# Analysis of Expanded Carrier Screening Panels for Use in UPMC Primary Care Clinics

by

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## Abstract

Carrier screening is a genetic test that determines if a person a carrier for an autosomal recessive or X-linked condition. It is used most often in preconception and prenatal care to allow individuals or couples to learn about their risk of passing down one of these conditions to future offspring. When first introduced in the 1970s, carrier screening was performed for certain ethnic groups who had a high incidence of genetic conditions like Tay-Sachs disease in Ashkenazi Jewish populations. The cystic fibrosis (CF) gene was discovered in 1989 and opened the door for expanded carrier screening (ECS). ECS panels are now recommended over traditional ethnicity-based screening as they are more equitable for individuals with multi-ethnic backgrounds, and they screen for hundreds of conditions compared to a select few in ethnicity-based screenings.

As next-generation sequencing has made genetic testing easier and more efficient, many labs have entered the commercialization of carrier screening. The purpose of this project was to analyze and compare ECS panels available in the United States and utilize these findings to develop a standardized ECS panel for use in a UPMC Primary Care Pilot Program. The pilot program aims to offer expanded carrier panel testing to patients at the preconception stage via their primary care provider through asynchronous genetic counseling.

This project is of public health significance due to the increasing demand for and availability of expanded carrier screening panels, as well as the increase in health equity it provides individuals in Pittsburgh and surrounding areas. Offering patients an ECS before they plan to

become pregnant will increase reproductive autonomy and knowledge of reproductive options. The pilot program will provide evidence for a full-scale program to increase standardization within the UPMC system and reduce the burden on prenatal genetic counseling clinics.

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# 1.0 Introduction

## 1.1 History of Carrier Screening

Carrier screening is a type of genetic test used to determine if a person is a carrier of a pathogenic variant associated with an autosomal recessive or X-linked condition. A pathogenic variant causes a gene to work incorrectly, causing disease (National Library of Medicine (US), 2021a). A carrier has a copy of the normal allele and a copy of the variant allele associated with disease. Carriers of autosomal recessive conditions typically do not show symptoms. If partners are carriers for the same condition, they have a 25% chance of having an affected child. (Gulani & Weiler, 2022). For X-linked conditions, individuals assigned female at birth are typically carriers and individuals assigned male at birth are typically affected (Basta & Pandya, 2022). Carriers of X-linked conditions have a 50% chance of passing it on to a future child. Children assigned female at birth are typically unaffected or mildly affected, while children assigned male at birth are more severely affected. The variability seen in individuals assigned female at birth is caused by x-inactivation, which is where one X chromosome is randomly inactivated in cells during development (Basta & Pandya, 2022; Maxfield Boumil & Lee, 2001; Rose & Wick, 2018). Carrier screening is used most often in preconception and prenatal care to allow individuals or couples to learn about their risk of passing down one of these conditions to biological offspring. Carrier screening began in the 1970s with targeted carrier screening for ethnic groups who had a high incidence rates of genetic conditions like Tay-Sachs disease in Ashkenazi Jewish populations (Kraft et al., 2019). Expanded carrier screening, also called pan-ethnic or universal screening, is a type of carrier screening where many conditions are screened for regardless of ethnicity. Expanded

carrier screening (ECS) is now recommended over traditional ethnicity-based screening as they are more equitable for individuals with multi-ethnic backgrounds and they screen for hundreds of conditions compared to a select few in ethnicity-based screenings (Henneman et al., 2016).

## 1.2 ACMG and ACOG Recommendations

The American College of Medical Genetics and Genomics (ACMG) is a professional organization comprised of clinical geneticists, clinical laboratory geneticists, and genetic counselors, that aims to increase use of genetics and genomics in healthcare. The American College of Obstetricians and Gynecologists (ACOG) is a professional organization comprised of obstetrician-gynecologists that aims to improve the health of all individuals assigned female at birth. Both ACMG and ACOG developed practice guidelines with working groups of experts in the field that are used to optimize patient care and encourage standardization across the United States. Both organizations endorse universal screening for cystic fibrosis and spinal muscular atrophy and have released statements on which genes they recommend be included on ECS panels (American College of Obstetricians and Gynecologists, 2017b; Gregg et al., 2021). ACMG recommends that every individual assigned female at birth be offered ECS for 97 autosomal recessive and 16 X-linked conditions during their preconception or prenatal care (Gregg et al., 2021). ACMG uses a four-tiered system where ECS panels should include tiers one through three with conditions that have a carrier frequency of greater than or equal to 1 in 200. ACOG recognizes ECS as an acceptable approach to preconception or prenatal carrier screening. ACOG also recommends every pregnant person be screened for the genes responsible for spinal muscular

atrophy (*SMN1, SMN2*) and cystic fibrosis (*CFTR*) (American College of Obstetricians and Gynecologists, 2017a, 2017b).

### 1.3 Introduction to Pilot Program

There is a lack of standardization for expanded carrier screening offerings within the UPMC system. Providers may be aware of the current ACMG and ACOG recommendations, however, they might not have the resources to implement these recommendations. Choosing an appropriate panel is complex due to the diversity of panel composition, technology differences, and variable insurance coverage policies (Henneman et al., 2016). Lab companies are not required to include ACMG or ACOG-recommended genes, which creates complexities for physician's choosing a test for their patients. The primary care pilot program will offer one ECS panel based on ACMG, ACOG, and the National Society of Genetic Counselors (NSGC) guidelines, health equity, and financial considerations for patients.

The pilot program will utilize asynchronous pretest genetic counseling through videos at a primary care appointment to ensure informed consent and will allow genetic counselors time to meet with patients who require an appointment to discuss family history of a genetic condition. Prenatal genetic counselors often only have time to see patients who are currently pregnant. Asynchronous genetic counseling at the primary care level provides access to an essential health tool at the preconception stage. One goal of the pilot program is to reach patients who are not currently pregnant when they have a greater number reproductive options available to them. (Gregg et al., 2021). These options include the use of donor eggs or sperm during conception, preimplantation genetic testing (PGT) to find out which embryos are or are not affected with the

condition, or adoption (Henneman et al., 2016). Primary care clinics are an ideal place to capture patients at this point of care.

Primary care providers (PCP) create long-lasting relationships with their patients and, due to knowing their patients on a personal level, are the optimal candidates to inform patients about carrier screening. UPMC Primary Care Clinics will offer a standard ECS panel to patients. PCPs will likely feel more comfortable understanding and discussing a single panel with patients compared to hand-selecting one of the hundreds of ECS panels on the market for each patient. The program will increase standardization within the UPMC system, thus increasing health equity. The primary care clinics chosen to run the program are representative of the population of Pittsburgh and a few focus on medically underserved communities including those seeking care at the UPMC Matilda H. Theiss Health Center. The Center is in the Hill District which is a grouping of predominantly African American neighborhoods within driving or public transit distance to downtown, Oakland, and the Strip District.

## 1.4 Specific Aims

Aim One: Analyze and compare different expanded carrier screening panel options using Concert Genetics.

Aim Two: Propose a standardized expanded carrier panel for use in UPMC Primary Care Clinics.

# 2.0 Background

## 2.1 Overview of Carrier Screening

### 2.1.1 Definition of Carrier Screening

Genetic testing is focused on the individual while genetic screening is focused on the population. Genetic testing is diagnostic and determines if an individual has a genetic condition. Carrier screening determines an individual's risk of passing a variant allele for a genetic condition to future offspring. Carrier screening is typically used for autosomal recessive and X-linked conditions. A carrier has a copy of the normal allele and a copy of the variant allele associated with the condition. No carrier screening panel can test for all variants that cause a genetic condition. Therefore, if an individual tests negative, there is a residual risk that they are still a carrier. Residual risk is calculated by subtracting the frequency of variant allele carriers detected by the specific panel and the carrier frequency of the condition in the population (Nussbaum et al., 2021). The goal of carrier screening is to identify the risk of offspring inheriting a genetic condition.

### 2.1.2 Genetic Understanding of Autosomal Recessive and X-Linked Conditions

Cystic fibrosis, Tay-Sachs disease, and sickle cell anemia are examples of autosomal recessive conditions. An individual with an autosomal recessive condition inherits two copies of the pathogenic allele. Both parents are asymptomatic carriers of the condition with one pathogenic

and one wild-type allele. If both parents are carriers, there is a 25% chance that their offspring will inherit the condition and a 50% that their offspring will be a carrier of the condition.

