EMPIRICA BIOSCIENCES

Genetic Risk Report

Name: John Doe
Sample type: saliva
Test type: whole-exome sequencing
ID: 0720_001
Date collected: July 22, 2020
Date tested: August 30, 2020

CONFIDENTIAL

NAME: JOHN DOE
DOB: June 15, 1982
SEX: MALE
DATE: SEPTEMBER 5, 2020

SUMMARY

- Based on genetic variants detected in this test, you have a high risk of developing six diseases.
- Follow the recommendations listed in the table below to reduce your risk or alleviate your symptoms.

DISEASE	*RISK LEVEL*	*RECOMMENDATIONS*
Abnormal brain structure	high	• MRI to evaluate brain structure • EEG to evaluate brain function • Regular exercise may help reduce the risk of decreasing brain function with age.
Critical congenital heart disease	high	• ECG to diagnose specific defects • The recommended treatment will be specific to the type and severity of the defect. It may include medication to lower blood pressure, correct your heart rhythm, or prevent blood clotting; an implantable device; or corrective surgery.
Dentinogenesis imperfecta, Shields type II	high	• Brush your teeth twice a day with a fluoride toothpaste and clean between your teeth every day. • Limit your intake of food and drinks with a high sugar content. • Abstain from or quit smoking and chewing tobacco. • Visit your dentist regularly.
Factor V Leiden thrombophilia	high	• Maintain a healthy weight. • Abstain from or quit smoking. • Get up and walk at least once every 2 hours if sitting for long periods, such as during travel. • Discuss taking blood-thinning medication, such as aspirin, with your healthcare provider.
Parkinson's disease	high	• Exercise regularly.

DISEASE	*RISK LEVEL*	*RECOMMENDATIONS*
Very early-onset inflammatory bowel syndrome		• Avoid pesticide and herbicide exposure.
	high	• Abstain from or quit smoking. • Identify and avoid foods that trigger symptoms. • Consult a dietitian. • Discuss a treatment plan with your healthcare provider to alleviate symptoms.

- Based on genetic variants detected in this test, you have a medium risk of developing five diseases.
- Follow the recommendations listed in the table below to reduce your risk or alleviate your symptoms.

DISEASE	*RISK LEVEL*	*RECOMMENDATIONS*
Blau syndrome	medium	• Discuss a treatment plan with your healthcare provider to alleviate symptoms of inflammation. • Consult with an ophthalmologist or optometrist regularly to monitor eyesight.
Fluoropyrimidine drug reaction	medium	• Avoid fluoropyrimidine drugs (e.g., the anti-cancer drugs, capecitabine, carmofur, doxiflurodine, fluorouracil, and tegafur), as you may have a life-threatening reaction to these drugs.
Noninsulin-dependent diabetes mellitus	medium	• Maintain a healthy weight. • Eat foods that are lower in fat and calories and higher in fibre. • Do not sit still for long periods of time. • Undertake 150 minutes of moderate to vigorous aerobic exercise per week, spread over at least 3 days.

NAME: JOHN DOE
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DISEASE	*RISK LEVEL*	*RECOMMENDATIONS*
Oculocutaneous albinism type 1	medium	• Avoid excess sun exposure. • Visit a dermatologist annually for a skin examination to detect melanoma.
Yao syndrome	medium	• Discuss a treatment plan with your healthcare provider to alleviate symptoms of chronic inflammation.

- An additional 12 disease-associated genetic variants were detected in this test.
- Based on their mode of inheritance, you have a low risk of developing these diseases and no further actions are recommended.

DISEASE	*RISK LEVEL*
Biotinidase deficiency	low
Dihydropyrimidine dehydrogenase deficiency	low
Exudative age-related macular degeneration 11	low
Hyperglycinuria/iminoglycinuria	low
Methylenetetrahydrofolate reductase deficiency	low
Nephrotic syndrome, type 2	low
Oestrogen resistance	low
Prekallikrein deficiency	low
Protoporphyria, erythropoietic, 1	low
Thrombocytopenia-absent radius syndrome	low
Reactive amyloid systemic amyloidosis	low
Uncombable hair syndrome	low

DETAILED REPORT

Disease: abnormal brain structure

Inheritance pattern: autosomal recessive

Major Symptoms:

- loss of brain cells in the cortex (cortical atrophy)
- small head circumference (microcephaly)
- damage to nerves that cause feeling and control movement (sensorineural polyneuropathy)

Gene: galactosylceramidase (*GALC*)

The *GALC* gene encodes an enzyme known as galactosylceramidase. This enzyme breaks down certain fats called galactolipids, which are found primarily in the nervous system and kidneys. In the nervous system, this process is part of the normal turnover of myelin, which is a protective covering around nerve cells.

