UNIVERSITY OF CALIFORNIA,
IRVINE

Temporal trends in cosmetic surgery in infancy for patients born with a disorder of sex development

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Genetic Counseling

by

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2017

DEDICATION

To my parents,
Cesar and Tota Menendez

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ACKNOWLEDGMENTS

Thank you to my thesis committee, Dr. M. Anne Spence, Dr. June-Anne Gold, and Dr. Eric Vilain, to Pam Flodman, to the UCI and UCLA data extraction team, to Dr. Elizabeth Hahn-Menendez, to the faculty in the Genetic Counseling Master's program at UCI, and to the class of 2017.

ABSTRACT OF THE THESIS

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University of California, Irvine, 2017

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Disorders of sex development (DSD) are congenital conditions in which chromosomal, gonadal, or anatomic sex development is atypical. Standard medical practice was to offer cosmetic genital surgery to DSD patients with genital ambiguity, however controversy persists surrounding early surgical intervention. This study reviews patients with DSD and ambiguous genitalia, in the ten years after the consensus meeting on disorders of sex development. A retrospective review of medical records from UCLA and UCI of children with DSD born between 2006-2016 was performed to determine if a decrease in surgery rates was associated with an increase in genetic testing. The eligible cohort of 167 patients was divided into 2 groups: patients born between 2006-2011 and patients born between 2012-2016. A significant decrease in surgery rate over time was observed, however there was not a significant increase in genetic testing over time. With a more robust evaluation of medical records, the observed trend of decrease in surgery and expected trend of increase in genetic testing is likely to be seen.

INTRODUCTION

When a child is born, most of the time there is not an issue when a physician assigns a sex to the child, it can be determined by looking at the child's genitals and palpating for gonads, testicular or ovarian. Most of the time this child's sex chromosomes will correspond to the typical presentation of XY for male and XX for female. However, for children born with a disorder of sex development (DSD), immediately identifying the child's sex is more complicated. The infant at birth may have ambiguous genitalia, or genitalia that does not correspond to their sex chromosomes, gonads, or other biological indicators associated with sex, male or female.

Disorders or differences of sex development are conditions in which the chromosomal, gonadal or phenotypic sex are atypical; atypical external genitalia are often the presenting feature [1]. In the newborn period, DSD is most often diagnosed because of ambiguous genitalia. The incidence of DSD with ambiguous genitalia is estimated at 1 in 4500 live births [1]. In a significant portion of DSD cases, it is not possible to identify a causative mutation or identifying a diagnosis, making genetic counseling difficult and potentially inhibiting optimal treatment. Despite many advancements in technology and the genetic basis of human sex development, a specific molecular diagnosis is found in only approximately 20% of cases of DSD [2].

Many terms are used, often interchangeably, to describe a person's biological sex assignment (Table I1). The term sex refers to a person's biological status and is typically categorized as male, female, or intersex (i.e., atypical combinations of features that usually distinguish male from female). There are a number of indicators of biological sex, including sex chromosomes, gonads, internal reproductive organs, and external genitalia. Gender refers to the

attitudes, feelings, and behaviors that a given culture associates with a person's biological, assigned at birth, sex [3]. The term gender is a socially construed concept, which takes into account the way a given culture has defined appropriate boundaries of male and female behavior. A person's gender develops from their biological status and what is reinforced by their cultural standards. When a child is born, it does not have a gender, but it does have a sex based on the biological profile and combination of elements listed above. When a child with a DSD is born, their sex can be difficult to assign. Physicians are charged with collecting all the information available on the child, chromosome analysis, and functionality of gonads by endocrine studies, both to determine the etiology of the disorder but also to be able to assign the child a sex, with the hope that the child's gender will match the sex assigned. Once the sex is assigned, then the question of how to manage the ambiguous genitalia must be addressed.

Many terms have been used historically to describe individuals with DSD, such as 'intersex,' 'pseudohermaphroditism', 'hermaphroditism', and 'sex reversal', and most of these terms are now considered pejorative and offensive by patients [2]. However, there are individuals with DSD who identify with the term intersex and reject the paradigm of binary sex categories in the human body. These individuals view the term DSD as a negative label that implies that atypical sex anatomy must be corrected with surgical or hormonal interventions [4]. Intended to be more inclusive, DSD describes a broader range of issues, including differences in sex differentiation, sex chromosome abnormalities, and embryonic anomalies of the genital or reproductive tracts. This umbrella term was proposed and defined as a congenital condition in which development of chromosomal, gonadal, or anatomical sex is atypical (Table I1). Currently, the literature of the medical community uses DSD when reporting clinical studies or focusing on biological mechanisms of sex development.

Table I1. Definitions

Sex	Sex (Sex assigned at birth) is typically assigned at birth (or before during ultrasound) based on the appearance of external genitalia. When the external genitalia are ambiguous other indicators (e.g., internal genitalia, chromosomal and hormonal sex) are considered to assign a sex with the aim of assigning a sex that is most likely to be congruent with the child's gender identity. For most people, gender identity is congruent with sex assigned at birth.
Gender	Refers to the attitudes, feelings and behaviors that a given culture associates with a person's biological sex. Behavior that is compatible with cultural expectations is referred to as gender-normative; behaviors that are viewed as incompatible with these expectations constitute gender non-conformity.
Gender Dysphoria	Discomfort or distress related to incongruence between a person's gender identity, sex assigned at birth, gender identity, and/or primary and secondary sex characteristics.
Intersex	A historically used term to describe ambiguous genitalia.
Disorder of sex development	A congenital condition in which development of chromosomal, gonadal, or anatomical sex is atypical.