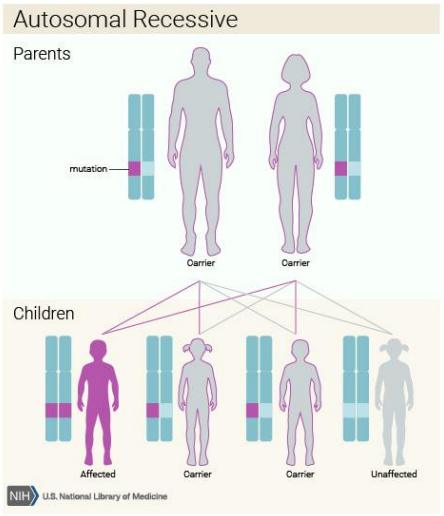


**Figure 1 Autosomal Recessive Inheritance**

*Note.* Autosomal recessive inheritance pattern diagram. From *What are the different ways a genetic condition can be inherited*?, by National Library of Medicine (US) (2021b). (https://medlineplus.gov/genetics/understanding/inheritance/inheritancepatterns/) (see Appendix A)

Fragile X syndrome, hemophilia A and B, and muscular dystrophy (Becker and Duchenne types) are examples of X-linked conditions. X-linked conditions can be either dominant or recessive. Individuals assigned female at birth typically have two X-chromosomes and individuals assigned male at birth typically have one X-chromosome and one Y-chromosome. In offspring assigned female at birth, one X-chromosome is inherited from each parent. In offspring assigned male at birth, the X-chromosome is inherited from an individual assigned female at birth and the Y-chromosome is inherited from an individual assigned male at birth. In X-linked dominant conditions, such as Fragile X syndrome, only one copy of the variant X-chromosome is required to cause the condition (National Cancer Institute, n.d.).

An individual assigned female at birth with a dominant X-linked condition has a 50% chance of passing the condition down to all offspring. An individual assigned male at birth, has a 100% chance of passing the condition on to offspring assigned female at birth.

An individual assigned female at birth who is a carrier for an X-linked recessive condition has a 50% chance of passing the condition on to offspring assigned male at birth and a 50% of having offspring assigned female at birth who are carriers.

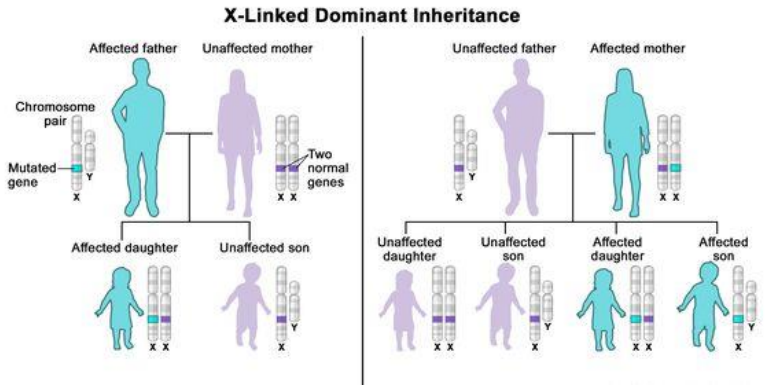


**Figure 2 X-linked Dominant Inheritance**

*Note.* X-linked dominant inheritance pattern diagram. From National Cancer Institute, n.d. (see Appendix A)

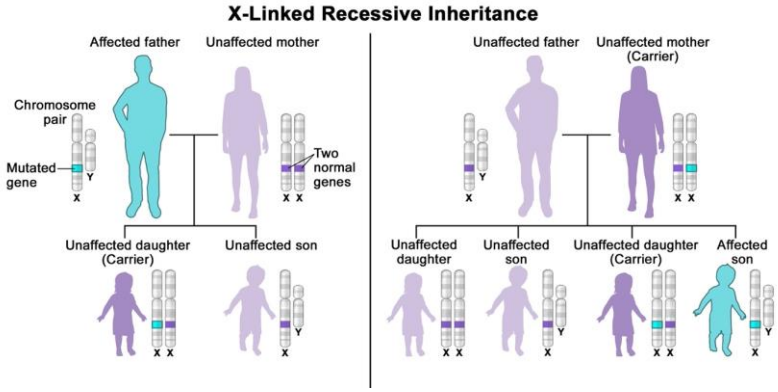


**Figure 3 X-linked Recessive Inheritance**

*Note.* X-linked recessive inheritance pattern diagram. From National Cancer Institute, n.d. (see Appendix A)

### 2.1.3 Targeted Carrier Screening

Targeted carrier screening is carrier screening for conditions based on ethnicity or family history. Traditionally, targeted carrier screening included conditions such as Tay-Sachs, hemoglobinopathies, and cystic fibrosis. In the 1970s, carrier screening was performed for certain ethnic groups who had a high incidence of genetic conditions like Tay-Sachs disease in Ashkenazi Jewish populations (Kraft et al., 2019). Ashkenazi Jews in North America have a carrier frequency of 1 in 31 for Tay-Sachs and incidence of the condition in every 1 in 3,500 births (Petersen et al., 1983). Ashkenazi Jews trace their ancestry back to Central and Eastern Europe and are at a higher risk of inheriting genetics conditions like Gaucher disease, cystic fibrosis, Tay-Sachs disease, familial dysautonomia, and spinal muscular atrophy due to their common ancestry (National Gaucher Foundation, n.d.). This common ancestry causes the founder effect where a small group of individuals from the same population become isolated from the original population (National Human Genome Research Institute, 2022b).

Hemoglobinopathies are a category of genetic conditions that impact red blood cells. Normal red blood cells are doughnut shape and contain hemoglobin. β-Thalassemia is an autosomal recessive blood condition that reduces the production of hemoglobin and lowers the amount of oxygen throughout the body. Affected individuals have anemia, slow growth, fatigue, and are at a higher risk for abnormal blood clots than unaffected individuals (Johns Hopkins Medicine, n.d.). β-Thalassemia has higher incidence rates in Mediterranean (carrier frequency 1 in 30-50) and Southeast Asian populations (carrier frequency 1 in 20) (BlueCross BlueShield of South Carolina, 2014; Cao et al., 1997). Population screening programs have been available for β-Thalassemia since the late 1970s in the Mediterranean Basin and are now available around the

world. In the United States, β-Thalassemia is on the Recommended Uniform Screening Panel (RUSP) and is a part of every state universal newborn screening program (NBS) (Health Resources & Services Administration, 2022).

Sickle cell disease (commonly called sickle cell anemia) is also a hemoglobinopathy and an autosomal recessive condition. The abnormal red blood cell is crescent shaped or sickle shaped. These red blood cells are more likely to get stuck in blood vessels and limit the flow of oxygen into other parts of the body. Sickle cell disease can cause anemia, stroke, and issues with the spleen, lungs, and kidneys (American College of Obstetricians and Gynecologists, 2022). Sickle cell has high incidence rates in individuals of African and Mediterranean descent. ACOG (2022) reports that "about 1 in 10 African Americans has sickle cell trait". An individual has sickle cell trait if they have one copy of the sickle cell allele and one copy of the wild-type allele. Individuals with the sickle cell trait typically do not have any symptoms of sickle cell disease. The initial carrier screening programs in the United States for sickle cell lacked sensitivity towards race as programs were aimed solely at African Americans. Today, sickle cell disease is on the RUSP and is included in all state universal newborn screening programs.

Cystic fibrosis (CF) is an autosomal recessive condition and causes a buildup of mucus in the lungs and airways due to the absence or reduction of cystic fibrosis transmembrane conductance regulator (CFTR) protein (Cystic Fibrosis Foundation, n.d.). The *CFTR* gene was discovered in 1989 by Dr. Lap-Chee Tsui, Dr. Francis Collins, and their teams (Riordan et al., 1989). Cystic fibrosis is common in individuals with Northern European ancestry with a carrier frequency of 1 in 30 and is the most common autosomal recessive condition in that population (Grody & Desnick, 2001; Ioannou et al., 2014). As pan-ethnic carrier screening panels became more widely used, CF was tested in all ethnic groups (Grody et al., 2001) and is now included in

the panel offered to all women at the preconception or prenatal stages (American College of Obstetricians and Gynecologists, 2020).

Limitations of ethnicity-based screening include inaccurate patient knowledge of ancestry, the fact that genetic conditions are not limited to a specific ethnic group, and screening for a limited number of conditions limits patient access to genetic knowledge (American Journal of Managed Care, 2018). First, it is difficult to assign an individual to a single ethnicity. For genetic testing purposes, ethnicity is typically self-reported. Condit et al. (2003) surveyed patients and found that 9% did not know their parents' ancestry and 40% could not identify the ancestry of all grandparents. Ethnicity-based screening relies on knowledge of ancestry and without accurate information, patients may be inadvertently limiting their genetic knowledge (Nazareth et al., 2015).