Variant: NM_000153.4:c.1162-4del

Zygosity: homozygous

You have two copies of the variant known as NM_000153.4:c.1162-4del, which results in the deletion of three nucleotides in the *GALC* gene. This variant has been reported to be associated with the major symptoms listed above.

Your risk

Variants in the *GALC* gene cause brain defects in an autosomal recessive manner, which means that two copies of a pathogenic variant are required to develop the defects. Because you have two copies of this variant, you have a high risk developing these symptoms. Severe forms of this disease typically manifest during infancy. Some *GALC* gene variants may also be associated with Parkinson's disease.

Disease: critical congenital heart disease

Inheritance pattern: unknown

Major Symptoms:

- Abnormal heart rhythms (arrhythmias)
- A bluish tint to the skin, lips, and fingernails (cyanosis)
- Shortness of breath
- Tiring quickly upon exertion
- Swelling of body tissue or organs (oedema)

Critical congenital heart disease refers to a group of serious heart defects that are present at birth. They usually occur when certain parts of the heart do not form correctly during

embryonic development.

Gene: GATA binding protein 4 (*GATA4*)

The *GATA4* gene encodes a type of protein known as a transcription factor. Transcription factors regulate the activity of other genes. In particular, the GATA4 protein regulates the activity of genes responsible for the development and function of the heart.

Variants: NM_002052.5:c.617-116T>C, NM_002052.5:c.997+56C>A, NM_002052.5:c.1146+177C>T, NM_002052.5:c.1147-107A>G

Zygosity: heterozygous

You have four variants in the *GATA4* gene, with one copy of each variant. Each of these variants is classified as pathogenic according to the American College of Medical Genetics and Genomics (ACMG) guidelines.

Your risk

The inheritance pattern of congenital heart disease is unknown. However, in general, having more than one disease-risk variant in the same gene can increase the risk, regardless of the inheritance pattern. Because you have four different pathogenic variants in the same gene, you are likely to have a high risk of developing these symptoms.

Disease: dentinogenesis imperfecta, Shields type II

Inheritance pattern: autosomal dominant

Major Symptoms:

- Weak and discoloured teeth

Dentinogenesis imperfecta, Shields type II is a rare and severe form of dentinogenesis imperfecta, a condition that affects tooth development. Both primary (baby) and adult teeth are affected and individuals with this condition usually have no normal teeth. Some people with this condition also have hearing loss.

Gene: dentin sialophosphoprotein (*DSPP*)

The *DSPP* gene encodes a protein known as dentin sialophosphoprotein. After this protein is produced, it is cut into two smaller proteins, which are components of dentin, the hard substance that makes up the protective layer in the middle of each tooth.

Variant: NM_014208.3:c.202A>T

Zygosity: heterozygous

You have one copy of the variant known as NM_014208.3:c.202A>T, which results in a change from an A to a T nucleotide at position 202 in the *DSPP* gene. This variant is classified as pathogenic according to the ACMG guidelines.

Your risk

Dentinogenesis imperfecta, Shields type II is inherited in an autosomal dominant manner, which means that only one copy of a pathogenic *DSPP* variant is required to develop the disease. Because you have one copy of this variant, you have a high risk of developing this disease.

Disease: factor V Leiden thrombophilia

Inheritance pattern: autosomal dominant

Major Symptoms:

- Increased risk of deep vein thrombosis
- Increased risk of pulmonary embolism

Factor V Leiden thrombophilia is an inherited disorder of blood clotting that results in an increased tendency to form abnormal blood clots that can block blood vessels. In people with factor V Leiden thrombophilia, the clotting process remains active longer than usual, increasing the chance of developing abnormal blood clots. People with factor V Leiden thrombophilia have a higher than average risk of developing a type of blood clot called a deep venous thrombosis. Factor V Leiden thrombophilia also increases the risk that clots will break away from their original site and travel through the bloodstream. These clots can lodge in the lungs, and cause a pulmonary embolism. However, only about 10 percent of individuals with the factor V Leiden mutation ever develop abnormal clots.