[1,3]

Historical Perspective of Management of DSD

Prior to the mid-20th century, medical management for DSD was guided by the belief that an individual's "true" sex was revealed by examination of the internal (gonadal) anatomy. In the mid-1950s, John Money and his colleagues at Johns Hopkins Hospital and School of Medicine observed adults with hermaphroditism and determined that regardless of sex, gender identity was consistent with sex of rearing [5]. Challenging the "true sex" notion, Money and his colleagues

developed the “optimal gender policy,” which proposes the brain is gender neutral at birth with gender evolving in response to experience, social learning, and hormone influences. Early sex assignment followed by cosmetic genital surgery were essential for the gender outcome to be accepted and successful for an individual’s psychological health. Early surgical intervention was necessary to ensure that an individual was socialized consistently with their assigned sex, regardless of gonadal or chromosomal outcome. One radical practice that was later highly criticized was the recommendation that children with penises judged to be too small for intercourse be reassigned female.

The notion that a child is born gender neutral has been contested by recent advances in sex differentiation in utero. It is now known that prenatal androgens participate in the differentiation process, by masculinizing the genitalia during steroid-sensitive periods of brain development. Some experimental research involving other mammalian species has shown that androgens also influence the development of regions of the brain responsible for sex differences in behavior [6].

After technological advances improved the understanding of sex differentiation, gonadal histology and later sex chromosomes became a major factor in assigning sex. Surgical advancements in the ability to normalize the appearance of genitalia, while still retaining sexually functional organs with the potential for fertility remain important factors in decision making in sex assignment. Contemporary management of DSD continues to use early genital surgery and early sex assignment to try to achieve the correctly assigned sex at birth and the hope to limit gender dysphoria as the child develops. More recently, parental input into medical management, including gender assignment and the impact of surgery on adult sexual sensitivity are being considered [7].

The Consensus Statement

In 2005, more than 50 international experts in the field of DSD, including the Lawson Wilkins Pediatric Endocrine society (renamed the Pediatric Endocrine Society in 2010) and the European Society for Paediatric Endocrinology, convened in Chicago and developed a consensus statement. A consensus statement is a general agreement or an accord which recognizes that the objections of a minority of participants in the process should be resolved as far as is practicable [8]. The consensus reached in 2005, published in 2006, was an agreement on the general principles of management of people with DSD. The statement acknowledged that sex assignment cannot solely be based on genital appearance but needs to include consideration of the diagnosis, surgical options, need for lifelong replacement therapy, the potential for fertility, views of the family, and circumstances relating to cultural practices [1]. The Statement made the following recommendations:

- Nomenclature should be revised to reflect careful consideration of the concerns of patients.
- Management must be carried out by an experienced multidisciplinary team, including mental health staff with expertise in DSD.
- All individuals should receive a sex assignment, but only after expert evaluation.
- Only surgeons with specific training/expertise should undertake surgical procedures.
- Feminizing surgery should only be considered in cases of severe virilization.
- Emphasis of surgical intervention in all cases should be on functional outcome rather than strictly on cosmetic appearance.

- Open communication with patients/families is essential and participation in decision-making is encouraged [1].

The following is a list of factors felt to be important in adult outcomes of DSD and is currently used to guide management [9]:

Probable adult gender identity
    Deference to psychosocial factors when outcome unpredictable
Psychosocial factors
    Family dynamic
    Social circumstance
    Cultural pressures
Fetal CNS androgen exposure
Specific diagnosis, if discernible
External genital development
    Ambiguous, female, male
    Surgical options for functional repair
Anticipated quality of sexual function
    Ability to preserve neurovascular unit for sensitivity
    Anatomy of postsurgical genitalia
Fertility potential
    Assisted or unassisted
    Presence of germ cells in ovarian or testicular tissue
    Uterine and other Mullerian-derived internal female development
    Male internal ductal and accessory gland development
Psychosocial risk for parents and individual
    Acceptable assignment considering cultural/social situation
    Inappropriate assignment leads to gender dysphoria
    Separate gender identity from gender role and sexual orientation
Minimize physical risk
    Gonadal cancer vs. preserving germ cells
    Renal and urinary tract damage

The 2006 Consensus Statement categorized different types of DSD based on karyotype results: 46,XX DSD, 46,XY DSD and sex chromosome DSD. Within each of these groups, the condition may occur due to a disorder of gonadal development, a disorder of androgen synthesis, or a disorder of androgen action.

46,XX DSD group

The 46,XX DSD is described as disorders related to androgen synthesis or action [1], as well as disorders of gonadal development. Disorders related to androgen synthesis is the most prevalent form of DSD, and over 90% are attributed to congenital adrenal hyperplasia (CAH). Current surgical practice is clitoroplasty, and is usually only recommended for severe virilization and careful attention is paid to preserving the neurovascular bundles, responsible for sensation in the clitoris [10]. The Consensus conference suggested female assignment for those with 46,XX CAH, since 95% develop female gender identity [11].

There are other rare types of 46,XX DSD including ovotesticular DSD, XX testicular DSD and gonadal dysgenesis. In ovotesticular DSD, one or both of the gonads are a mix of ovarian and testicular tissue. Biopsy is often required to make this diagnosis and sex of rearing is more complex as questions of potential fertility and child bearing come into play. 46,XX testicular DSD occurs most often when there had been a translocation of SRY or another gene that may be responsible for testicular development. External genitalia are typically virilized [10]. There is no consensus regarding surgical management for this group.

For those with a 46,XX karyotype, ovarian differentiation, and moderate genital ambiguity, the most likely outcome and therefore gender assignment is female [12]. There is usually no gender issue in this group, except for severely masculinized 46,XX individuals. However, Houk and Lee (2010) propose that a male gender assignment be considered for the 46,XX infant with male genitalia, because there is a high risk of gender dysphoria in those patients assigned female, regardless of karyotype. Male assignment in this case does not necessitate any surgical reassignment that may cause impairment of genital sensitivity. However

typically assignment of virilized 46,XX DSD patients is usually female when ovaries and internal organs are present, regardless of the extent of virilization of the external genitalia [13].

