California Prenatal Screening Program Provider Handbook Addendum, April 2024

Screening for sex chromosome aneuploidies (SCAs), also known as X and Y chromosome variations, through the PNS Program

As of April 2024, the California Prenatal Screening (PNS) Program has added to its screening panel the most common SCAs, also known as X and Y chromosome variations, using cell-free DNA (cfDNA) screening. In this document, the term SCA will be used henceforth. SCAs are genetic conditions that involve an atypical number of sex chromosomes. Aneuploidies can occur due to errors during meiosis, resulting in extra or missing sex chromosomes.

Adding SCAs to the California PNS panel is in keeping with the American College of Medical Genetics and Genomics (ACMG) publication from December 2022 that "strongly recommends" offering noninvasive prenatal screening for SCAs, in addition to trisomy 21, 18, and 13.

I.The SCAs Screened

The California PNS Program will screen for the four most common SCAs which are Turner syndrome (XO), Klinefelter syndrome (XXY), Trisomy X (XXX) and XYY.

For screenings through the PNS Program, mosaic aneuploidies cannot be distinguished.

The four SCAs screened for:

1. **Turner syndrome (XO):** Turner syndrome can lead to various physical and fertility conditions, such as short stature, ovarian dysfunction, and cardiac defects. Pregnancies carrying a fetus with Turner syndrome have a high incidence of miscarriage.

   Management of Turner syndrome may include the use of steroids coupled with growth hormones in childhood and puberty, to increase final adult height. Cardiac problems associated with Turner syndrome are an ongoing concern and may eventually require surgery. The success rate of treatment for cardiac problems is very high.

2. **Klinefelter (XXY):** Klinefelter syndrome can result in reduced fertility, tall stature, gynecomastia, and other physical and developmental differences.

   Management for Klinefelter syndrome may begin with early intervention services, which may include speech, occupational, physical, or developmental therapy, and educational assistance as soon as needs are identified. Androgen replacement therapy in childhood, allows for development of masculine secondary sex characteristics.

3. **Trisomy X (XXX):** Trisomy X often goes undiagnosed as it may not cause noticeable symptoms. However, some individuals may experience learning difficulties, delayed speech and motor skills, and an increased risk of delayed puberty and slightly increased risk of seizures.

   Management for trisomy X may begin with early intervention services, which may include speech, occupational, physical, or developmental therapy, and educational assistance starting as soon as needs are identified.

4. **XYY:** Most individuals with XYY syndrome do not display any distinctive physical features or developmental issues. However, some may have slightly taller stature and an increased risk of learning difficulties or behavioral issues.

   Management for XYY may begin with early intervention services, which may include speech, occupational, physical, or developmental therapy, and educational assistance starting as soon as needs are identified.

Klinefelter syndrome (XXY), Trisomy X (XXX), and XYY have similar behavioral and emotional difficulties and include an increased risk for developmental delays, speech language disorders, social emotional difficulties, and cognitive impairments.

These treatment options as discussed above, are not an exhaustive list and serve as general guidelines for providers offering both prenatal and postnatal care. For all these syndromes, providers should consult the guidelines of Fetal Medicine Foundation (FMF), the Society of Maternal Fetal Medicine (SMFM) or other recognized organizations that focus on the field of maternal-fetal health. A screen or even a diagnosis based on the genetics results alone does not mean that there will be symptoms in all cases. Not all individuals who screen positive or are diagnosed based on confirmatory tests will go on to have symptoms associated with SCA conditions.

II. Educating pregnant individuals

Provider responsibility

Terminology

The California PNS Program uses the term **"X and Y chromosome variations"** in pregnant individual health education. Disability rights advocates have found the term "sex chromosome aneuploidy" to be confusing and stigmatizing. "X and/or Y chromosome variations" is technically more accurate but cumbersome. Community members, providers, and disability rights advocates collaborated in workshops with PNS Program staff to enhance understanding on terminology used by people affected by SCAs.

The PNS Program also uses the terminology, **"an increased chance of a genetic condition or birth defect"** instead of "a screen positive result" with pregnant individuals. Providers are encouraged to use the same terminology with individuals to be consistent.

Communicating about the PNS Program

Providers are obligated to give pregnant individuals information about the California PNS Program. Once pregnant individuals have received pertinent PNS program information, an informed choice on whether they want to participate in prenatal screening, through the voluntary PNS Program can be made. If the pregnant individual chooses prenatal screening through the California PNS Program, it will include screening for SCAs. Pregnant individual must sign the consent form as with the current program.

Prescreening education

When explaining SCAs, with pregnant individuals, one key aspect to emphasize is the wide range of presentations associated with SCAs, which can vary from mild to severe cases. By highlighting this variability, you can help pregnant individuals understand that the effects of SCAs may differ significantly among individuals. In addition to SCAs variability, the topics of *Fetal Sex and Follow Up Diagnostic Services* should be discussed with pregnant individuals that are voluntarily choosing to participate in the PNS program.

Providers are obligated to tell pregnant individuals that SCA screening may not be as accurate when compared to the other genetic conditions and birth defects the PNS Program screens for (trisomy 21, 18, 13, and Neural Tube Defect).

If screening finds an increased chance of SCAs, pregnant individuals need to understand only diagnostic testing will provide a clear answer.

