 61 cases both partners were negative for all diseases tested. In 1,816 cases (96.8%), at least one partner tested positive (i.e. was a genetic carrier). 208 (11.1%) reproductive couples were classified as at-risk (Figure 1). The designation of at-risk was based on both partners identified as carriers of the same autosomal recessive disorder or the identification that the female partner is a carrier of an X-linked disease. Some couples were at risk for more than one disease. 151 autosomal recessive and 61 X-linked at-risk scenarios were identified. Five couples were possibly at risk due to inconclusive hemoglobin evaluations or indeterminate HexA enzyme analysis. Seven couples were at risk for two diseases, and one additional pair was possibly at risk for two diseases (described below).

Diseases identified: At-risk couples were most often at risk to have affected offspring with the following diseases: hereditary hemochromatosis, HFE-related (HFE) (76/208 cases); glucose-6-phosphate dehydrogenase deficiency (G6PD) (42/208 cases); and cystic fibrosis (CF) (31/208 cases). Additional diseases for which couples were at risk are listed in Table 2. Seven reproductive couples (3.4%) were at risk for two diseases including G6PD and primary congenital glaucoma; G6PD and Charcot-Marie Tooth diease, GJB1-related; CF and HFE; sickle cell disease and G6PD; HFE and Smith-Lemli-Opitz syndrome; and HFE and Tay-Sachs disease.

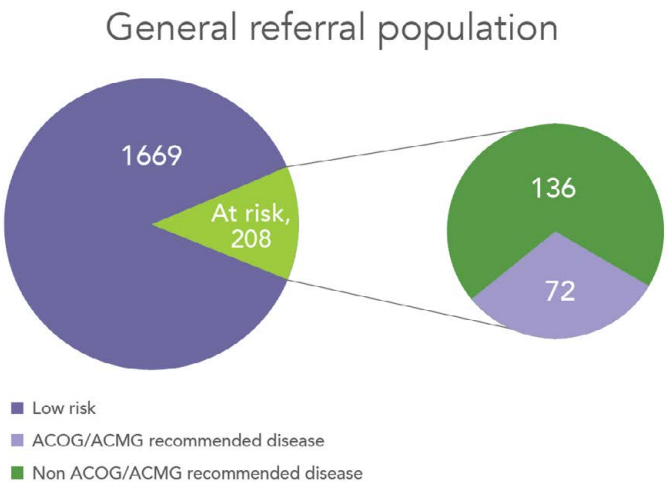

Figure 1: General referral population results. At-risk cases were those where both partners were carriers for the same autosomal recessive disease or where the female partner was a carrier for an X-linked disease. Diseases with an ACOG or ACMG recommendation are cystic fi brosis, spinal muscular atrophy, Fragile X syndrome, thalassemias, hemoglobinopathies, and diseases more commonly found in the Ashkenazi Jewish population.

Table 2: Quantification of at-risk cases and description of the diseases for which their offspring were at risk.
In the general referral population cohort, one additional couple was possibly at risk for alpha thalassemia and four couples were possibly at risk for Tay-Sachs disease due to non-specific variant hemoglobinopathy evaluation and indeterminate Hexosaminidase A enzyme values, respectively.

Disease	General referral population Identified at-risk couples	Single practice population Identified at-risk couples
Hereditary hemochromatosis, HFE-related (HFE)	76	16
Glucose-6-phosphate dehydrogenase deficiency (G6PD)*	42	33
Cystic Fibrosis (CFTR)†	31	-
Fragile X (FMR1) * †	17	9
Familial Mediterranean fever (MEFV)	12	9
Spinal muscular atrophy (SMN1)†	10	1
Beta hemoglobinopathy (HBB)	7	-
Alpha thalassemia (HBA1/HBA2)†	5	-
Charcot-Marie-Tooth disease, GJB1-related (GJB1)*	3	1
Medium-chain acyl-CoA dehydrogenase deficiency (ACADM)	2	1
GJB2-related nonsyndromic hearing loss (GJB2)	2	1
Primary congenital glaucoma (CYP1B1)	2	1
Gaucher (GBA)†	1	-
Congenital disorder of glycosylation, type I (PMM2)	1	-
Tay-Sachs (HEXA)†	1	1
Methylmalonic aciduria, cblC type (MMAA)	1	-
Smith-Lemli-Opitz syndrome (DHCR7)	1	-
Phenylalanine hydroxylase deficiency (PAH)	1	1
Alpha-1 Antitrypsin (SERPINA1)	-	1
Glycogen Storage Disease type IA (G6PC)†	-	1
Congenital amegakaryocytic thrombocytopenia (MPL)†	-	1

* denotes X-linked disease.
† denotes disease with ACOG or ACMG guideline for carrier testing.