46,XY DSD Group

The 46,XY DSD is a heterogeneous group typically with variable degrees of under-virilization. Those with disorders of gonadal development can also be seen in 46,XY DSD and include ovotesticular DSD, congenital anorchia and gonadal dysgenesis [14]. The 46,XY group also includes disorders of testosterone synthesis (such as 17β-hydroxysteroid dehydrogenase-III deficiency (17β-HSD3)), as well as disorders of testosterone action (such as partial androgen insensitivity syndrome (PAIS) or complete androgen insensitivity syndrome (CAIS)) or testosterone metabolization (such as 5α-reductase type-2 deficiency). Most 46,XY DSD that do not have a definitive molecular diagnosis are often categorized as PAIS. Children with a 46,XY karyotype, testicular function, partially virilized external genitalia, androgen exposure *in utero* have a most likely outcome of male gender, and a male gender assignment would likely be encouraged [13]. Male assignment is recommended for those with 5α-reductase deficiency, because 60% later identify themselves as male, and for 17β-HSD3 deficiency, because more than 50% later switch to male gender identity [11].

Sex Chromosome DSD

Sex chromosome DSD is defined as absence or addition of sex chromosomes or mosaicism. Examples are Turner syndrome (45,X0), Kleinfelter syndrome (46,XXY), or mosaicism. The most common form of mosaicism is mixed gonadal dysgenesis (45X, 46XY). Mixed gonadal dysgenesis has a high rate of ambiguous genitalia [10], including asymmetrical genitalia: one side containing a scrotum containing a gonad and the other side containing labia

majora and a streak gonad, with or without testicular and/or ovarian tissues [10]. In this situation, physicians have the question of gender assignment, timing of surgery, and making a decision to keep or remove the gonads. Table I2, adapted from Pasterski et al., 2010, outlines the various diagnoses of DSD [15].

Cosmetic Surgery Recommendations

The Consensus Statement does not provide detailed recommendations for the indications, timing, procedure or evaluation of outcome for DSD surgery. However, a few guidelines were provided. The Statement recommended that genital surgery for a child raised as a female only be considered in cases of severe virilization. Surgery of the clitoris should not be performed solely for reasons of cosmetic appearance [1], however whether or not to perform clitoroplasty for children with a large clitoris raised as female remains controversial. For children with severe virilization, genital surgery should be considered 'in infancy.' Recommendations for masculinizing genitoplasty are vague within the Consensus Statement. The goal of surgical treatment for ambiguous genitalia is to allow the development of adequate external genitalia and the removal of organ structures that are opposite to the assigned sex. Other aims of surgery include restoring the genitalia so that penetrative intercourse (male or female) is possible, facilitate reproduction when possible, and avoid stigmatization due to abnormal genitalia [12]. Historically, recommendations for timing of surgery was before 2 years of age, which is the time when the child becomes aware of his/her genitals and gender. The current rates of surgery in the United States among children with atypical genitalia are unknown, as there have been no multicenter, prospective studies on this topic [16].

Table I2: Nomenclature for DSD

Sex Chromosome DSD	**46,XY DSD**	**46,XX DSD**
A. 47,XXY (Kleinfelter syndrome and variants)	A. Disorders of gonadal testicular development	A. Disorders of gonadal (ovarian) development
B. 45,X (Turner syndrome and variants)	1. Complete or partial gonadal dysgenesis (e.g., *SRY, SOX9, SFI, WT1, DHH*, etc.)	1. Gonadal dysgenesis
C. 45,X/46,XY (missed gonadal dysgenesis	2. Ovotesticular DSD	2. Ovotesticular DSD
D. 46,XX/46,XY (chimerism)	3. Testis regression	3. Testicular DSD (e.g., *SRY* +, dup *SOX9, RSP01*)
	B. Disorders in androgen synthesis or action	B. Androgen excess
	1. Disorders of androgen synthesis	1. Fetal
	a. LH receptor mutations	a. 3 β-hydroxysteroid dehydrogenase (*HSD3B2*)
	b. Smith-Lemli-Opitz syndrome	b. 21-hydroxylase (*CYP21A2)*
	c. Steroidogenic acute regulatory protein mutations	c. P450 oxidoreductase (*POR)*
	d. Cholesterol side-chain cleavage (*CYP11A1*)	d. 11 β-hydroxylase (*CYP11B1*)
	e. 3 β-hydroxysteroid dehydrogenase (*HSD3B2*)	e. Glucocorticoid receptor mutations
	f. 17 β-hydroxysteroid dehydrogenase (*HSD17B3*)	2. Fetoplacental
	g. 5 α-reductase 2 (*SRD5A2*)	a. Aromatase deficiency (*CYP19*)
	2. Disorders of androgen action	b. Oxidoreductase deficiency (*POR*)
	a. Androgen insensitivity syndrome	3. Maternal
	b. Drugs and environmental modulators	a. Maternal virilizing tumors (e.g., luteomas)
	C. Other	b. Androgenic drugs
	1. Syndromic associations of male genital development (e.g., cloacal anomalies; Robinow, Aarskog, hand-foot-genital popliteal pterygium)	C. Other
	2. Persistent Müllerian duct syndrome	1. Syndromic associations (e.g., cloacal anomalies)
	3. Vanishing testis syndrome	2. Müllerian agenesis/hypoplasia (e.g., *MURCS)*
	4. Isolated hypospadias (*CXorf6*)	3. Uterine abnormalities (e.g., *MODY5*)
	5. Congenital hypogonadotropic hypogonadism	4. Vaginal atresia (e.g., KcKusick-Kaufman)
	6. Cryptorchidism (*INSL3, GREAT*)	5. Labial adhesions

Reasons against cosmetic surgery in infancy

Some clinicians and DSD advocacy groups are against performing cosmetic surgery in infancy for individuals with DSD, citing poor outcomes of surgery. Some research has shown that early genitoplasty can affect a person's sexual satisfaction [17, 18], and substantial pain due to repeated procedures in infancy/childhood may affect quality of life. Some advocacy groups and some physicians now recommend delaying surgery to allow the patient to participate in the decision-making regarding surgical intervention [19]. Parents have the legal right to make decisions on medically necessary procedures for their infants, however, cosmetic genital surgeries are not medically necessary. Others may argue that it could be medically necessary. Some DSD activists have argued that genital surgery should be delayed until the child can legally assent [20].