Second, genetic conditions do not only exist in specific ethnic groups (Edwards et al., 2015). Traditionally, those of Ashkenazi Jewish ancestry were at a higher risk of genetic conditions such as CF, familial dysautonomia, Gaucher disease, and Tay-Sachs (National Gaucher Foundation, n.d.). With the increase of inter-ethnic relationships, the presence of genetic conditions has dispersed into all ethnic groups. Due to the prevalence of certain genetic conditions in multiple ethnic groups, ACOG recommended that all individuals who are pregnant or considering pregnancy be offered screening for CF and SMA and have a red blood cell count conducted to assess risk of anemia and a hemoglobinopathy (American College of Obstetricians and Gynecologists, 2017b, 2022).

Third, limiting the number of conditions screened in a panel restricts the genetic information available to patients (Nazareth et al., 2015). A study by Peyser et al. (2019) conducted ethnicity-based carrier screening with panels ranging from four to ten conditions, depending on

self-reported ancestry. The study also conducted ECS with the Counsyl (Myriad) Foresight panel with 100 conditions. With the ethnicity panel only 8.5% of carriers were identified and 29.4% of carriers were identified with the ECS panel (Peyser et al., 2019). This study highlights that far less carriers were identified with ethnicity-based screening alone. The best approach to maximize the amount of genetic information available to patients is to offer ECS.

### 2.1.4 Expanded Carrier Screening

Expanded carrier screening, also called pan-ethnic or universal screening, is a type of carrier screening panel that can screen for several hundred conditions, most of which are rare, and is available to all patients, regardless of their ethnic background (American College of Obstetricians and Gynecologists, 2017a). Conditions included in ECS panels typically have a well-defined phenotype, cause some type of impairment, have a carrier frequency of 1 in 100 or greater, are early onset, and have a tremendous impact on quality of life where early diagnosis can lead to various opportunities for intervention (American College of Obstetricians and Gynecologists, 2017a; Edwards et al., 2015). ECS seeks to increase the detection of at-risk couples by being more equitable for individuals with muti-ethnic background (Henneman et al., 2016).

## 2.2 Components of Expanded Carrier Screening

### 2.2.1 Criteria for Conditions Included in Expanded Carrier Screening

#### 2.2.1.1 Wilson Jungner Criteria

James Maxwell Glover Wilson and Gunner Jungner published a report for the World Health Organization in 1968 that listed the criteria for which conditions are suitable for screening (Wilson & Jungner, 1968). The availability of an acceptable treatment, a disease natural history that is understood, and the symptoms are detectable early in life are criteria that are relevant in the case of carrier screening. Genetic conditions included in ECS panels should require medical intervention, have a well-defined phenotype, and have a benefit in outcome of prenatal diagnosis (Edwards et al., 2015). This criterion has been modified for various population-level genetic screening including newborn screening in the United States. With advances in genetic technology, updated criteria have been proposed that focus on informed choice, patient education, and cost-effectiveness (Andermann et al., 2008). Professional organizations look to the Wilson Jungner criteria as the gold standard and take it into consideration when making guidelines for best practices of ECS.

#### 2.2.1.2 Joint Statement from ACMG, ACOG, NSGC, PQF, and SMFM

In 2015, the American College of Medical Genetics and Genomics (ACMG), American College of Obstetricians and Gynecologists (ACOG), National Society of Genetic Counselors (NSGC), Perinatal Quality Foundation, and Society for Maternal-Fetal Medicine released a joint statement on the use of ECS in reproductive medicine (Edwards et al., 2015). The statement broke down current guidelines by ACMG, ACOG, and NSGC for hemoglobinopathies, conditions

common in Ashkenazi Jewish population, cystic fibrosis, spinal muscular atrophy, and Fragile X syndrome (Edwards et al., 2015). The main points of the statement include that individuals assigned female at birth of reproductive age should be offered carrier screening at the preconception stage, pre-screen and post-screen genetic counseling should be completed, a standard set of criteria for conditions screened was established and education of both providers and patients on genetics is crucial. Criteria of conditions screened include the following: if the condition causes a cognitive disability, a need for medical intervention, has an impact on quality of life, if a prenatal diagnosis could improve outcome, or if the condition requires educating the guardians on special needs (Edwards et al., 2015).

#### 2.2.1.3 ACOG

The American College of Obstetricians and Gynecologists released two committee opinions in 2017 on recommendations for carrier screening. ACOG states ethnicity-based, pan-ethnic, and expanded carrier screening are acceptable options for carrier screening (American College of Obstetricians and Gynecologists, 2017a). A proposed ECS panel includes 16 autosomal recessive conditions and Fragile X, all of which meet the criteria listed in the joint statement (American College of Obstetricians and Gynecologists, 2017a; Edwards et al., 2015) (see Appendix C). ACOG also recommends that every individual assigned female at birth considering pregnancy be screened for cystic fibrosis and spinal muscular atrophy (American College of Obstetricians and Gynecologists, 2017b).

#### 2.2.1.4 ACMG

The American College of Medical Genetics and Genomics recommends ECS in a four-tier system and that every individual assigned female at birth in preconception or prenatal care be

screened for the 97 autosomal recessive and 16 X-linked conditions listed in tier three (Gregg et al., 2021) (see Appendix B). Tier one is population neutral and includes screening for cystic fibrosis, spinal muscular atrophy, and risk-based screening. Tier two includes tier one and conditions that have a carrier frequency greater than or equal to 1 in 100 and have a moderate or severe phenotype. Tier three includes tiers one and two, and those with a carrier frequency of greater than or equal to 1 in 200. Tier four includes tier one-three and conditions that have a carrier frequency less than 1 in 200 (Gregg et al., 2021). ACMG recommends tier four only be considered when there is a possible consanguineous relationship or when family medical history justifies use of the tier four screening (Gregg et al., 2021).

#### 2.2.1.5 National Society of Genetic Counselors

The National Society of Genetic Counselors is a professional organization of genetic counselors in the United States. NSGC released a systematic evidence review of ECS literature that highlighted patient, provider, and test outcomes. The results showed that genetic counselors were comfortable with using ECS while obstetricians and gynecologists preferred traditional carrier screening approaches over ECS due to barriers such as time and the want for panels to be recommended by professional organizations (Ramdaney et al., 2022). A practice guideline is being developed and includes NSGC's recommendation for ECS over ethnicity-based carrier screening (Sagaser et al., ?). Previous professional recommendations focus on the inclusion of conditions with moderate or severe phenotypes, NSGC does not include a list of conditions but recommends conditions that could cause changes to reproductive plans (Gregg et al., 2021) (Sagaser et al., ?).

### 2.2.2 Genetic Counseling Aspects

Genetic counseling is a critical component of ECS. Both pre- and post-screening counseling are important to make sure individuals undergoing ECS understand the risks, benefits, and limitations of carrier screening, including the possibility of residual risk, which is the chance an individual is a carrier for a condition after a negative screening result (American College of Obstetricians and Gynecologists, 2017a). ACMG, ACOG, and NSGC stress the importance of pre-screening education and informed consent which includes discussion around the conditions screened and the limitations of the panel (Edwards et al., 2015). Counseling of pre-screening results does not have to be completed by a genetic counselor. Preconception pre-screening counseling should be completed by the physician who is offering ECS. Increasing the number of physicians who can give pre-screening counseling can increase the number of individuals who can use ECS as an option in reproductive planning.

### 2.2.3 Commercialization of Expanded Carrier Screening

There are three main genetic testing models: direct-to-consumer, physician-mediated, and clinic-based. Direct-to-consumer (DTC) genetic testing allows tests to be ordered online by the consumer. Physician-mediated genetic testing allows for a physician to order a test for a patient from a commercial company. Clinic-based genetic testing allows for a physician to order a test for a patient from within the hospital or clinic (National Human Genome Research Institute, 2022a). All genetic testing models have been integrated into the mass market since the completion of the Human Genome Project in 2003 and the first DTC companies were founded around 2005. Expanded carrier screening did not become commercialized until Counsyl released the first

universal carrier test in early 2010 that screened for 105 autosomal recessive conditions (Chokoshvili et al., 2017; Srinivasan et al., 2010). This panel launched the ECS market and now there are many companies that offer different versions of ECS panels ranging drastically in the number of conditions screened.