Gene: factor V (*F5*)

The *F5* gene provides instructions for making a protein called coagulation factor V. This protein plays a critical role in the formation of blood clots in response to injury. Blood clots are required to prevent excessive bleeding after injury, but abnormal blood clots can block blood flow.

Variant: NM_000130.5:c.1601

Zygosity: heterozygous

You have one copy of a variant in the *F5* gene known as the factor V Leiden mutation. This variant is classified as pathogenic according to the ACMG guidelines.

Your risk

Factor V Leiden thrombophilia is inherited in an autosomal dominant manner, which means that only one copy of a pathogenic variant is required to develop the disease. Approximately 10% of individuals with the factor V Leiden mutation develop an abnormal blood clot, compared to approximately 0.1% of the general population. Other factors that increase your risk of a blood clot include increasing age, obesity, injury, surgery, smoking, and other mutations in *F5* or other genes of the blood clotting system.

Disease: Parkinson's disease

Inheritance pattern: autosomal dominant (for NM_005781.4:c.2630G>A)

Major Symptoms:

- tremor
- slow movement
- muscle stiffness
- impaired balance and coordination
- soft or slurred speech

Parkinson's disease is a progressive disorder of the nervous system. It affects several regions of the brain, especially an area called the substantia nigra that controls balance and movement. Many Parkinson's disease symptoms occur when nerve cells (neurons) in the substantia nigra die or become impaired. Normally, these cells produce a chemical messenger called dopamine, which transmits signals within the brain to produce smooth physical movements. When these dopamine-producing neurons are damaged or die, communication between the brain and muscles weakens. Eventually, the brain becomes unable to control muscle movement. Most cases of Parkinson's disease are thought to result from a complex interaction of environmental and genetic factors. Approximately 15% of people with Parkinson's disease have a family history of this disorder.

Gene: tyrosine kinase non receptor 2 (*TNK2*)

The *TNK2* gene encodes a protein that regulates the activity of another protein known as CDC42Hs. CDC242Hs affects numerous cell signalling pathways and is necessary for nerve growth.

Variant: NM_005781.4:c.2630G>A

Zygosity: heterozygous

You have one copy of a variant in the *TNK* gene known as NM_005781.4:c.2630G>A. This variant has been identified in affected family members of several families with inherited Parkinson's disease. However, the severity of symptoms and the age of onset of the disease in individuals with this variant are likely to be affected by other genetic and environmental factors.

Your risk

This variant in the *TNK* gene has been identified in affected family members of several families with inherited Parkinson's disease. However, the severity of symptoms and the age of onset of the disease in individuals with this variant are likely to be affected by other genetic and environmental factors. Other factors that increase your risk of developing Parkinson's disease include increasing age and exposure to toxins, such as herbicides and pesticides.

Disease: very early-onset inflammatory bowel syndrome

Inheritance pattern: autosomal recessive

Major Symptoms:

- chronic diarrhea
- blood in the stools or black, tar-like stools
- abdominal pain
- fatigue
- weakness
- weight loss
- loss of appetite
- vomiting

Very early-onset inflammatory bowel disease typically develops in children before the age of 6 years. The symptoms differ from other forms of inflammatory bowel disease that develop later in life and may not respond to the same treatments.

Gene: cytochrome b-245 alpha chain (*CYBA*)

The *CYBA* gene encodes a protein that is part of a group of proteins that form an enzyme complex called NADPH oxidase, which plays an essential role in the immune system. NADPH oxidase is primarily active in immune system cells known as phagocytes and it is also thought to regulate the activity of another type of immune cells known as neutrophils. These cells play a role in adjusting the inflammatory response to optimize healing and reduce injury to the body.

Variant: NM_000101.4:c.214T>C

Zygosity: homozygous

You have two copies of a variant in the *CYBA* gene known as NM_000101.4:c.214T>C, which results in a change from a T to a C nucleotide at position 214. This variant is classified as "likely pathogenic" according to the ACMG guidelines.