Another reason stated against early cosmetic surgery on infants with DSD is the high rate of gender dysphoria among individuals with DSD. Gender dysphoria is defined as discomfort or distress related to incongruence between a person's sex assigned at birth and their gender identity (Table I1). Gender dysphoria occurs more frequently in individuals with DSD than in the general population [11]. In another review study, mean incidence of gender dysphoria rates associated with each DSD are 63% for 5α-RD2 deficiency, 57% for 17β-HSD3 deficiency, 20% for PAIS, 5% for CAIS, 39% for cloacal exstrophy, 100% for penile agenesis, 29% for mixed gonadal dysgenesis, 12.5% for ovotesticular DSD, and 44% for other diagnoses [21]. These data indicate that the rate of gender dysphoria and gender change is higher among individuals with DSD than the rate of transgenderism in the non-DSD population [22]. Because of the high rate of gender dysphoria, some argue that genital surgery should be delayed until the gender identity in the individual with DSD is confirmed, to avoid additional genital reversal surgeries.

Reasons endorsing cosmetic surgery in infancy

While some argue against early surgery for individuals with DSD, other clinicians argue for it. In contrast to previously mentioned arguments, some DSD specialists argue that early surgery is thought to be psychologically beneficial to the child because surgery to 'normalize' the appearance of genitalia aids in gender development and lessens the stigma of the disorder. Another assumed psychological benefit of early surgery is that the infant would not remember the trauma associated with surgery [23]. Additionally, some outcome studies performed on individuals with DSDs report satisfaction with long-term results of genitoplasty, both in appearance and functionality [24, 16, 23].

Early surgery has been justified by physicians treating newborns with DSD as a strategy to relieve parental distress. When parents find out about a newborn's genital ambiguity, they are likely thrust into a situation of high anxiety. A study of parents' recollections of their coping with a new DSD diagnosis found that high levels of emotional distress are correlated with increased cognitive confusion and understanding of the DSD diagnosis [15]. Parents feel pressure to quickly arrive at decisions regarding gender assignment and genital surgery to avert stigmatization [25]. A false sense of urgency and fear of stigmatization can push parents to agree to genital surgery without adequately understanding the long-term consequences, such as gender dysphoria [26].

DSD's are even collectively rare conditions. Parents of a newborn with a DSD may have no knowledge of the condition, or understanding of sex determination or differentiation especially when atypical development occurs. Parents' confusion about the condition is a contributing factor to stress and anxious symptoms for the parents of a child with DSD [26].

Some parents have felt that surgery will relieve their distress and address other concerns that they have with regards to their child's condition. However, study of parents' understanding of the relationship between the biology of sex development (molecular diagnosis and genital phenotype) and psychosexual differentiation (gender development) remains a deficit in the literature [27].

Molecular Diagnosis of DSD

Specific molecular diagnoses are only identified in approximately 20% of cases of DSD [2]. The majority of DSD cases cannot be explained with genetic analysis. However, with the increased development of genetic diagnostic tools, more children with DSD should receive more precise diagnoses. Increased genetic testing and diagnoses will lead to a better understanding of DSD conditions and DSD causative genes, and better genetic counseling which can provide information about recurrence risks and reproductive options to families.

Parents with children afflicted with a genetic disease place high value on obtaining a genetic diagnosis [4]. In a study that reviews parental perspectives of the benefits of genetic testing in children with congenital deafness, parents identified the primary benefit of genetic testing as increased understanding of their child's condition [28], and this increased understanding may lead to better psychological outcomes for parents.

Hypothesis

Since the Consensus Statement was published in 2006, progress in genomic analysis has allowed for an increase in genetic testing for patients with DSD. Increased testing may also lead to an increase in a diagnosis of the DSD with a specific gene alteration. Once a parent is given a

diagnosis, they may be able to understand how their child was born with ambiguous genitalia, and put an end to the "diagnostic odyssey" that many parents suffer when they do not have an explanation for their child's condition. Having a diagnosis for their child with a DSD may ease a parent's discomfort and anxiety. A confirmatory genetic diagnosis can be used to assist in the decision for sex assignment, and decrease the desire for early cosmetic surgeries. When a genetic evaluation is performed on a DSD patient, it increases the possibility that a diagnosis will be obtained, relieving part of the parental anxiety and uncertainty, and the need to rush to surgical choices made by physicians treating the infant with DSD and their parents. An early genetic diagnosis may be critical for the clinical management and life-long choices for the patient with DSD. It could also be detrimental if it forces physicians or the child's parents in a particular direction, either sex assignment or for surgical intervention.

The hypothesis of this study is that an increase in molecular diagnostic tools is associated with a decrease in early surgery. The aim of this study is to demonstrate the diagnostic approach of clinicians, such as the use of molecular genetic technology, and identify any associations with increased use of diagnostic tools with a decrease in early surgery. The secondary aims of the study are to quantify how many patients with DSD received early cosmetic surgeries and how many patients received diagnoses over the course of 10 years, since the Consensus Statement was published. The cohort of eligible patients will be divided into two groups, those born between 2006-2011, and those born between 2011-2016. The second group should have an increased use of diagnostic tools and a decrease in early surgery.

METHODS

This study was designed to assess changes in surgery patterns for children born with a DSD. DSD is a broad term that encompasses congenital conditions in which development of chromosomal, gonadal or anatomical seen is atypical. In the newborn period, DSD is most often diagnosed because of ambiguous genitalia. An application for human subjects research project (HS#2017-3562) was registered with the UC Irvine Institutional Review Board (UCI IRB) as Exempt from Federal regulations in accordance with 45 CFR 46 101. The research protocol was completed and evaluated by the appropriate IRB committee in the Human Research Protections Department of the UC Irvine Office of Research. The protocol was approved under exempt review category 4 on June 27, 2017.