Most ECS panels on the market use the physician-mediated or clinic-based genetic testing models. Physician-mediated and clinic-based genetic testing are both great options for use in precision medicine clinics. Physician-mediated allows for results to be disclosed via the company, typically through a virtual genetic counseling session. Clinic-based requires a healthcare professional to be involved at every step of the process, including results disclosure (National Human Genome Research Institute, 2022a). DTC testing is not regulated like physician-mediated and clinic-based testing. DTC companies are not always Clinical Laboratory Improvement Amendments (CLIA) certified and College of American Pathologists (CAP) accredited. DTC results are not validated and lack a personalized interpretation for the patient (Horton et al., 2019). For these reasons, DTC genetic testing is not typically used in clinical settings.

## 2.3 Role of Primary Care in Expanded Carrier Screening

### 2.3.1 Definition of Primary Care

Primary care is an integral part of healthcare services where clinicians provide a wide variety of care to patients and tend to provide care to patients for long periods of time. Clinicians involved in primary care include physicians, nurse practitioners, and physician assistants. Primary care providers (PCPs) typically work in internal medicine or family medicine practices (Institute

of Medicine Committee on the Future of Primary, 1994). A primary care practice is a patient's medical home and PCPs treat patients and their families across their lifetimes. Long-established relationships between clinicians and patients promotes trust and can lead to better health outcomes for patients (Anderson & Dedrick, 1990).

### 2.3.2 Impact of Primary Care on an Individual's Health

Routine primary care visits are correlated with increased use of preventative care methods and overall decreased healthcare costs (Hostetter et al., 2020). Preventative care methods can include vaccinations, colonoscopies, mammograms, blood pressure tests, and mental health screenings (U.S. Department of Health & Human Services, 2022). PCPs also coordinate patient care with specialists. For patients assigned female at birth, PCPs are typically responsible for providing preconception care (Wilkes, 2016). Gynecologists also provide preconception care for individuals assigned female at birth when it comes to reproductive health.

### 2.3.3 Current Use of Expanded Carrier Screening in Primary Care

There is limited literature available on primary care uptake of expanded carrier screening. A study found that 89% of primary care physicians have referred a patient to genetic services (Truong et al., 2021) and 60% have ordered a genetic test for breast cancer, colon cancer, Huntington disease, or sickle cell (Shields et al., 2008). These results show that primary care physicians are open to patients utilizing genetic services and possibly offering ECS panels in the future. ECS pilot programs are in development in the United States, but there has been success with programs internationally. In the Netherlands, couple-based ECS was offered by a general

practitioner (GP) and 90% of the couples who received pre-screening counseling proceeded with the panel (Schuurmans et al., 2019). In the United States, reproductive physicians are likely to offer ethnicity-based screening or a combination of ethnicity-based and ECS and it is rare for PCPs to offer any type of carrier screening (Briggs et al., 2018).

### 2.3.4 Future Benefits of Expanded Carrier Screening in Primary Care

Expanded carrier screening increases the opportunity of reproductive choice. When completed at the preconception stage, an individual wanting to become pregnant could become more aware of the reproductive options they have for conceiving a child (Henneman et al., 2016). Another benefit of ECS implementation in primary care is the potential reduction of stigmatization of genetic conditions. ECS offers a universal range of conditions and those conditions can occur in any ethnic group, regardless of the traditional at-risk populations (van der Hout et al., 2019). Increased use of ECS in primary care settings may also allow the word ‘carrier’ to become more commonly used and therefore reduce the negativity associated with the word. Provider confidence in their genetics knowledge may increase when they discuss screening with patients during pre-screening counseling and patients could learn more from being present in those appointments (Schuurmans et al., 2019). Finally, health equity may be increased by meeting patients where they are in their medical homes. This is especially important for primary care clinics with underserved and underrepresented populations.

## 2.4 Implications on Public Health Genetics

### 2.4.1 Use of Genetic Screening as a Measure of Public Health

The goal of genetic screening is to identify at-risk individuals to allow for early intervention and possible mitigation of symptoms (Shen et al., 2022). Hereditary breast and ovarian cancer, Lynch syndrome, and familial hypercholesterolemia screening programs are prioritized by the Centers for Disease Control and Prevention (CDC) under their Tier 1 genomic applications as "having significant potential for positive impact on public health" (2014). Pilot population genetic screening programs for these conditions have been successful and illustrate that screening programs aid in identifying individuals who would, without screening, not know that they were at risk for a genetic condition.

Newborn screening (NBS) is one of the most widely recognized applications of genetic screening in the United States. NBS started in the 1960s with screening for phenylketonuria by pricking a newborns heel and placing the blood sample on filter paper (National Institute of Child Health and Human Development, 2017). Today, NBS consists of a heel prick, pulse oximetry, and a hearing test. Each state has a NBS program, but the conditions screened can vary by state. The Secretary of the Department of Health and Human Services adopted the Recommended Uniform Screening Panel (RUSP) which is a list of core and secondary conditions that states should include in their NBS panels (American College of Medical Genetics and Genomics, 2006; Health Resources & Services Administration, 2022). The RUSP currently contains 35 core and 26 secondary conditions. NBS programs have led to the identification of over 13,000 newborns with a genetic condition each year and 98% of children born every year are screened (Centers for Disease Control and Prevention, 2012).

### 2.4.2 Use of Expanded Carrier Screening as a Measure of Public Health

There are multiple public health benefits of expanded carrier screening including increased reproductive autonomy and equity. First, access to ECS increases reproductive autonomy by giving individuals earlier access to consider family planning options (van der Hout et al., 2019). If ECS was completed in the preconception stage, options can include the use of donor eggs or sperm during conception, preimplantation genetic testing (PGT) to find out which embryos are or are not affected with the condition, or adoption (Henneman et al., 2016). If ECS was completed during the prenatal stage, chorionic villus sampling or amniocentesis can be performed for prenatal diagnosis (Bajaj & Gross, 2014).

Second, ECS increases equity of genetic services. ECS panels are universal and include conditions that are traditionally common in specific ethnic groups, like Tay-Sachs disease in the Ashkenazi Jewish population. It is now common to find Tay-Sachs and other traditionally ethnic-specific in other populations. For example, Harbison et al. (2018), reported a high number of self-reported non-Jewish white individuals who were found to be carriers for Tay-Sachs and Fanconi anemia type C compared to expected values. The expansion of ECS into the primary care space has allowed for non-genetics health professionals to become more involved in the genetic testing process, thus extending the reach of genetic services to more individuals.

# 3.0 Methods

## 3.1 Database Search

Information on current expanded carrier screening panels was initially collected using the Concert Genetics Search and Compare Tests feature (www.concertgenetics.com). The search query "expanded carrier screening" resulted in 110 panels from 29 different lab companies. This project collected data on 27 ECS panels from 9 lab companies. The majority of unincluded lab companies were university medical systems that used major lab company panels or did not have panels that fit the ECS classification. Major lab companies A-I were included in this data. For this project, an ECS panel was classified as carrier screening panel that includes genes in addition to *CFTR* and *SMN1*. Information was also collected from laboratory websites and by contacting customer service representatives via email and phone. A spreadsheet was created and includes information from each ECS panel on gene information, whether the panel included ACMG- and ACOG-recommended genes, screening methodology, billing information, financial assistance programs, and the availability of genetic counselors to discuss screening results with patients.

## 3.2 Analysis of ECS Panels

Variability in number of total genes included in panels was analyzed by comparing the minimum, maximum, and mean number of total genes. For panels with opt-in genes, these genes were included in the number of total genes. Opt-in genes were associated with variable or adult-

onset presentation of the condition and are not typically recommended for inclusion in ECS panels by ACMG or ACOG (American College of Obstetricians and Gynecologists, 2017a; Gregg et al., 2021). Variability in the number of ACMG-recommended genes included in panels was analyzed by comparing the number of ACMG-recommended genes included and the percentage of total genes in the panel that are ACMG-recommended. Variability in the number of ACOG-recommended genes included in panels was analyzed by comparing the number of ACOG-recommended genes included and the percentage of total genes in the panel that are ACOG-recommended. Variability in number of total genes screened between companies was analyzed by comparing the number of ECS panels offered by each company, minimum, maximum, and range within each company.

# 4.0 Results

## 4.1 Variability in the Number of Genes Screened

As shown in Table 1, there was a range of 555 total genes analyzed among the 27 panels. Panel 12 was the smallest and panel 11 was the largest. The mean number of total genes analyzed was 208. All panels included at least 14 ACMG-recommended genes and the mean number included was 64 genes. Panels 7, 8, and 9 included all ACMG-recommended genes. Panels 12, 18, 16, and 7 only included genes that are ACMG-recommended. The largest panel (11) includes the second highest number of ACMG-recommended genes (108), but only 19% of the total genes are ACMG-recommended. It is evident that the larger the panel, the more ACMG-recommended genes are included. However, in most large panels, ACMG-recommended genes only account for 15-30% of the total number of genes in each panel (Figure 4).

