Disorders of Sex Development – Overview
Disorders of sex development (DSDs) occur when sex development does not follow the course of typical male or female patterning. Types of DSDs include congenital development of ambiguous genitalia, disjunction between the internal and external sex anatomy, incomplete development of the sex anatomy, and abnormalities of the development of gonads (such as ovotestes or streak ovaries) (1). Sex chromosome anomalies including Turner syndrome and Klinefelter syndrome as well as sex chromosome mosaicism are also considered to be DSDs.

DSDs can be caused by a wide range of genetic abnormalities (2). Determining the etiology of a patient’s DSD can assist in deciding gender assignment, provide recurrence risk information for future pregnancies, and can identify potential health problems such as adrenal crisis or gonadoblastoma (1, 3).

Sex chromosome aneuploidy and copy number variation are common genetic causes of DSDs. For this reason, chromosome analysis and/or microarray analysis typically should be the first genetic analysis in the case of a patient with ambiguous genitalia or other suspected disorder of sex development. Identifying whether a patient has a 46,XY or 46,XX karyotype can also be helpful in determining appropriate additional genetic testing.

Abnormal/Ambiguous Genitalia Sequencing Panel
Our Abnormal/Ambiguous Genitalia Sequencing Panel includes sequence analysis of 72 genes associated with both syndromic and non-syndromic DSDs. This comprehensive panel evaluates a broad range of genetic causes of ambiguous or normal genitalia, including conditions in which abnormal genitalia are the primary physical finding as well as syndromic conditions that involve abnormal genitalia in addition to other congenital anomalies.

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<th>Abnormal/Ambiguous Genitalia Sequencing Panel (72 genes)</th>
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<td>AKR1C2</td>
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46,XY Disorders of Sex Development/Complete Gonadal Dysgenesis Sequencing Panel
The 46,XY Disorders of Sex Development/Complete Gonadal Dysgenesis (46,XY DSD/CGD) Sequencing Panel includes sequence analysis of 26 genes associated with disorders of sex development (DSD) or complete gonadal dysgenesis (CGD) in patients with a 46,XY karyotype. Individuals with 46,XY CGD (also known as 46,XY sex reversal) have a 46,XY karyotype in conjunction with normal female external genitalia, “streak” gonads, absent sperm production, and presence of a uterus and fallopian tubes. 46,XY CGD has been associated with mutations or copy number variations in several genes, including SRY, DHH, NR5A1, and SOX9 (with campomelic dysplasia) (2).
46,XY DSDs are characterized by one or more of the following in an individual with a 46,XY karyotype: ambiguous genitalia with mild to severe penoscrotal hypospadias, dysgenetic gonads, reduced/absent sperm production, and Müllerian structures that range from absent to presence of a uterus and fallopian tubes (4). Example of genes associated with 46,XY DSDs include AKR1C2, CYB5A, GATA4, and SRD5A2. In addition, a 46,XY DSD phenotype may be syndromic, as in Mowatt-Wilson syndrome (5), X-linked lissencephaly-2 (6), ATR-X syndrome (7), and Smith-Lemli-Opitz syndrome (8).

| AKR1C2 | CYB5A | HCCS | SOX9 |
| AMH   | CYP11A1 | HSD17B3 | SRD5A2 |
| AMHR2 | CYP17A1 | LHCGR | SRY |
| AR    | DHCR7   | MAMLD1 | WT1 |
| ARX   | DHH     | MAP3K1 | ZFPM2 |
| ATRX  | DYNC2H1 | NR5A1  |  |
| B3GALTL | GATA4 |  |  |

**46,XX Disorders of Sex Development/Complete Gonadal Dysgenesis Sequencing Panel**
The 46,XX Disorders of Sex Development/Complete Gonadal Dysgenesis (46,XX DSD/CGD) Sequencing Panel includes 9 genes associated with disorders of sex development (DSD) or complete gonadal dysgenesis (CGD) in patients with a 46,XX karyotype. A range of phenotypes may be observed in patients with 46,XX DSD/CGD, from mullerian aplasia and hyperandrogenism (9) or ovarian dysgenesis (10), to adrenal hyperplasia with overvirilization. There are syndromic forms of 46,XX DSDs, including Peters-Plus syndrome (11) and WAGR syndrome (12). 46,XX complete gonadal dysgenesis (also referred to as 46,XX sex reversal, 46,XX true hermaphroditism, or ovotesticular DSD) may be observed in patients with presence of the SRY gene (13), in patients with copy number variations in SOX3 (14), or due to mutations in other genes, such as RSPO1 (15). Please note that due to the presence of a pseudogene, the CYP21A2 gene is not included on this panel.

| B3GALTL | HCCS | RSPO1 |
| CYP11B1 | NR5A1 | WNT4 |
| CYP19A1 | PSMC3IP | WT1 |

**Test methods:**
Comprehensive sequence coverage of the coding regions and splice junctions of all genes in the panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp.

**Abnormal or Ambiguous Genitalia Sequencing Panel (72 genes sequencing)**
- Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
- Cost: $4000
- CPT codes: 81407
- Turn-around time: 8 weeks

**Note:** We cannot bill insurance for the above test.

**46,XY DSD/CGD Sequencing Panel (26 genes sequencing)**
- Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
- Cost: $3000
- CPT codes: 81407
- Turn-around time: 8 weeks

**Note:** We cannot bill insurance for the above test.
46,XX DSD Sequencing Panel (9 genes sequencing)

Sample specifications: 3 to 10 cc of blood in a purple top (EDTA) tube
Cost: $2000
CPT codes: 81407
Turn-around time: 8 weeks

Note: We cannot bill insurance for the above test.

Results:
Results, along with an interpretive report, will be faxed to the referring physician. Additional reports will be provided as requested. All abnormal results will be reported by telephone.

For more information about our testing options, please visit our website at dnatesting.uchicago.edu or contact us at 773-834-0555.

References:

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS’ NEEDS