The study approach used de-identified data abstracted from the electronic medical records from 2 institutions, University of California, Irvine (UCI), and University of California, Los Angeles (UCLA). Participants from UCI and UCLA were identified using the diagnosis codes in Appendix A. By necessity, as data were explored, additional variables were defined and/or calculated from the extracted data. A timeline for data acquisition is provided in Appendix B. Details from de-identified charts were obtained using ICD-9, ICD-10 and CPT codes, including diagnosis, karyotype or other genetic testing, sex assignment, number of DSD related surgeries (defined as the number of exposures to general anesthesia for DSD-related exploratory or surgical procedures). Eligibility requirements included the following:

Inclusion criteria:

- Born between 1/1/2006 – 12/31/2016
- Diagnosed with a DSD (see Appendix A)

Exclusion criteria:

- Patients who were diagnosed after 3 years of age were excluded.

- Male and female patients who were diagnosed with a non-specific congenital anomaly of the genitalia without a specific diagnosis were excluded. An example of a non-specific ICD-9 code is 752.9 – Other specified anomalies of genital organs. If a patient was only diagnosed with this code and no other code, the etiology of the anomaly of genital organs in this case may or may not be caused by a DSD, but without further information available at this time, this example patient would be excluded from the eligible cohort.
- Male and female patients who were only diagnosed with CAH or adrenogenital disorders without any other specified or unspecified anomaly of the genitals were excluded. Females with CAH who are less severely affected may not present with ambiguous genitalia. Males have no signs of CAH at birth [29].
- Male patients with unspecified hypospadias, distal hypospadias, or penile/balanic hypospadias were excluded. Distal hypospadias is not considered by all practitioners to be a DSD [30]. An unspecified hypospadias may be proximal, but without further information available at this time, these patients have been excluded from the eligible cohort.
- Patients coded with DNR or palliative care were excluded. These patients had many congenital anomalies and would most likely not survive past infancy. Thus, the parents of these patients were most likely not considering cosmetic genital surgery.

The range from birth to 3 years of age was chosen because the according to the American Academy of Pediatrics, the period from 6 weeks to approximately 15 months of age generally seems to be the optimal time for surgery, with regard to emotional development. The period from 24 to 36 months of age is also time when the trauma of surgery is relatively less difficult. [31]. The ages at diagnosis presented here are the ages of the patients when they first presented to a clinic at either UCI or UCLA. It is possible the patient was diagnosed at an earlier age at a different institution.

The following demographic data were collected:

- Race and ethnicity
- Assigned sex at birth
- Birth year
- Age of patient at diagnosis
- Age of patient at procedure

The reasons for exclusion are detailed in Table M1. Out of the 347 patients identified at UCI, 19 patients were eligible for the study. Out of 1,347 patients identified at UCLA, 167 patients were eligible for the study. There was a total of 186 patients eligible for the study.

Table M1. Eligible and non-eligible patients

	UCI	UCLA	TOTAL
Eligible	19	167	186
Reasons for exclusion			
Unspecified abnormality of genitalia	257	547	804
Unspecified or distal hypospadias	60	572	632
Coded for Palliative care or DNR status	0	5	5
Males with CAH	5	14	19
Females with CAH but no other genital abnormalities	1	4	5
Diagnosed beyond 3 years of age	5	38	43
TOTAL	347	1,347	1,694

Analyses were conducted using IBM SPSS version 24. Data were manually entered an Excel spreadsheet. To ensure accuracy of data entry, a 25% sample was randomly selected, and data were reviewed for error. About a 3% error rate was discovered and corrected, which reduced the error rate to approximately 2% over the overall cohort. Data were examined for missing information. Because UCI and UCLA are institutions located 45 miles apart, it is possible that there was overlap between eligible patients at UCI and eligible patients at UCLA. The demographics and diagnoses of the cohort of eligible patients from UCI was compared to that of the UCLA eligible cohort. No overlapping patients were identified via demographic and diagnoses data, however, it is still possible that some of these patients overlap, if a patient received different diagnoses at the two institutions, or if they were racially and ethnically categorized differently between the two institutions.

The cohort of eligible patients was divided into two groups: Patients born between 2006-2010, and those born between 2011-2016. Individuals with birthdates prior to 01/01/2006 were not available electronically, and there would have been much difficulty in obtaining their medical records. To evaluate whether surgeries decreased over time and genetic testing increased over time, the cohort was arbitrarily divided into 2 birth date categories: category 1

included birth dates between 01/01/2006 and 12/31/2011 (118 individuals); and category 2 included birth dates between 01/01/2012 and 12/31/2016 (68 individuals). Category 1 includes the 6 years just after the publication of the Consensus Statement. Category 2 contains the 5 years closest to present day. Similar data analyses conducted by Adam et al. (2012) categorize birth categories in a similar manner [32]. This study reviewed prenatal genetic testing and ambiguous genitalia, dividing the eligible patients into different cohorts based on birth year.

Demographic variables containing assigned sex and race are presented in Table M2. To analyze race categories, new variables were created to group together some of the race categories. White, non-Hispanic and Hispanic categories were not altered. Black, Asian, and Native-American categories were very small, and thus were grouped together with Other/Multiple Races. Association between categorical variables including assigned sex, diagnosis-type, and race/ethnicity were analyzed using Pearson chi-square tests as well as Fisher's exact test with a significance level of 0.05. Continuous variables including age and birth year were compared using chi-square tests. Chi-square tests were also used to compare surgery rates and genetic testing in the two time-periods. A distribution of genetic testing is presented in Table M3. The "unspecified" genetic testing category refers to a CPT code labeled "Cyto-Molecular Report." It is unclear if this refers to a specific genetic test being performed, and thus is excluded from further analyses in the Results section. Additional variables were created that combined the genetic testing into 2 groups: One including karyotype, microarray, and FISH probe, representing genetic tests for deletions and duplications; and another group including single gene/panel testing and exome testing, representing genetic tests for sequence variation. A distribution of diagnoses divided by timeframes across sites is presented in Table M4, Table M5, and Table M6, respectively. Because UCI did not have any recorded surgeries,

this site was left out of the analyses, and justification for doing so can be found in the Discussion section. Figures containing all birth years, surgery rates, and genetic testing are presented in Figure M1, Figure M2, and Figure M3 respectively. The figures were divided by site. Nominal p values were reported; no correction was made for multiple comparison.