All panels included at least 13 ACOG-recommended genes and the mean number included was 21. Both panels from Lab H, 23 and 24, included all 24 ACOG-recommended genes (Table 1). 12 panels were only missing *SMN2* from the ACOG list.

**Table 1 Gene Variability Per Panel**

| Lab | Panel | Number of Genes Analyzed | Number of ACMG-recommended Genes (113 total) | Number of ACOG-recommended Genes (24 total) |
|---|---|---|---|---|
| A | 1 | 166 | 89 | 22 |
| A | 2 | 421 | 88 | 22 |
| B | 3 | 25 | 23 | 23 |
| B | 4 | 156 | 61 | 23 |
| B | 5 | 421 | 89 | 23 |
| C | 6 | 30 | 24 | 18 |
| C | 7 | 113 | 113 | 22 |
| C | 8 | 427 | 113 | 23 |
| C | 9 | 436 | 113 | 23 |
| D | 10 | 115 | 106 | 23 |
| D | 11 | 569 | 108 | 23 |
| E | 12 | 14 | 14 | 14 |
| E | 13 | 141 | 52 | 21 |
| E | 14 | 523 | 82 | 23 |
| E | 15 | 523 | 82 | 23 |
| F | 16 | 15 | 15 | 14 |
| F | 17 | 178 | 67 | 23 |
| G | 18 | 15 | 15 | 13 |
| G | 19 | 28 | 23 | 18 |
| G | 20 | 106 | 47 | 19 |
| G | 21 | 276 | 76 | 23 |
| G | 22 | 422 | 86 | 23 |
| H | 23 | 78 | 49 | 24 |
| H | 24 | 154 | 62 | 24 |
| I | 25 | 23 | 22 | 16 |
| I | 26 | 85 | 55 | 22 |
| I | 27 | 151 | 64 | 22 |
| **Means** | | **208** | **108** | **21** |

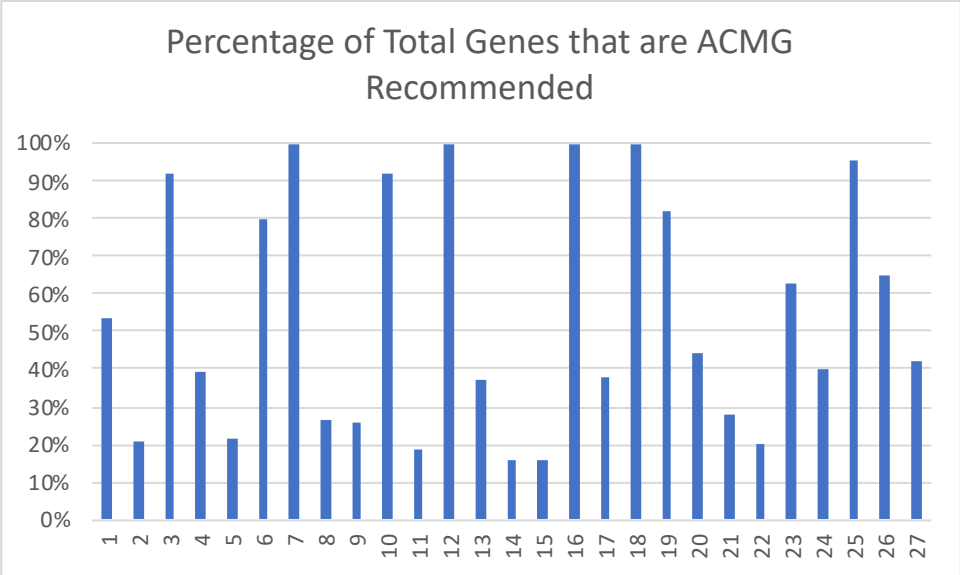


**Figure 4 Percentage of Total Genes that are ACMG-Recommended**

Table 2 highlights the commonly missing ACMG-recommended genes from the ECS panels analyzed. A total of 18 ACMG-recommended genes are missing from at least 22 of the panels. Panels 7, 8, and 9 from Lab C were the only panels that included all 113 ACMG-recommended genes.

**Table 2 Commonly Missing ACMG-Recommended Genes**

| Gene Name | Condition and Inheritance Pattern | Carrier Frequency (from Gregg et al. (2021)) | Panels Included |
|---|---|---|---|
| *ABCA3* | Surfactant metabolism dysfunction, pulmonary 3 (AR) | <1/100 to ≥1/150 | 7, 8, 9 |
| *AFF2* | Mental retardation, X-linked, associated with fragile site FRAXE (XLR) | - | 7, 8, 9 |
| *ANO10* | Spinocerebellar ataxia 10 (AR) | <1/50 to ≥1/100 | 7, 8, 9 |
| *CCDC88C* | Congenital hydrocephalus 1 (AR) | <1/100 to ≥1/150 | 7, 8, 9 |
| *CLCN1* | Congenital myotonia | <1/150 to ≥1/200 | 7, 8, 9 |

| | | | |
|---|---|---|---|
| | (AR) | | |
| *CYP11A1* | Adrenal insufficiency, congenital, with 46, XY sex reversal, partial or complete | <1/100 to ≥1/150 | 7, 8, 9 |
| *DYNC2H1* | Short-rib thoracic dysplasia 3 with or without polydactyly (AR) | ≥1/50 | 7, 8, 9 |
| *FMO3* | Trimethylaminuria (AR) | <1/100 to ≥1/150 | 7, 8, 9 |
| *LRP2* | Donnai–Barrow syndrome (AR) | <1/150 to ≥1/200 | 7, 8, 9, 14, 15 |
| *MCPH1* | Primary microcephaly 1 (AR) | <1/100 to ≥1/150 | 7, 8, 9 |
| *MID1* | Opitz GBBB syndrome, type I (GBBB1) (XLR) | - | 7, 8, 9 |
| *MVK* | Hyper-IgD syndrome and Mevalonic aciduria (AR) | <1/150 to ≥1/200 | 7, 8, 9 |
| *NAGA* | Schindler disease, types 1 and 3 (AR) | <1/50 to ≥1/100 | 7, 8, 9 |
| *OCA2* | Oculocutaneous albinism brown and type II (AR) | <1/50 to ≥1/100 | 7, 8, 9 |
| *PLP1* | Spastic paraplegia 2, X-linked (SPG2) (XLR) | - | 7, 8, 9 |
| *SLC19A3* | Basal ganglia disease, biotin-responsive (AR) | <1/100 to ≥1/150 | 7, 8, 9 |
| *TNXB* | Ehlers–Danlos-like syndrome due to tenascin-X deficiency (AR) | ≥1/50 | 7, 8, 9 |
| *TYR* | Oculocutaneous albinism types 1A and 1B (AR) | ≥1/50 | 7, 8, 9 |

Table 3 highlights the panel variability with the 9 lab companies with number of panels, minimum maximum, and the range in number of genes screened. Lab G had the most panels

offered (5) and Labs A, D, F, and H had the fewest panels offered (2). Lab H had the smallest range of 76 genes and Lab E had the largest range of 509 genes.

**Table 3 Lab Company Panel Variability**

| Lab | Number of Panels | Minimum | Maximum | Range |
|---|---|---|---|---|
| A | 2 | 166 | 421 | 255 |
| B | 3 | 25 | 421 | 396 |
| C | 4 | 30 | 436 | 406 |
| D | 2 | 115 | 569 | 454 |
| E | 4 | 14 | 523 | 509 |
| F | 2 | 15 | 178 | 163 |
| G | 5 | 15 | 422 | 407 |
| H | 2 | 78 | 154 | 76 |
| I | 3 | 23 | 151 | 128 |

Table 4 highlights the opt-in genes that were included in both panels 9 and 11. These genes are associated with variable or adult-onset presentation of the condition and are not typically recommended for inclusion in ECS panels by ACMG or ACOG (American College of Obstetricians and Gynecologists, 2017a; Gregg et al., 2021). Panel 9 included 9 total opt-in genes and panel 11 included 13 opt-in genes.