Your risk

Very early-onset inflammatory bowel syndrome is an autosomal recessive disease, which means that two copies of the *CYBA* variant are required to develop the disease. Because you have two copies of a likely pathogenic *CYBA* gene variant, you have a high risk of developing this disease.

Disease: Blau syndrome/Yao syndrome

Inheritance pattern: autosomal dominant (Blau)/polygenic (Yao)

Major Symptoms:

- skin rash (dermatitis)
- arthritis
- inflammation and swelling of the middle of the eye (uveitis, Blau syndrome only)

- limited joint mobility
- recurrent fever

Blau syndrome and Yao syndrome are autoimmune diseases that are both caused by variants in the *NOD2* gene. Both syndromes are chronic inflammatory diseases, but Blau syndrome symptoms typically appear in childhood, whereas Yao syndrome develops in adulthood.

Gene: nucleotide-binding oligomerization domain-containing 2 (*NOD2*)

The *NOD2* gene encodes a protein that has an important role in the immune system. The NOD2 protein is active in various types of cells that help defend against invading bacteria and viruses. It recognizes the infection and stimulates the immune system to respond.

Variant: NM_022162.3:c.2798+158C>T

Zygosity: heterozygous

You have one copy of a variant in the *NOD2* gene known as NM_022162.3:c.2798+158C>T. This variant is classified as pathogenic according to the ACMG guidelines. Pathogenic NOD variants usually result in an overactive protein that causes excess immune system activity.

Your risk

Blau syndrome symptoms typically appear in childhood, therefore if you have not yet experienced these symptoms, you have a low risk of serious illness, but you may experience some symptoms, because it is inherited in an autosomal dominant manner. This variant is also found in individuals with Yao syndrome, but the development of this disease is likely to require more than one pathogenic variant in *NOD2* or a related gene.

Disease: fluoropyrimidine drug reaction

Inheritance pattern: autosomal dominant

Major Symptoms:

- inflammation and ulcers in the gastrointestinal tract
- mouth sores, abdominal pain, nausea, diarrhoea
- low numbers of white blood cells (neutropenia)
- low numbers of platelets (thrombocytopenia)
- redness and swelling of the skin

Severe, life-threatening reactions to fluoropyrimidine drugs can occur in susceptible individuals. These drugs include the anti-cancer drugs, capecitabine, carmofur, doxiflurodine, fluorouracil, and tegafur.

Gene: dihydropyrimidine dehydrogenase (*DPYD*)

The *DPYD* gene encodes an enzyme known as dihydropyrimidine dehydrogenase. This

enzyme breaks down molecules called pyrimidines, which are building blocks of DNA, RNA, and cell energy molecules. After they are broken down, the molecules are excreted by the body or used for other cellular processes. If there is not enough DPYD present, fluoropyrimidine drugs can accumulate to toxic levels.

Variant: NM_001160301.1:c.85T>C

Zygosity: heterozygous

You have one copy of a variant in the *DPYD* gene known as NM_001160301.1:c.85T>C, which results in a change from a T to a C nucleotide at position 85. This variant is classified as pathogenic according to the ACMG guidelines.

Your risk

Dihydropyrimidine dehydrogenase deficiency is an autosomal recessive disease that requires two copies of a *DPYD* gene variant to develop. Since you have only one copy of the variant, you are not likely to develop this disease. However, individuals with one copy of this *DYPD* gene variant may also have life-threatening reactions to fluoropyrimidine drugs. Healthcare workers should be notified of this potential reaction when you are asked about drug allergies.

Disease: noninsulin-dependent diabetes mellitus

Inheritance pattern: polygenic

Major Symptoms:

- high blood glucose levels
- increased thirst or hunger
- frequent urination
- weight loss
- blurred vision
- fatigue
- sores that do not heal

Noninsulin-dependent diabetes mellitus, also known as type 2 diabetes, is a disease characterised by abnormally high blood sugar levels. In this type of diabetes, the body does not produce insulin properly. Insulin is a hormone produced by the pancreas that helps regulate blood sugar levels. Type 2 diabetes usually begins in middle age or later and the symptoms develop slowly over many years.

Gene: wolframin ER transmembrane glycoprotein (*WFS1*)

The *WFS1* gene encodes a protein known as wolframin, which is thought to regulate calcium levels in cells. Calcium is required by cells for various functions, including the correct folding of proteins into their active shape. In the pancreas, wolframin may control the folding of proinsulin into mature insulin, which then controls blood sugar levels.