Table M2. Sex and Race, Frequency, Percentages (*N*=186), both sites combined

	2006-2011		2012-2016	
Assigned Sex at birth	**N**	**%**	**N**	**%**
Male	96	81.4	53	77.9
Female	22	18.6	15	22.1
TOTAL	**118**	**100.0**	**68**	**100.0**
Race				
White, non-Hispanic	37	31.4	21	30.9
Hispanic	34	28.8	28	41.2
Black	8	6.8	2	2.9
Asian	8	6.8	6	8.8
Native American	1	0.8	0	0.0
Other	9	7.6	6	8.8
Pt Refused/Unknown	21	17.8	5	7.4
TOTAL	**118**	**100.0**	**68**	**100.0**

Table M3. Types of Genetic testing, Frequency, Percentages, both sites*

	UCI				UCLA			
	2006-2011		2012-2016		2006-2011		2012-2016	
Genetic Test	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Karyotype	1	100.0	6	42.9	4	14.8	7	28.0
Microarray	0	0.0	8	57.1	3	11.1	6	24.0
Single Gene/Panel	0	0.0	0	0.0	0	0.0	3	12.0
FISH probe	0	0.0	0	0.0	0	0.0	1	4.0
Exome	0	0.0	0	0.0	1	3.7	3	12.0
Unspecified	0	0.0	0	0.0	19	70.4	5	20.0
Total number of tests performed	**1**	**100.0**	**14**	**100.0**	**27**	**100.0**	**25**	**100.0**

*One individual patient may have received more than one type of genetic testing

Table M4. Diagnoses, Frequency, Percentages, both sites combined

	2006-2011		2012-2016	
Diagnosis	**N**	**%**	**N**	**%**
Indeterminate sex, unspecified	30	22.9	22	25.0
Vaginal agenesis	2	1.5	1	1.1
Micropenis	29	22.1	23	26.1
Adrenogenital disorders	8	6.1	7	8.0
Androgen insensitivity	4	3.1	1	1.1
Scrotal Transposition	13	9.9	6	6.8
Proximal Hypospadias	30	22.9	23	26.1
Epispadias	15	11.5	5	5.8
Total	131	100.0	88	100.0

Table M5. Diagnoses, Frequency, Percentages, UCLA patients

	2006-2011		2012-2016	
Diagnosis	**N**	**%**	**N**	**%**
Indeterminate sex, unspecified	30	23.4	13	18.1
Vaginal agenesis	2	1.6	1	1.4
Micropenis	26	20.3	19	26.4
Adrenogenital disorders	8	6.3	6	8.3
Androgen insensitivity	4	3.1	1	1.4
Scrotal Transposition	13	10.2	5	6.9
Proximal Hypospadias	30	23.4	22	30.6
Epispadias	15	11.7	5	6.9
Total	128	100.0	72	100

Table M6. Diagnoses, Frequency, Percentages, UCI patients

	2006-2011		2012-2016	
Diagnosis	**N**	**%**	**N**	**%**
Indeterminate sex, unspecified	0	0.0	9	56.1
Vaginal agenesis	0	0.0	0	0.0
Micropenis	3	100.0	4	25.0
Adrenogenital disorders	0	0.0	1	6.3
Androgen insensitivity	0	0.0	0	0.0
Scrotal Transposition	0	0.0	1	6.3
Proximal Hypospadias	0	0.0	1	6.3
Epispadias	0	0.0	0	0.0
Total	3	100.0	16	100

Figure M1. Number of DSD patients seen at UCLA (*N*=167) and number of early cosmetic surgeries performed between birth years 2006-2016.