**Table 4 Opt-In Genes Found in Both Panels 9 and 11**

| Gene | Condition | Inheritance Pattern | Variable Presentation or Late-Onset | Notes |
|---|---|---|---|---|
| *F2* | Prothrombin-related thrombophilia | AR | Variable presentation | Bleeding disorder, 2 types: hypothrombinemia (more severe) and dysprothrombinemia |
| *F5* | Factor V Leiden thrombophilia | AR | Variable presentation | Bleeding disorder |
| *G6PD* | Glucose-6 phosphate dehydrogenase deficiency | XLD | Variable presentation | Most patients asymptomatic until triggered by |

| | | | | |
|---|---|---|---|---|
| | | | | drug/food/infection, hemolytic anemia |
| *HFE* | Hereditary hemochromatosis type 1 | AR | Late-onset | Excess iron accumulation |
| *SERPINA1* | Alpha-1 antitrypsin deficiency | AR | Late-onset | Presents as emphysema (more common) or liver disease |

Note: Information in Table 4 was collected from the Online Mendelian Inheritance in Man Database (Online Mendelian Inheritance in Man, 2016a, 2016b, 2018, 2020, 2022)

### 4.2 Self-Pay Price

Self-pay price data was collected because only one lab company is currently contracted with UPMC, and patients would most likely pay out-of-pocket for the full cost of testing. It is important to note that every lab company offers a financial assistance program based on the patient's household size and income. The type and amount of financial assistance given varied by company with some companies offering partial discounts and other entirely waiving the cost of the panel. Panels 26 and 27 offered different pricing based on the sex of the patient. Panel 26 charged $1,680 for patients assigned female at birth and $1,640 for patients assigned male at birth. Panel 27 charged $2,010 for patients assigned female at birth and $1,970 for patients assigned male at birth. For comparisons against the other panels, the average of the two self-pay prices of panels 26 and 27 were calculated.

The average self-pay price per panel was $458. Figure 5 shows that all panels from Lab I skew the average self-pay price. Without Lab I, the average self-pay price per panel would have been $308. All panels from Labs A, F, and H offered the lowest self-pay price at $249. 27 had the highest self-pay price at $1,990. Figure 6 makes clear that all lab companies, except for Lab I, keep their prices under $400. Additionally, Lab C is the only company that offers a discount of

merged partner reports for an additional $100. Merged partner reports include carrier screening results for an individual assigned female at birth and an individual assigned male at birth.

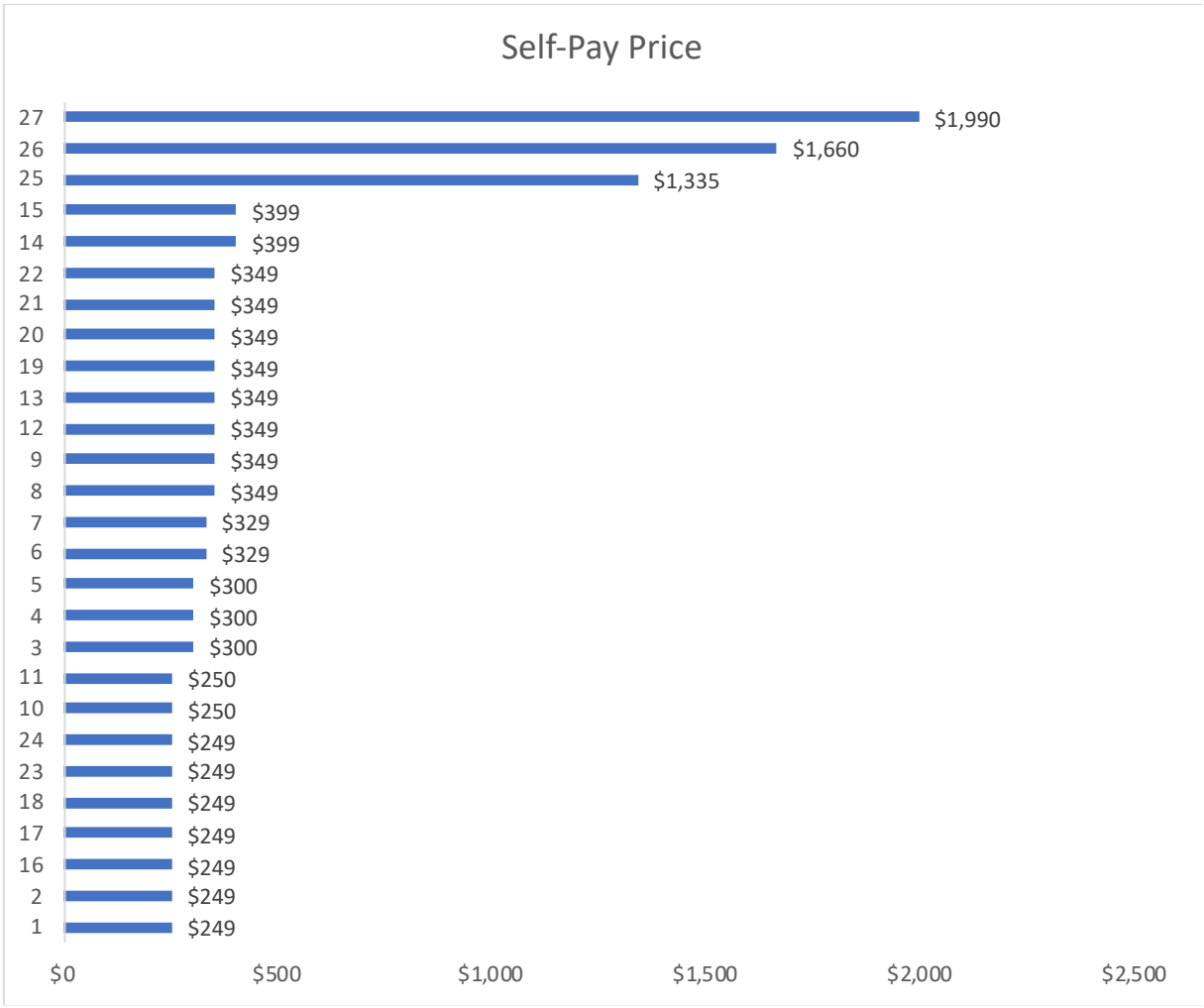


**Figure 5 Self-Pay Price by Panel**

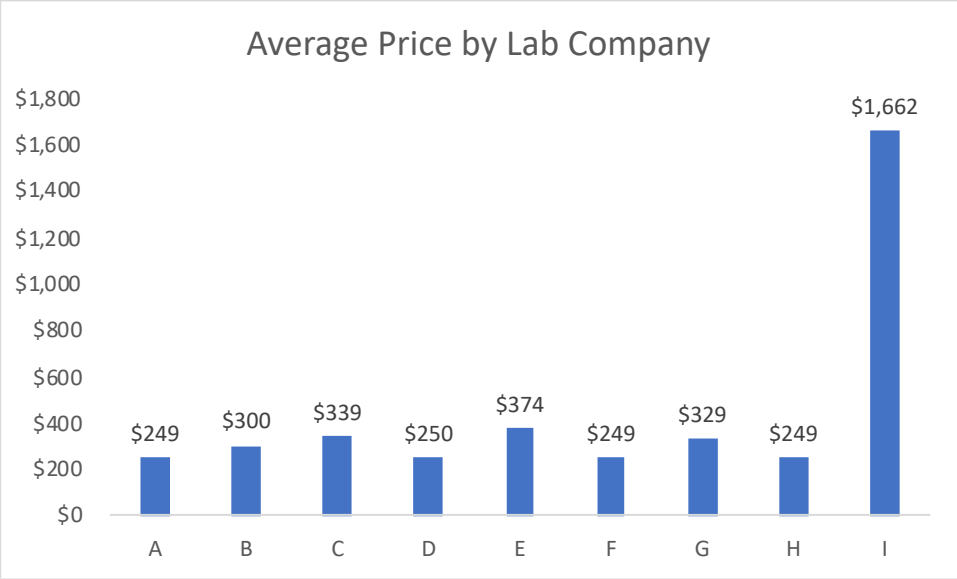


**Figure 6 Average Self-Pay Price by Lab Company**

### 4.3 Laboratory Considerations

All lab companies were Clinical Laboratory Improvement Amendments (CLIA) certified and College of American Pathologists (CAP) accredited, except for Lab H. Lab H was only CLIA certified. These programs ensure lab companies meet required standards to maintain the accuracy of test results. All panels had the ability to detect Fragile X Syndrome using repeat expansion technology. Every panel offered X-linked gene exclusion options, except for 25. The only x-linked gene in 25 was *FMR1*, which is associated with Fragile X Syndrome.