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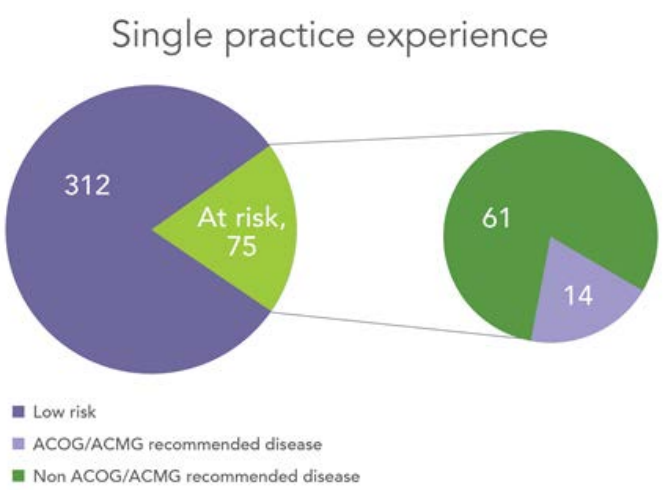

Figure 2: Single Practice results. At-risk cases were both partners were carriers for the same autosomal recessive disease or where the female partner was a carrier for an X-linked disease. Diseases with an ACOG or ACMG recommendation are cystic fibrosis, spinal muscular atrophy, Fragile X syndrome, thalassemias, hemoglobinopathies, and diseases more commonly found in the Ashkenazi Jewish population.

It was also found that 34.6% (72/208) of at-risk cases involved a disease included in published carrier testing recommendations from ACOG and/or the American College of Medical Genetics and Genomics (ACMG) (Figure 1). The remaining 65.4% (136/208) of at-risk cases were at risk for a disease not included in these recommendations.

A single practice, representing a routinely applied expanded carrier testing approach

Demographics: The distribution of self-reported ethnicity is detailed in Table 1. Caucasian/white was the most commonly reported ethnicity (40.1%) followed by other or mixed (25.6%), Ashkenazi Jewish (17.4%), and Asian (5.9%).

At-risk reproductive couples: 1,115 females underwent carrier testing at a single, multi-provider clinic. Of those, 547 (49.1%) tested positive for at least one disease. 387 male partners were subsequently tested, which is a 72.1% uptake in partner testing. 774 test results and orders were reviewed, representing the 387 couples who completed testing. All individuals in this cohort had identical carrier testing which included evaluation for ≥200 autosomal recessive and X-linked genetic diseases. 75 reproductive couples (19.4%) were classified as at-risk cases (Figure 2). 35 autosomal recessive and 43 X-linked at-risk scenarios were identified. One couple was at risk for two different autosomal recessive diseases, and two couples were at risk for both an X-linked and an autosomal recessive disease.

Diseases identified: At-risk cases were most often at risk to have affected offspring with the following diseases: G6PD (33/75 cases); HFE (16/75 cases); familial Mediterranean fever (FMF; 9/75 cases); and fragile X syndrome (9/75 cases). Additional diseases for which couples were at risk are listed in Table 2. Two reproductive couples (3.4%) were at risk for two diseases including G6PD and FMF. One pair was at risk for two autosomal recessive diseases (FMF and SMA). 14 (18.7%) at-risk cases involved a disease included in published carrier testing recommendations from ACOG and/or ACMG, while 61(81.3%) at-risk cases did not involve a recommended disease (Figure 2).