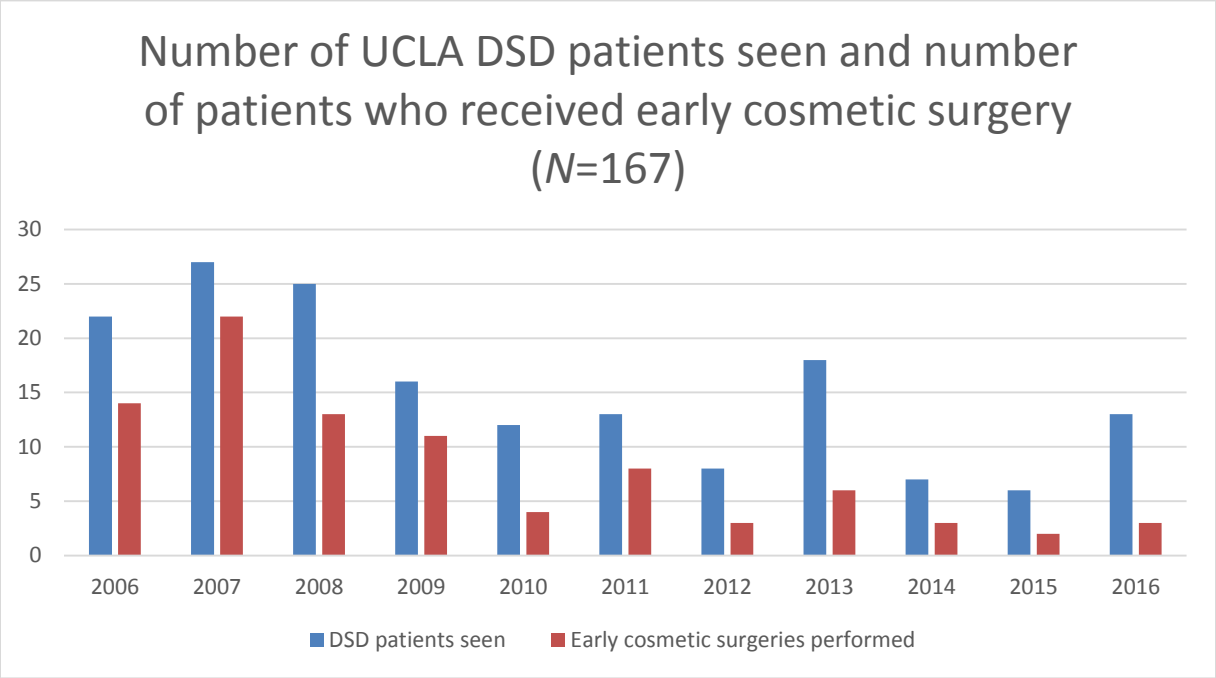


Figure M2. Number of DSD patients seen at UCI (*N*=19) and number of early cosmetic surgeries performed between birth years 2006-2016.

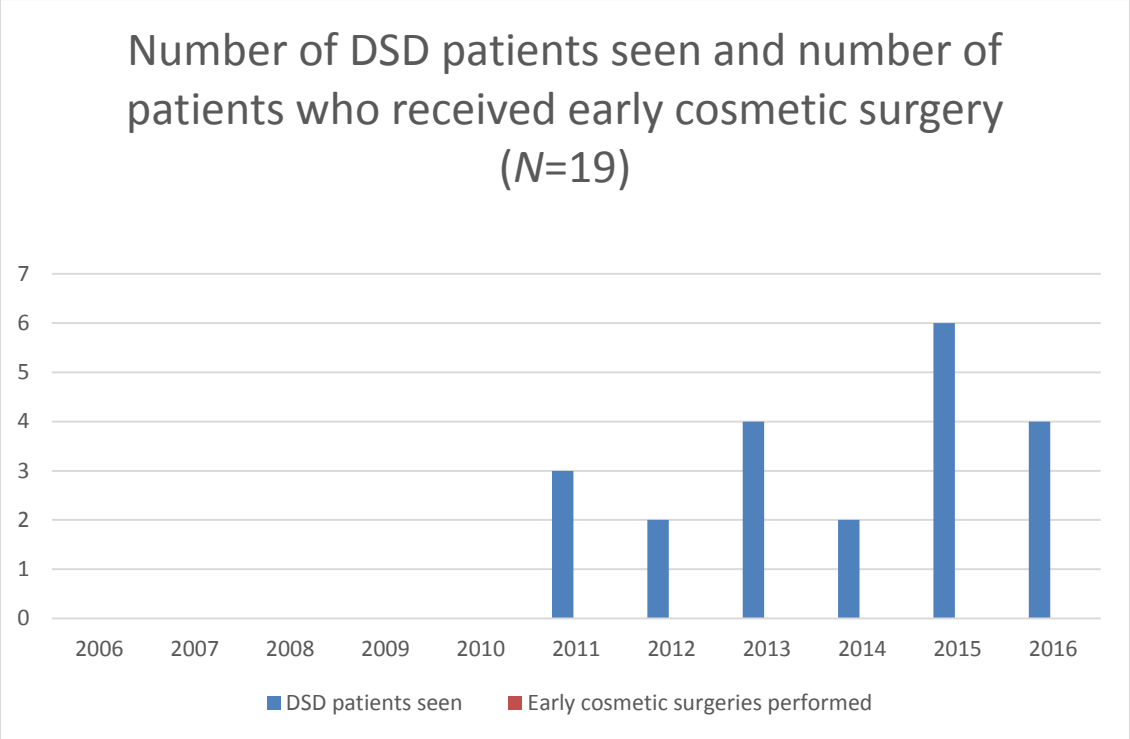
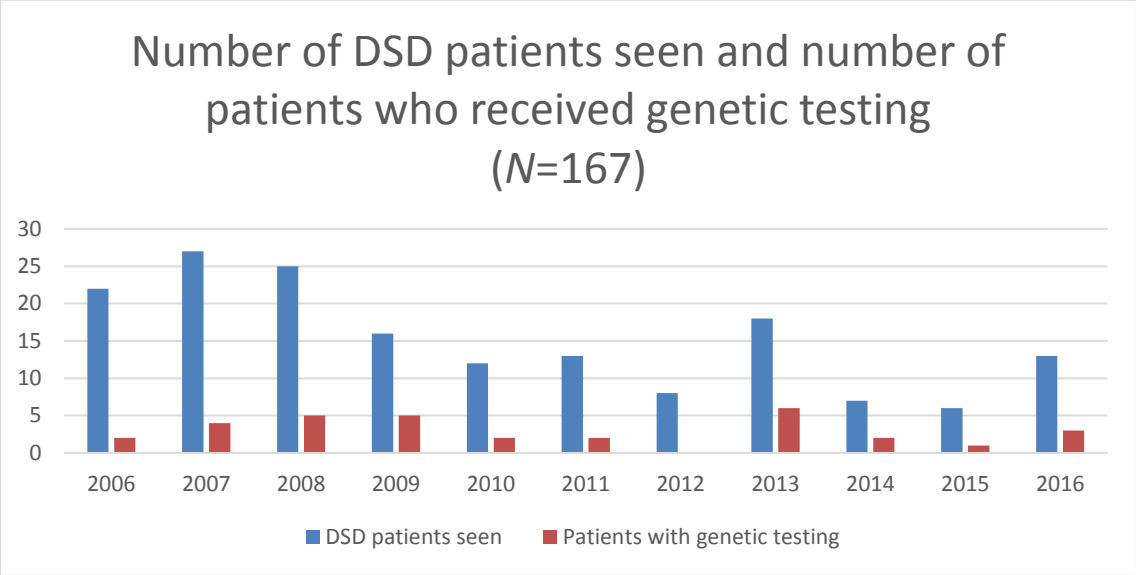


Figure M3. Number of DSD patients seen at UCLA (*N*=167) and number of UCLA patients who received genetic testing between the birth years 2006-2016.