A total of 21 panels used full gene sequencing and 7 panels used common variant sequencing. Lab A is the only lab that exclusively offered common variant sequencing. Labs B, C, D, F, G, and H exclusively offered full gene sequencing. Labs E and I offered a combination of full gene sequencing and common variant sequencing. All panels only reported pathogenic or likely pathogenic results, except for panel 14. A total of 14 panels reported out pathogenic or likely

pathogenic results and variants of uncertain significance (VUS). There was an option to have this panel not report VUS. Pathogenic means the variant allele is associated with the genetic condition. Likely pathogenic means the variant is likely associated with the condition. A VUS is a variant allele that has not yet been associated with a genetic condition.

### 4.4 Patient Experience

Turnaround time (TAT) is the time it takes a lab company to receive a patient sample, run the ECS panel, and return the results back to the patient. The TAT ranged from 7 to 24 days per panel, with an average of 14 days. All lab companies accepted blood samples. Table 5 shows that Lab E and I only accepted blood samples, while the other labs accepted both blood and saliva sample options. Labs B and C also accepted buccal swabs and extracted DNA and Lab D accepted gDNA in addition to blood and saliva (Table 5). A total of 6 lab companies offered kits to be shipped to patients. It is important to note that only buccal swab and saliva samples could be collected at home by the patient. Blood, extracted DNA, and gDNA samples must be collected within a medical office or laboratory sample collection center. Only panel 14 accepted prenatal samples or genetic samples from a fetus, typically collected using amniocentesis or chorionic villus sampling.

All lab companies were equal in their availability of customer service and online ordering portals. Every lab company staffed genetic counselors who were available to discuss ECS panel results with patients at no additional charge.

**Table 5 Lab Company Ease of Testing**

| Lab Name | Turnaround Time (TAT) | Accepts Prenatal Samples | Sample Types Accepted | Ship Kits to Patients |
|---|---|---|---|---|
| A | 12 days | No | Blood or Saliva | Yes |
| B | 14 days | No | Blood, Saliva, Buccal Swab, or Extracted DNA | No |
| C | 14 days | No | Blood, Saliva, Buccal Swab, or Extracted DNA | Yes |
| D | 11 days | No | Blood, Saliva, or gDNA | Yes |
| E | 17 days | Yes (only for 14) | Blood | No |
| F | 14 days | No | Blood or Saliva | Yes |
| G | 14 days | No | Blood or Saliva | Yes |
| H | 12 days | No | Blood or Saliva | Yes |
| 1 | 14 days | No | Blood | No |

# 5.0 Discussion and Conclusions

## 5.1 Missing ACMG- and ACOG-Recommended Genes

Table 2 lists the commonly missing ACMG-recommended genes from the panels analyzed, the corresponding condition, inheritance pattern, and carrier frequency. A total of 18 ACMG-recommended genes are missing from at least 22 of the panels. Lab C is the only company that included all 113 ACMG-recommended genes in every panel.

Interestingly, 3 of the genes (*DYNC2H1, TNXB, TYR*) excluded from most panels are associated with conditions that have a greater than 1 in 50 carrier frequency. *DYNC2H1* is associated with short-rib thoracic dysplasia 3 with or without polydactyly, which is fatal during the prenatal and perinatal periods (Genetic and Rare Disease Information Center (GARD), 2023). Lab companies may choose to exclude *DYNC2H1* from ECS panels because patients have family history of the condition since the carrier frequency is so high. Molecular analysis of the *TNXB* gene is difficult as there is a pseudogene, *TNXA*, that is nearly identical to *TNXB*. Diagnosis of Ehlers–Danlos-like syndrome due to tenascin-X deficiency requires both molecular testing and serum screening (Demirdas et al., 2017). Mutations in *TYR* are associated with Oculocutaneous albinism types 1A and 1B. Differentiation between the types of OCA is dependent on no or residual tyrosinase enzyme activity (Online Mendelian Inheritance in Man, 2021). Taylor (1987) commented that even though prenatal diagnosis is available, he did not agree with the use of prenatal diagnosis because elective abortions that result are not easily defendable. The negative connotation associated with prenatal diagnosis of OCA1A and 1B has likely led to the current exclusion of *TYR* in ECS panels. The remaining ACMG-recommended genes in Table 2 have

lower carrier frequencies, with the most being in the less than 1 in 100 and greater than or equal to 1 in 150 range (n = 6). This carrier frequency range is important because ACMG recommends conditions with a carrier frequency of greater than or equal to 1 in 200 and ACOG recommends conditions with a carrier frequency of greater than or equal to 1 in 100 to be considered for ECS panels (American College of Obstetricians and Gynecologists, 2017a; Gregg et al., 2021).

The only commonly missing ACOG-recommended gene was *SMN2* and was included in panels 23 and 24. *SMN1* and *SMN2* are genes associated with Spinal Muscular Atrophy (SMA). *SMN2* is a pseudogene of *SMN1* and is not necessary in a carrier screening setting. Around 95% of SMA cases are associated with a deletion of exon 7 in *SMN1* (Wirth, 2000). *SMN2* copy number is used to predict the severity of the phenotype in an affected individual. The more copies of *SMN2* an individual has, the milder the phenotype associated with the condition (Prior, 2020). Additionally, it is interesting to note that all but 2 genes from the ACOG list are also ACMG-recommended (*BCKDHA* and *SMN2*). *BCKDHA* was included in 19 out of 27 panels (70%).

### 5.2 Panel Size Variation Within Lab Companies

All lab companies had at least 2 ECS panels, with Lab G having the most with 5 panels. Multiple panels per company allowed for a range in panel sizes. Table 3 illustrates Lab H had the smallest range of 76 genes and Lab E had the largest range of 509 genes. Larger panels allow for more ACMG- and ACOG-recommended genes to be included (Table 1). Most lab companies charged the same price for all their panels or only $20-50 more for larger panels.

Panels 9 and 11 included opt-in genes that are associated with variable or adult-onset presentation of the condition. Panel 9 included *BCHE*, *F2*, *F5*, *G6PD*, *HFE*, *LDLRAP1*, *LPL*,

*MTHFR*, and *SERPINA1*. Panel 11 included *BTD, F2, F5, F11, G6PD, GP1BA, GP6, HFE, HGD, MCCC1, MCCC2, MEFV, SERPINA1*. Table 4 describes the genes included in both panels, condition, inheritance pattern, and designation of variable presentation or late-onset. Carrier testing is not the most appropriate situation to be screening for these conditions. ACOG recommends screening for conditions with a well-defined phenotype and have an onset early in life (American College of Obstetricians and Gynecologists, 2017a). ACMG recommends screening for conditions in tiers one through three. Tier four includes conditions those carrier frequencies are below 1 in 200 and whose natural history is not as well known (Gregg et al., 2021). Most of the opt-in genes would fall into tier four. These genes are not typically included in carrier screening due to their variable presentations that lead to a poorly-defined phenotype and the late-onset nature of some of the conditions. Carrier screening results only show the risk of an individual passing an allele to a future offspring. Implications of screening for these conditions in patients are like those of testing children for adult-onset genetic conditions. There is no need to be informed of the information prior to the child's adult years and patients may fear facing discrimination for being a carrier (Shkedi-Rafid et al., 2015).

### 5.3 Inclusion of Non-ACMG and ACOG-Recommended Genes

A total of 625 genes included in the 27 ECS panels were not recommended by ACMG or ACOG. The gene *IVD* appeared in 19 out of the 27 panels. *IVD* is associated with Isovaleric acidemia and effects 1 out of 230,000 children in the United States (Baby's First Test, 2022). *IVD* is also included on the Recommended Uniform Screening Panel (RUSP) for newborn screening (Health Resources & Services Administration, 2022). There were 22 genes that were included in

at least 15 of the panels and of those, 6 are included on the RUSP. The carrier frequencies ranged from 1 in 112 to 1 in 324 with 5 genes being associated with conditions with unknown carrier frequencies due to their rarity.

A benefit to including non-recommended genes in ECS panels is to develop a greater knowledge of carrier status for conditions included on the RUSP. This knowledge further increases reproductive autonomy of the patient and does not require waiting until after a child is born to see the results of the newborn screening panel. A limitation to including non-recommended genes in ECS panels is that there is no restriction to what companies can include in their panels. Some genes included in at least 15 panels had unknown carrier frequencies because the conditions they are associated with are so rare (*ALDH3A2*, *CLN5*, *HADHA*, *MEFV*, *MTTP*).