Discussion

Carrier testing approaches

In the general referral population, individuals were tested for one to more than 220 genes. Stepwise testing for the male partner was also commonly observed. A stepwise approach typically involves testing the female partner first, followed by testing her reproductive partner specifically for any recessive disease(s) she was found to carry. Regardless of the number of genes tested or whether a stepwise (vs. tandem) approach is taken, there is currently no right or wrong way to conduct carrier testing in practice. Ethnicity-based, pan-ethnic, and expanded approaches are all acceptable carrier testing strategies according to ACOG (ACOG 690, 2017) [2].

Diseases identified and demographics

Comparing general referral population data to results of a routine, expanded approach used by a single practice, the diseases identified for at-risk cases showed some similarities and differences. HFE was the most common autosomal recessive disease identified for both cohorts. Diseases that were only identified in the general referral population which used various testing approaches included cystic fibrosis; beta hemoglobinopathies; Gaucher disease; congenital disorder of glycosylation type I; methylmalonic aciduria, cblC type; and Smith-Lemli-Optiz syndrome. Conversely, diseases that were only identified in the single practice population which used an expanded carrier screening approach were alpha-1 antitrypsin deficiency; glycogen storage disease type IA; and congenital amegakaryocytic thrombocytopenia.

Ethnicity breakdown of the cohorts was also markedly different. Ashkenazi Jewish ethnicity was higher in the single practice population (17.4%) vs. general referral population (3.2%). A similar trend was seen for Sephardic Jewish ethnicity (2.5% in the single practice population vs. 0.5% in the general referral population). However, the general referral population included more individuals with African American background (9.1%) compared to the single practice population (4.1%). The general referral population also had more individuals with Hispanic background compared to the single practice cohort (18.5% and 4.3%, respectively). The difference in patient ethnicity profiles affected the diseases identified and positivity rates due to ethnicity-specific carrier frequencies and detection rates.

In order to understand the impact of different carrier testing protocols, it is important to quantify the number of at-risk reproductive couples identified. In the general referral population, 208 at-risk cases were identified, representing 11.1% of couples tested. Alternatively, 75 at-risk cases were identified in the single practice cohort, representing 19.4% of all couples tested. These data suggest that a routinely applied, expanded approach to carrier testing will result in the identification of more at-risk reproductive couples when compared to more selective protocols, as could be expected. Quantification of identified at-risk couples allows healthcare providers to establish accurate expectations around detection and the required infrastructure to support at-risk reproductive couples.

The choice of carrier testing strategy by a referring health practitioner is influenced by medical society guidelines. In the general referral cohort, 72 reproductive couples (34.6% of total at-risk couples) were identified to be at risk for diseases with current ACOG/ACMG recommendations, while the remaining 136 (65.9%) reproductive couples were at risk for diseases not included in the current testing recommendations. Therefore, the majority of at-risk reproductive couples would have been missed, had their testing been limited to diseases included in the current guidelines. With increasing adoption of expanded carrier testing, providers should anticipate and prepare for the counseling needs associated with identifying more at-risk reproductive couples.

This study identified 76 couples at risk for hereditary hemochromatosis and 42 couples at risk for G6PD. While screening for these disorders is clinically available and included on some expanded carrier testing panels, they are associated with mild and sometimes reduced penetrance disease presentations. As expanded carrier panels increase in size and included disorders have varying disease severity, pre- and post-test counseling must address patient concern, or lack of

concern, for reproductive risk for these disorders. As demonstrated in this study, reproductive risk for these two disorders was identified in 56.7% of at-risk couples, therefore healthcare providers can expect to identify these risks often if included on their chosen carrier panel.