Fetal sex

Pregnant individuals can choose cfDNA screening but **opt out** of being informed about the predicted sex of the fetus. If the pregnant individual has a screen-positive result, it is likely that they will be informed of the sex of their fetus since individual SCAs are usually unique to either females or males. Pregnant individuals should be informed before screening that if they receive a screening result that shows an increased chance for SCAs, they may be told the sex of the fetus.

Follow-up diagnostic services

Pregnant individuals should know a critical difference between the California PNS Program, and the commercial cfDNA screening companies is the inclusion of follow-up services. If prenatal screening through the PNS Program shows an increased chance of SCAs in the fetus, the PNS Program offers follow-up services at no additional cost at a state-approved Prenatal Diagnosis Center (PDC). These services include genetic counseling, ultrasound exam, and diagnostic testing (chorionic villus sampling {CVS} or amniocentesis).

Sharing a screen-positive result with pregnant individuals

The PNS Program always recommends diagnostic tests to confirm a screen-positive result or any other result that indicates increased risk. These additional tests may provide more information about the specific condition and its potential impact.

It is important to reiterate that the symptoms and severity of SCAs, can vary widely between individuals. Genetic testing, medical evaluation, and appropriate management by healthcare professionals are critical for diagnosis, treatment, and support for individuals with these conditions.

SCAs do not usually cause any obvious symptoms early in childhood, and even the later onset symptoms may be difficult to spot.

Children in elementary or secondary school may present with language delay, learning disabilities, or behavioral problems. The older child or adolescent may have symptoms discovered during an endocrine evaluation for delayed or incomplete pubertal development.

Some SCAs may be diagnosed when adults are evaluated for infertility or breast malignancy.

Intersex

Intersex refers to individuals who have physical or biological characteristics that do not fit strictly within male or female categories. These variations can arise from a variety of factors, including differences in hormonal, gonadal, or anatomical development. Intersex conditions can occur due to a range of genetic, hormonal, or environmental factors.

Understanding the specific relationship between intersex and SCAs involves recognizing that some intersex individuals may have an SCA as an underlying cause of their intersex traits. SCAs can result in intersex variations, as the presence of atypical chromosomal configurations can impact the development of reproductive organs, secondary sexual characteristics, and hormone levels. It is important to note that not all intersex variations are caused by SCAs, and not all individuals with SCAs are intersex.

III. PNS Program Process

Placing screening orders

As with the current program, providers will place orders for the screening panel including SCAs through the CalGenetic Portal.

Clinical providers should know that the primary difference with the addition of SCAs to the cfDNA panel, will be seen on the patient result mailers.

Getting results

Screening results will appear similar to current PNS Program mailer result text.

- **cfDNA SCA Screen-Positive** – There is an increased risk for an SCA, and the pregnant individual is authorized for referral to a state-approved PDC.
- **cfDNA SCA Screen-Negative** – No increased chance for a SCA, no follow-up authorized.
- **SCA Inconclusive** – Sample unable to be analyzed, see below for more information.

Inconclusive Result

An "inconclusive result" instead of "no call result" is the terminology used for SCAs. SCA "inconclusive results" will not be authorized for redraw as is a "no call result" for autosomal genetic conditions screened by the PNS Program (e.g., trisomy 21, 18, and 13). The reason for an SCA inconclusive result is not always due to low fetal fraction. Empirically, inclusive results are not as likely to resolve to a positive or negative result with repeated testing.

The pregnant individual with an inconclusive result through the PNS Program will be eligible for follow-up at a state-approved PDC. These screening results will be differentiated from atypical and indeterminate findings. The testing lab will send these findings in the lab comments.

For these atypical and indeterminate findings, the PNS Program will also authorize a referral for follow-up services at a PDC.

Low fetal fraction affecting the entire cfDNA screening panel will be eligible for a single redraw.

If the testing lab could not obtain results for trisomy 21, 18, and 13 due to low fetal fraction or other specimen inadequacy, then SCA results will not be reported. The pregnant individual may be eligible for redraw/retest.

Screening eligibility

SCA and twin gestations

SCA detection via cfDNA screening in the California PNS Program is only available for monozygotic twins. SCA screening is not available for multiple gestation of two (dizygotic twins) or more fetuses. Maternal plasma analyzed with cfDNA has shown that the circulating fetal DNA from both placentas can vary leading to inaccurate results. Dizygotic twin pregnancies may proceed through the PNS Program but can only receive results for T21, T18, T13, and fetal sex.

Some pregnancy conditions are not eligible for cfDNA screening through the PNS Program, including those with:

- Fetal reduction
- Fetal loss
- A diagnosis of a fetal chromosome or structural anomaly
- Solid organ transplant or bone marrow transplant for the pregnant individual
- Malignancy in the pregnant individual

Fees

If pregnant individuals have Medi-Cal or private health insurance and choose to participate in the California PNS Program, their fees will be covered, with only a few exceptions.

Effective July 1, 2024, the fees are $344 for cfDNA screening and $85 for maternal serum alpha-fetoprotein (MSAFP) screening.

About 9 out of 10 program participants do not pay for the prenatal screening themselves. Medi-Cal or private health insurance must cover the program fees with exceptions for self-insured employers and out-of-state health plans. There is no co-payment, co-insurance, deductible, or any other form of cost sharing, required of covered families.