### 5.4 Significance of VUS Reporting

Panel 14 was the only panel that offered to report variants of uncertain significance (VUS). It is reassuring that most panels analyzed did not report VUS. ACMG does not support the reporting of VUS in carrier screening settings except for in partners of identified carriers (Gregg et al., 2021). VUS may or may not be associated with a genetic condition. Vears et al. (2018) stated that VUS found in genes not associated with the conditions screened should not be reported. VUS results may change as new evidence associates these variants with conditions. There is no standard practice in place to reinform patients of VUS results.

Disclosing VUS results can also greatly impact a patient or couple's experience with carrier screening as VUS results could create more anxiety and uncertainty during an already stressful period in a patient's life. One would typically not test a pregnancy or make decisions about a

pregnancy based on a VUS result. ECS panels should not report VUS results as this would just be information a family would have to sit with.

### 5.5 ECS Panel Selection Process

One aim of this project was to recommend a panel for use in the UPMC Primary Care Clinic Pilot Program. Several aspects were taken into consideration when choosing a panel including gene inclusion, laboratory considerations of turnaround time, sample types, sequencing type, and possibility of VUS reporting, self-pay price, and patient experience with an option to ship kits to patients, availability of genetic counselors, and availability of customer service. Most lab companies, except for Lab I, were not covered under the UPMC Health Plan, so patients would likely pay out of pocket for the panel. The ideal panel for the pilot program would include a high number of both ACMG- and ACOG-recommended genes, have a lower self-pay price, include a variety of accepted sample types, and have company staffed genetic counselors available to discuss results with patients. The availability of company-staffed genetic counselors helps ease the burden put on prenatal genetic counselors at UPMC to discuss initial ECS panel results with patients.

Panel 8 is likely the best panel for UPMC Primary Care Pilot Program. All 113 ACMG-recommended genes and 23 out of 24 ACOG-recommended genes are included. Only *SMN2* is missing from the ACOG recommendations and as discussed earlier, is not necessary in carrier screening settings. Panel 8 can test a range of biological samples, including blood, saliva, buccal swabs, or extracted DNA samples, and kits can be shipped to patients. The self-pay price of panel 8 is $349 and is well below the average panel price of $458. An additional benefit of panel 8 is that it allows both

individuals in a couple to have a merged couple report that will show the carrier screening results in one document to enhance couple specific counseling.

## 5.6 Conclusions

In this study, 27 expanded carrier screening panels from Labs A-I were analyzed. Substantial variability between panels with the total number of genes ranging from 14 to 569, with an average of 208. The number of ACMG-recommended genes ranging from 14 to 113, with an average of 64, and the number of ACOG-recommended genes ranging from 13 to 24 genes, with an average of 21. Lab D was the most successful in capturing ACMG-recommended genes with an average of 107. Lab H was the most successful in capturing ACOG-recommended genes with an average of 24. The self-pay prices of the panels ranged from $249 to $1,990, with an average of $458 per panel. All companies had customer service available, company-employed genetic counselors, and an online ordering to support ease of testing and increase the overall patient experience.

Expanded carrier screening panels can be a vital part of preconception care. ECS panels increase reproductive autonomy and increase the knowledge of reproductive options with birthing people. The results above show drastic differences between panels and the use of consistent criteria from professional organizations when designing panels could increase the homogeneity between panels. The UPMC Primary Care pilot program will offer one ECS panel to patients, thus increasing standardization within the UPMC system and increasing health equity. Based on the information collected and analyzed, the best option for the UPMC Primary Care Pilot Program is likely panel 8. This panel included all 113 ACMG-recommended genes, 23 out of 24 ACOG-

recommended genes, accepted 4 sample types, can ship testing kits to patients, the self-pay price is $349, and the lab company only charges $100 more for a merged partner report.

# Appendix A Copyright Permission Form

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**Appendix Figure 1 Copyright Permission Form**

# Appendix B ACMG-Recommended Genes

## Appendix Table 1 ACMG-Recommended Genes

| Gene Name | Inheritance Pattern | Gene Name | Inheritance Pattern |
|---|---|---|---|
| *ABCA3* | AR | *GAA* | AR |
| *ABCC8* | AR | *GALT* | AR |
| *ABCD1* | XL | *GBA* | AR |
| *ACADM* | AR | *GBE1* | AR |
| *ACADVL* | AR | *GJB2* | AR |
| *ACAT1* | AR | *GLA* | XL |
| *AFF2* | XL | *GNPTAB* | AR |
| *AGA* | AR | *GRIP1* | AR |
| *AGXT* | AR | *HBA1* | AR |
| *AHI1* | AR | *HBA2* | AR |
| *AIRE* | AR | *HBB* | AR |
| *ALDOB* | AR | *HEXA* | AR |
| *ALPL* | AR | *HPS1* | AR |
| *ANO10* | AR | *HPS3* | AR |
| *ARSA* | AR | *IDUA* | AR |
| *ARX* | XL | *L1CAM* | XL |
| *ASL* | AR | *LRP2* | AR |
| *ASPA* | AR | *MCCC2* | AR |
| *ATP7b* | AR | *MCOLN1* | AR |
| *BBS1* | AR | *MCPH1* | AR |
| *BBS2* | AR | *MID1* | XL |
| *BCKDHB* | AR | *MLC1* | AR |
| *BLM* | AR | *MMACHC* | AR |
| *BTD* | AR | *MMUT* | AR |
| *CBS* | AR | *MVK* | AR |
| *CC2D2A* | AR | *NAGA* | AR |
| *CCDC88C* | AR | *NEB* | AR |
| *CEP290* | AR | *NPHS1* | AR |
| *CFTR* | AR | *NR0B1* | XL |
| *CHRNE* | AR | *OCA2* | AR |
| *CLCN1* | AR | *OTC* | XL |
| *CLRN1* | AR | *PAH* | AR |
| *CNGB3* | AR | *PCDH15* | AR |
| *COL7A1* | AR | *PKHD1* | AR |
| *CPT2* | AR | *PLP1* | XL |
| *CYP11A1* | AR | *PMM2* | AR |
| *CYP21A2* | AR | *POLG* | AR |
| *CYP27A1* | AR | *PRF1* | AR |
| *CYP27B1* | AR | *RARS2* | AR |
| *DHCR7* | AR | *RNASEH2B* | AR |
| *DHDDS* | AR | *RPGR* | XL |
| *DLD* | AR | *RS1* | XL |
| *DMD* | XL | *SCO2* | AR |
| *DYNC2H1* | AR | *SLC19A3* | AR |
| *ELP1* | AR | *SLC26A2* | AR |
| *ERCC2* | AR | *SLC26A4* | AR |
| *EVC2* | AR | *SLC37A4* | AR |
| *F8* | XL | *SLC6A8* | XL |
| *F9* | XL | *SMN1* | AR |
| *FAH* | AR | *SMPD1* | AR |
| *FANCC* | AR | *TF* | AR |
| *FKRP* | AR | *TMEM216* | AR |
| *FKTN* | AR | *TNXB* | AR |
| *FMO3* | AR | *TYR* | AR |
| *FMR1* | XL | *USH2A* | AR |
| *FXN* | AR | *XPC* | AR |
| *G6PC* | AR | | |

# Appendix C ACOG-Recommended Genes

## Appendix Table 2 ACOG-Recommended Genes

| Condition | Gene Name | Inheritance Pattern |
|---|---|---|
| Familial Hyperinsulinism | *ABCC8* | AR |
| Medium-chain acyl-CoA Dehydrogenase Deficiency | *ACADM* | AR |
| Canavan Disease | *ASPA* | AR |
| Maple syrup urine disease type 1A | *BCKDHA* | AR |
| Maple syrup urine disease type 1B | *BCKDHB* | AR |
| Bloom Syndrome | *BLM* | AR |
| Cystic Fibrosis | *CFTR* | AR |
| Smith-Lemli-Opitz Syndrome | *DHCR7* | AR |
| Familial Dysautonomia | *ELP1* | AR |
| Fanconi anemia C | *FANCC* | AR |
| Fragile X Syndrome | *FMR1* | XL |
| Glycogen Storage Disease Type 1A | *G6PC* | AR |
| Galactosemia Type I | *GALT* | AR |
| Guacher Disease | *GBA* | AR |
| α-thalassemia | *HBA1* | AR |
| | *HBA2* | AR |
| β-thalassemia | *HBB* | AR |
| Sickle Cell Anemia | | |
| Tay-Sachs Disease | *HEXA* | AR |
| Mucolipidosis type IV | *MCOLN1* | AR |
| Phenlyketonuria | *PAH* | AR |
| Spinal Muscular Atrophy | *SMN1* | AR |
| | *SMN2* | AR |
| Neimann-Pick disease type A | *SMPD1* | AR |
| Joubert Syndrome | *TMEM216* | AR |

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