Limitations

In this study, identifying reproductive partners relied on the inclusion of this information on the test requisitions. As not all referring healthcare providers provide partner information, it is very likely that reproductive couples were missed in this analysis, particularly with respect to the general referral cohort. Additionally, not all reproductive partners of identified carriers are available for or amenable to carrier testing; thus, more at-risk reproductive couples likely exist that cannot be captured due to lack of follow-up partner testing. As demonstrated by the single practice cohort, 72.1% of male partners were tested when a female patient was identified as a carrier of an autosomal recessive disease or G6PD. While carrier testing is a patient choice, there are implications when an individual declines testing: in this the single practice cohort, 186 patients had unknown reproductive risk due to lack of follow-up partner testing. With an observed at-risk pair rate of up to 19.4%, as many as 36 additional at-risk couples may have been missed in this cohort. 100% compliance with follow-up partner testing, or tandem carrier testing, would be required in order to provide the most accurate reproductive risk information. Five cases had possible reproductive risk identified due to indeterminate HexA enzyme level or variant (non-specific) hemoglobinopathy evaluation. Further genetic testing, such as gene sequencing for one or both individuals, may help clarify reproductive risk for these reproductive couples. All ethnicities were self-reported by the individual being tested and may not reflect their true ethnic background. Extrapolating these findings into clinical practice is difficult as each practice has a unique ethnic mix affecting disease positivity rates.

Future directions for research on identifying reproductive risk via carrier testing may include exploring patient socio-demographics that might influence test uptake including age, socio-economic status, and insurance payer. Additionally, exploring the cost-effectiveness of expanded carrier testing would be helpful in determining disease relevance for future test curation.

Conclusion

This study demonstrates the yield of at-risk reproductive couples identified via expanded carrier testing. The number of genes tested does ultimately affect positivity rate for an individual, and consequently, the chance of identifying at-risk reproductive couples – a core tenet of carrier testing. The data presented here support the benefits of routinely applying expanded carrier testing, including partner testing, as a best practice for maximizing the identification of at-risk reproductive couples. Disadvantages of routinely applying expanded carrier testing must also be considered, including the downstream implications of additional partner testing, potential for increased diagnostic testing for at-risk pregnancies, and/or referrals for reproductive endocrinology for PGT-M. Implementing an expanded carrier testing protocol, including partner testing as often as possible, is an effective way to identify couples that are at risk to have a child with a genetic disorder and allow those couples to make personalized reproductive decisions. Providers should be prepared for the additional genetic counseling and other clinic resources that may be required to support the reproductive choices of these individuals. If a referring clinic is considering moving towards offering expanded carrier screening to their patients, the data presented here may support their patients and staff to make the transition as smoothly as possible.

Contributors List

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Conflicts of Interest

CT, MLT, KW, KHH, and SW are full time employees of and hold stock in Progenity Inc.

MLT is the Founder and Managing Director of Genetix Consulting, LLC.

RL is a fulltime employee of Thermo Fischer Scientific.

BS is a fulltime employee of Genome Medical.

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Supplemental Materials

Diseases and genes included in the 220+ gene panel implemented in the single practice cohort. In addition to these genes, patients also had a hemoglobin evaluation and hexosaminidase A enzyme screen. The general referral population cohort screening included one to all of these diseases depending on provider and patient preference.