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Variant: NM_006005.3:c.461-9A>G

Zygosity: heterozygous

You have one copy of a variant in the *WFS1* gene known as NM_006005.3:c.461-9A>G, which results in a change from an A to a G nucleotide. This variant is classified as pathogenic according to the ACMG guidelines.

Your risk

Diabetes has a complex mode of inheritance that involves many different genes and lifestyle factors. Several studies have shown an association between this gene variant and type 2 diabetes. Since you have only one copy of this gene variant and no other pathogenic variants in genes associated with type 2 diabetes, you have a medium risk of developing these symptoms. Other risk factors for diabetes include being overweight, high blood pressure, physical inactivity, an unhealthy diet, and high cholesterol levels.

Disease: oculocutaneous albinism, type 1

Inheritance pattern: polygenic

Major Symptoms:

- fair skin and hair
- blue eyes
- abnormal vision
    - involuntary eye movement
    - poor depth perception
    - blurred vision
    - crossed eyes
    - light sensitivity

Oculocutaneous albinism, type 1 is a disease characterised by low pigmentation of the skin and hair and reduced visual acuity. Vision problems can typically be corrected with prescription spectacles.

Gene: tyrosinase (*TYR*)

The *TYR* gene encodes an enzyme known as tyrosinase, which is located in melanocytes, a type of cell that produces the pigment, melanin. Tyrosinase is responsible for the first step in melanin production.

Variant: NM_000372.5:c.1205G>A

Zygosity: heterozygous

You have on copy of a variant in the *TYR* gene known as NM_000372.5:c.1205G>A, which results in a change from a G to an A nucleotide at position 1205. This variant is classified as pathogenic according to the ACMG guidelines.

Your risk

Oculocutaneous albinism, type 1 has a complex inheritance pattern that may involve more than one variant in the *TYR* gene and/or other related genes. Since you have only one copy of this gene variant and no other pathogenic variants in the *TYR* gene or other oculocutaneous albinism type 1 susceptibility genes, you are not likely to develop these symptoms. However, you may have an increased sensitivity to sun exposure and an increased risk of melanoma.

Other Diseases

An additional 12 pathogenic variants were detected, as listed in the table below. Two copies of these variants are required for their associated diseases to develop. As you only have one copy, you are unlikely to develop these diseases. However, you may pass this variant on to your children. Your children are at risk of developing these diseases, only if your partner is also a carrier of a pathogenic variant in these genes.

DISEASE	***GENE***	***VARIANT (classification)***
Biotinidase deficiency https://ghr.nlm.nih.gov/gene/BTD#conditions	*BTD*	NM_000060.2:c.133G>A (pathogenic)
Dihydropyrimidine dehydrogenase deficiency https://ghr.nlm.nih.gov/condition/dihydropyrimidine-dehydrogenase-deficiency	*DYPD*	NM_001160301.1:c.85T>C (pathogenic)
Exudative age-related macular degeneration 11 https://ghr.nlm.nih.gov/condition/age-related-macular-degeneration#genes	*CST3*	NM_000099.4:c.73G>A (likely pathogenic)
Hyperglycinuria/iminoglycinuria https://rarediseases.info.nih.gov/diseases/8424/iminoglycinuria	*SLC6A19*	NM_001003841.3:c.1017-4G>A (pathogenic)
Methylenetetrahydrofolate reductase deficiency https://rarediseases.info.nih.gov/diseases/2734/homocystinuria-due-to-mthfr-deficiency	*MTHFR*	NM_005957.5:c.665C>T (pathogenic)
Nephrotic syndrome, type 2 https://ghr.nlm.nih.gov/condition/congenital-nephrotic-syndrome	*NPHS2*	NM_014625.3:c.-51G>T (likely pathogenic)
Oestrogen resistance https://ghr.nlm.nih.gov/condition/congenital-nephrotic-syndrome	*CCDC170*	NM_025059.4:c.1810G>A (likely pathogenic)
Prekallikrein deficiency	*KLBK1*	NM_000892.5:c.428G>A