Disease Name	Gene
Achalasia-addisonianism-alacrima syndrome	AAAS
Progressive Familial Intrahepatic Cholestasis, Type II	ABCB11
Pseudoxanthoma elasticum	ABCC6
Familial Hyperinsulinism, ABCC8-Related	ABCC8
Adrenoleukodystrophy, X-Linked	ABCD1
Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency	ACADM
Very Long-Chain Acyl-CoA Dehydrogenase Deficiency	ACADVL
Beta-ketothiolase Deficiency	ACAT1
Adenosine Deaminase Deficiency	ADA
Ehlers-Danlos Syndrome, Type VIIC	ADAMTS2
Aspartylglycosaminuria	AGA
Glycogen Storage Disease, Type III	AGL
Primary Hyperoxaluria, Type I	AGXT
Autoimmune Polyglandular Syndrome, Type 1	AIRE
Sjogren-Larsson Syndrome	ALDH3A2
Hereditary Fructose Intolerance	ALDOB
Hypophosphatasia	ALPL
Glycine encephalopathy, AMT-related	AMT
MEDNIK syndrome	AP1S1
Metachromatic Leukodystrophy, ARSA-Related	ARSA
Mucopolysaccharidosis, Type VI (Maroteaux-Lamy)	ARSB
Argininosuccinate Aciduria	ASL
Canavan Disease	ASPA
Citrullinemia, Type I	ASS1
Ataxia-Telangiectasia	ATM
Wilson Disease	ATP7B
Bardet-Biedl Syndrome, BBS1-Related	BBS1
Bardet-Biedl Syndrome, BBS10-Related	BBS10
Bardet-Biedl Syndrome, BBS12-Related	BBS12
Pseudocholinesterase deficiency	BCHE
Maple Syrup Urine Disease, Type 1A	BCKDHA
Maple Syrup Urine Disease, Type 1B	BCKDHB
GRACILE, Bjornstad Disease, Leigh Disease, c III Deficiency	BCS1L
Bloom Syndrome	BLM
Bartter Syndrome, Type IV	BSND
Biotinidase Deficiency	BTD
Desbuquois dysplasia, type I	CANT1
Limb-Girdle Muscular Dystrophy, Type 2A	CAPN3
Homocystinuria, CBS-Related	CBS
Usher Syndrome, Type ID	CDH23
Cystic Fibrosis (CF)	CFTR
Choroideremia, X-Linked	CHM
Neuronal Ceroid Lipofuscinosis, CLN5-Related	CLN5
Neuronal Ceroid Lipofuscinosis, CLN6-Related	CLN6
Neuronal Ceroid Lipofuscinosis, CLN8-Related	CLN8
Usher Syndrome, Type III	CLRN1
Achromatopsia, CNGA3-related	CNGA3
Achromatopsia, CNGB3-Related	CNGB3
Alport Syndrome, COL4A3-Related	COL4A3
Alport Syndrome, COL4A5-Related, X-Linked	COL4A5
Dystrophic Epidermolysis Bullosa, COL7A1-Related	COL7A1
Carnitine Palmitoyltransferase I Deficiency	CPT1A
Carnitine Palmitoyltransferase II Deficiency	CPT2
Cystinosis	CTNS

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Pycnodysostosis	CTSK
Corticosterone Methyloxidase Deficiency	CYP11B2
Congenital Adrenal Hyperplasia, 17-Alpha-Hydroxylase Deficiency	CYP17A1
Aromatase Deficiency	CYP19A1
Primary Congenital Glaucoma	CYP1B1
Vitamin D-dependent rickets, type I	CYP27B1
Omenn syndrome/Severe Combined Immunodeficiency, Athabascan type	DCLRE1C
Smith-Lemli-Opitz Syndrome	DHCR7
Retinitis Pigmentosa 59	DHDDS
Dyskeratosis congenita, DKC1-related (X-linked)	DKC1
Dihydrolipoamide Dehydrogenase Deficiency	DLD
Fetal akinesia deformation/Congenital Myasthenic Syndrome, DOK7-Related	DOK7
Dihydropyrimidine Dehydrogenase Deficiency	DPYD
Limb-Girdle Muscular Dystrophy, Type 2B	DYSF
Hypohidrotic ectodermal dysplasia, EDAR-related	EDAR
Emery-Dreifuss Muscular Dystrophy, X-Linked	EMD
Ethylmalonic Encephalopathy	ETHE1
Hemophilia A (X-linked)	F8
Hemophilia B, X-Linked	F9
Tyrosinemia, Type I	FAH
Fanconi Anemia, Type A	FANCA
Fanconi Anemia, Type C	FANCC
Fumarase Deficiency	FH
Fukuyama/Walker-Warburg Syndrome, FKTN-Related	FKRP
FKTN-related disorders	FKTN
Fragile X Syndrome	FMR1
Glycogen Storage Disease, Type Ia	G6PC
Glucose-6-Phosphate Dehydrogenase Deficiency, X-Linked	G6PD
Glycogen Storage Disease, Type II	GAA
Krabbe Disease	GALC
Galactokinase Deficiency	GALK1
Hyperphosphatemic familial tumoral calcinosis	GALNT3
Galactosemia	GALT
Guanidinoacetate Methyltransferase Deficiency	GAMT
Gaucher Disease	GBA
Glycogen Storage Disease, Type IV	GBE1
Glutaric Acidemia, Type I	GCDH
GDF5-related disorders	GDF5
Charcot-Marie-Tooth disease, GJB1-related (X-linked)	GJB1
Nonsyndromic Hearing Loss and Deafness: GJB2-Related DFNB1	GJB2
Fabry Disease, X-Linked	GLA
GM1 Gangliosidosis	GLB1
Glycine Encephalopathy, GLDC-Related	GLDC
Inclusion Body Myopathy 2	GNE
Mucolipidosis, Type II/III Alpha/Beta	GNPTAB
Bilateral Frontoparietal Polymicrogyria	GPR56 (ADGRG1)
Primary Hyperoxaluria, Type II	GRHPR
Long Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency	HADHA
Congenital Neutropenia, HAX1-Related	HAX1
Alpha-Thalassemia	HBA1
Alpha-Thalassemia	HBA2
Sickle Cell Disease/Beta-Thalassemia/beta-hemoglobinopathies	HBB
Tay-Sachs Disease	HEXA
Sandhoff Disease	HEXB
Hereditary hemochromatosis, HFE-related	HFE
Hereditary hemochromatosis, HFE2-related	HFE2 (HJV)
Alkaptonuria	HGD
Mucopolysaccharidosis, Type IIIC (Sanfilippo C)	HGSNAT
Holocarboxylase Synthetase Deficiency	HLCS

3-Hydroxy-3-Methylglutaryl-CoA Lyase Deficiency	HMGCL
Hermansky-Pudlak Syndrome, HPS3-Related	HPS3
17-beta-hydroxysteroid dehydrogenase deficiency, type III	HSD17B3
D-Bifunctional Protein Deficiency	HSD17B4
3-Beta-Hydroxysteroid Dehydrogenase Deficiency, Type II	HSD3B2
Mucopolysaccharidosis, Type II (Hunter Syndrome), X-Linked	IDS
Mucopolysaccharidosis, Type I (Hurler Syndrome)	IDUA
Familial Dysautonomia	IKBKAP (ELP1)
Severe Combined Immunodeficiency, IL2RG-Related, X-Linked	IL2RG
Isovaleric Acidemia	IVD
Familial Hyperinsulinism, KCNJ11-Related	KCNJ11
Junctional Epidermolysis Bullosa, LAMB3-Related	LAMB3
Leber Congenital Amaurosis, LCA5-Related	LCA5
Luteinizing hormone resistance	LHCGR
Stuve-Wiedemann Syndrome	LIFR
Cholesteryl Ester Storage Disease	LIPA
Autosomal recessive woolly hair/hypotrichosis	LIPH
Lipoprotein Lipase Deficiency	LPL
Leigh Syndrome, French-Canadian	LRPPRC
Chediak-Higashi syndrome	LYST
Alpha-Mannosidosis	MAN2B1
Mucolipidosis, Type IV	MCOLN1
Familial Mediterranean Fever	MEFV
Neuronal Ceroid Lipofuscinosis, MFSD8-Related	MFSD8
Methylmalonic Aciduria, MMAA-Related	MMAA
Methylmalonic Aciduria, MMAB-Related	MMAB
Methylmalonic Aciduria, Type cblC	MMACHC
Congenital Disorder of Glycosylation, Type IB	MPI
Congenital Amegakaryocytic Thrombocytopenia	MPL
Hepatocerebral Mitochondrial DNA Depletion Syndrome, MPV17-Related	MPV17
Ataxia-telangiectasia-like disorder	MRE11A
Myotubular myopathy, MTM1-related (X-linked)	MTM1
Abetalipoproteinemia	MTTP
Methylmalonic Acidura, MUT-Related	MUT
Usher Syndrome, Type IB	MYO7A
Nijmegen Breakage Syndrome	NBN
Nemaline Myopathy 2	NEB
Niemann-Pick Disease, Type CI/D	NPC1
Niemann-Pick Disease, Type CII	NPC2
Nephrotic Syndrome, Type 1	NPHS1
Steroid Resistant Nephrotic Syndrome	NPHS2
Enhanced S-Cone Syndrome	NR2E3
3-Methylglutaconic Aciduria, Type III	OPA3
Ornithine Transcarbamylase Deficiency, X-Linked	OTC
Phenylalanine Hydroxylase Deficiency	PAH
Propionic Acidemia, PCCA-Related	PCCA
Propionic Acidemia, PCCB-Related	PCCB
Usher Syndrome, Type IF	PCDH15
Pyruvate Dehydrogenase Deficiency, PDHA1-Related, X-Linked	PDHA1
Pyruvate Dehydrogenase Deficiency, PDHB-Related	PDHB
Prolidase deficiency	PEPD
Mitochondrial complex IV deficiency	PET100
Zellweger Spectrum Disorders, PEX6-Related	PEX6
Rhizomelic Chondrodysplasia Punctata, Type I	PEX7
Glycogen Storage Disease, Type VII	PFKM
3-Phosphoglycerate Dehydrogenase Deficiency	PHGDH
Autosomal Recessive Polycystic Kidney Disease	PKHD1
Congential Disorder of Glycosylation, Type IA	PMM2
Muscle-Eye-Brain Disease, POMGNT1-Related	POMGNT1