DISEASE	*GENE*	*VARIANT (classification)*
https://ghr.nlm.nih.gov/condition/prekallikrein-deficiency		(pathogenic)
Protoporphyria, erythropoietic, 1 https://rarediseases.info.nih.gov/diseases/4527/erythropoietic-protoporphyria	*FECH*	NM_014208.3:c.202A>T (likely pathogenic)
Thrombocytopenia-absent radius syndrome https://ghr.nlm.nih.gov/condition/thrombocytopenia-absent-radius-syndrome	*RBM8A*	NM_005105.4:c.487C>T (pathogenic)
Reactive amyloid systemic amyloidosis https://rarediseases.org/rare-diseases/amyloidosis/	*SAA1*	NM_199161.5:c.209C>T (pathogenic)
Uncombable hair syndrome https://rarediseases.info.nih.gov/diseases/5404/uncombable-hair-syndrome	*PADI3*	NM_016233.2:c.881C>T (pathogenic)

NEXT STEPS

- Follow the recommendations listed in the Summary section to reduce your disease risk.
- Discuss these results with your healthcare provider or a genetic counselor. They may refer you to a specialist who can provide you with further information on how these results affect your health.
- Share the information in this report with your family members, as this variant has been inherited from either one of your parents, and each of your siblings has at least a 50% chance of having the same variant. There is also at least a 50% chance that it will be passed down to your children.
- Discuss an appropriate screening program with your healthcare provider.
- Contact us if you have an questions regarding this report.

ABOUT THIS TEST

We use DNA sequencing technology to analyze the entire protein-coding region of the genes listed in this report. DNA extracted from your saliva sample is prepared using proprietary sequence capture technology and the DNA sequence of the targeted genes is determined using an Illumina next-generation sequencing instrument. Bioinformatic analysis is then used to identify variants based on a comparison of your DNA sequence with the DNA sequence of a reference genome. Detected variants are classified according to the American College of Medical Genetics guidelines as benign (harmless), likely benign, pathogenic (disease-causing), likely pathogenic, or of unknown significance. These classifications are based on data from robust scientific studies and/or the location

of the variant within a function-critical region of the gene. Only those variants classified as likely pathogenic or pathogenic are included in this report.

LIMITATIONS OF THIS TEST

This test does not provide a disease diagnosis. The presence of a pathogenic gene variant indicates an increased risk of disease. It does not mean that you will definitely develop the disease in your lifetime. Consult with your health care provider or a genetic counsellor to determine how your results affect your ongoing health care plan. Do not make any changes to your current medication or ongoing medical care without consulting your healthcare provider.

This test focuses on a set of genes that are known to impact disease risk and provide actionable results. However, there may be other genes not specifically tested here that affect your disease risk. There may also be non-genetic factors that increase your risk of disease.

The information included in this report is based on published research on the genes tested. New scientific data regarding genetic risk are continually being published in the scientific literature. In the event that this additional information is relevant to your test results, we will amend your records accordingly and send you an updated report.

GLOSSARY

ACMG: The American College of Genetics and Genomics

Autosomal dominant: a pattern of disease inheritance involving a gene located on a non-sex chromosome, whereby two copies of the gene variant are required to cause the disease

Autosomal recessive: a pattern of disease inheritance involving a gene located on a non-sex chromosome, whereby only one copy of the gene variant is required to cause the disease

Heterozygous: the state in which a given genetic site has a different DNA sequence on the maternal and paternal chromosome

Homozygous: the state in which a given genetic site has the same DNA sequence on the maternal and paternal chromosome

Nucleotide: the molecular building blocks that join together to make up a strand of DNA. There are four different nucleotides - adenine (A), cytosine (C), guanine (G), and thymine (T).

Pathogenic: capable of causing disease

Polygenic: involving more than one gene

Variant: a location within the genome where the genetic sequence differs between individuals. A variant can be classified as pathogenic (disease-causing), benign (harmless), or of unknown significance.

Zygosity: the degree of similarity between specific DNA sequences of corresponding genes on the paternal and maternal chromosomes.

SOURCES

1. Genetics Home Reference (https://ghr.nlm.nih.gov/)
2. ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/)
3. Mayo Clinic (www.mayoclinic.org)
4. Orphanet (www.orpha.net)

5. Genetic and Rare Diseases Information Center (https://rarediseases.info.nih.gov/)
6. National Organization for Rare Disorders (https://rarediseases.org)

Reviewed by:_____ Date:_____