Neuronal Ceroid Lipofuscinosis, PPT1-Related	PPT1
Arts syndrome (X-linked) / Charcot-Marie-Tooth disease, PRPS1-related (X-linked)	PRPS1
Mitochondrial Myopathy and Sideroblastic Anemia	PUS1
Glycogen Storage Disease, Type V	PYGM
Carpenter Syndrome	RAB23
Severe combined immunodeficiency, RAG1-related	RAG1
Leber Congential Amaurosis, RDH12-Related	RDH12
Cartilage-Hair Hypoplasia	RMRP
Aicardi-Goutieres syndrome, RNASEH2C-related	RNASEH2C
Juvenile Retinoschisis, X-Linked	RS1
Dyskeratosis Congenita, RTEL1-Related	RTEL1
Spastic Ataxia of Charlevoix-Saguenay (ARSACS)	SACS
Tumoral calcinosis, normophosphatemic	SAMD9
Aicardi-Goutières Syndrome, SAMHD1-Related	SAMHD1
Shwachman-Diamond syndrome	SBDS
Geroderma osteodysplastica	SCYL1BP1 (GORAB)
Alpha-1 Antitrypsin Deficiency	SERPINA1
Limb-Girdle Muscular Dystrophy, Type 2D	SGCA
Limb-Girdle Muscular Dystrophy, Type 2E	SGCB
Gitelman Syndrome	SLC12A3
Andermann Syndrome (Hereditary Motor and Sensory Neuropathy with Agenesis of the Corpus Callosum)	SLC12A6
Salla Disease	SLC17A5
Ornithine Translocase Deficiency/hyperornithinemia hyperammonemia homocitrullinuria	SLC25A15
SLC26A2-Related Skeletal Dysplasias/atelosteogenesis type 2	SLC26A2
Pendred Syndrome	SLC26A4
Arthrogryposis, mental retardation and seizures	SLC35A3
Glycogen Storage Disease, Type Ib	SLC37A4
Acrodermatitis Enteropathica	SLC39A4
Corneal Dystrophy and Perceptive Deafness Syndrome	SLC4A11
Creatine Transporter Defect, SLC6A8-Related, X-linked	SLC6A8
Spinal Muscular Atrophy (SMA)	SMN1
Spinal Muscular Atrophy (SMA)	SMN2
Niemann-Pick Disease, Type A/B	SMPD1
Amish infantile epilepsy syndrome	ST3GAL5
Congenital Lipoid Adrenal Hyperplasia	STAR
Multiple Sulfatase Deficiency	SUMF1
Hereditary Hemochromatosis, TFR2-Related	TFR2
Lamellar Ichthyosis, Type I	TGM1
Joubert Syndrome 2	TMEM216
Neuronal Ceroid Lipofuscinosis, TPP1-Related	TPP1
Aicardi-Goutieres syndrome, TREX1-related	TREX1
Mulibrey nanism	TRIM37
Early onset myopathy w/ fatal cardiomyopathy	TTN
Ataxia with Vitamin E Deficiency	TTPA
Crigler-Najjar syndrome	UGT1A1
Usher Syndrome, Type IC	USH1C
Pontocerebellar Hypoplasia, VRK1-Related	VRK1
Xeroderma pigmentosum, XPC-related	XPC
Spastic paraplegia, ZFYVE26-related	ZFYVE26