RESULTS

The data comparing eligible patients to excluded patients across all sites and timeframes were presented in Table M1. Because there was a decrease in patients across timeframes, additional analysis was performed to investigate the distribution of exclusion criteria across timeframes (Table R1). The purpose of the additional analyses was to determine if there was a uniform decrease in the number of eligible and excluded patients across time periods, and that this pattern was not exclusively seen in the eligible cohort. The eligible cohort had approximately two thirds of the diagnosed patients in the first time-period, and approximately one third of the diagnosed patients in the second time-period. Two of the reasons for exclusion was an unspecified abnormality of genitalia, and an unspecified or distal hypospadias. Again, for both reasons of exclusion, approximately two-thirds of the patients with this diagnosis were in the first time-period, and one-third of the patients were in the second time-period, indicating a homogeneous cohort of eligible and excluded patients based on diagnoses. Statistical analysis also indicates a homogeneous cohort.

Table R1. Test of association between time-period and Inclusion/Exclusion groups, UCLA patients

	UCLA				
	2006-2011	%	2012-2016	%	Total
Eligible	115	68.9	52	31.3	167
Reason for exclusion					
Unspecified abnormality of genitalia	356	65.1	191	34.9	547
Unspecified or distal hypospadias	349	61.0	223	39.0	572

$X^2(2)=4.16$, $p=0.12$

The distribution of DSD patients seen at both sites and the number of early cosmetic surgeries performed between birth years 2006-2016 is presented in Figure M1. The data were

stratified into 2 time-frames, 2006-2011 and 2012-2016. A table categorizing the data by assigned sex and race and a test of association is presented in Table R2. For sex assignment, the same frequency was seen in patients assigned male and patients assigned female. Statistical significance was not needed since the frequencies are almost identical. Because some of the race categories had very few participants, they were grouped together into the Other category (as described in the Methods section). The statistical analysis shows these groups are homogeneous.

Table R2. Sex and Race by Time-Period, UCLA patients*

	2006-2011		2012-2016		Test of Association
Assigned Sex at birth	**N**	**%**	**N**	**%**	
Male	93	80.9	42	80.8	
Female	22	19.1	10	19.2	
TOTAL	**115**	**100.0**	**52**	**100.0**	
Race					
White, non-Hispanic	37	39.4	19	40.4	$X^2(2)=0.02$, p=0.99
Hispanic	32	34.0	16	34.0	
Other	25	26.6	12	25.6	
TOTAL	**94**	**100.0**	**47**	**100.0**	

*Removed 26 patients who refused/unknown race category data for the purposes of analysis.

The distribution of genetic testing at both sites across both timeframes can be seen presented in Table M3. Additional analyses were presented in Table R3 for patients at UCLA. There was an increase in the frequency of the types of testing across time periods, but not of statistical significance. A large number of unspecified genetic testing was removed from this analysis because it was unknown data.

Table R3. Types of Genetic testing by Time-Period, UCLA patients*

	2006-2011		2012-2016		Test of Association
Genetic Test	**N**	**%**	**N**	**%**	p=0.26**
Karyotype, Microarray, FISH probe combined	7	87.5	14	70.0	
Single Gene/Panel, Exome combined	1	12.5	6	30.0	
Total number of tests performed	**8**	**100.0**	**20**	**100.0**	

*Removed 24 unspecified genetic testing for the purposes of analysis.
**Fisher's exact test was utilized instead of Pearson's chi-square test because of small sample size.

An analysis of the change in cosmetic surgery rates across timeframes is presented in Table R4. The surgery rate decreased across time periods. In the first time-period, approximately two-thirds of the patients had surgery. In the second-time period, only one-third of the participants had surgery. This finding was statistically significant.

Table R4. Did the percent of patients who had cosmetic genital surgery change in the second half of the timeframe? (UCLA)

	2006-2011		2012-2016	
	N	**%**	**N**	**%**
Had surgery	72	62.6	17	32.7
Did not have surgery	43	37.4	35	67.3

$X^2(1)=12.88$, p=0.0003

An analysis of the change in genetic testing rates across timeframes is presented in Table R5. While the frequency of patients who received genetic testing increased slightly, this was not a statistically significant finding.

Table R5. Did the percent of patients who had genetic testing change in the second half of the timeframe? (UCLA)

	2006-2011		2012-2016	
	N	**%**	**N**	**%**
Had Genetic testing	22	19.1	12	23.1
Did not have Genetic testing	93	80.9	40	76.9

$X^2(1)=0.34$, p=0.56

An analysis of the association between assigned sex and decision to have cosmetic genital surgery for patients born between 2006-2011 is presented in Table R6. A higher proportion of males had surgery than females. Approximately two-thirds of the male patients had surgery, and about 40% of the female patients had surgery. This finding was statistically significant.

Table R6. Is there an association between sex assignment and decision to have cosmetic genital surgery for patients born between 2006-2011? (UCLA)

	Had surgery		Did not have surgery		Total	
	N	**%**	**N**	**%**	**N**	**%**
Female	9	40.9	13	59.1	22	100.0
Male	63	67.7	30	32.3	93	100.0

$X^2(1)=5.47$, p=0.02

An analysis of the association between assigned sex and decision to have cosmetic genital surgery for patients born between 2012-2016 was performed in Table R7. Similar to the patients born between 2006-2011, more male than female patients had surgery, however this finding was not statistically significant. In addition, the rate of surgery decreased for both males and females.

Table R7. Is there an association between sex assignment and decision to have cosmetic genital surgery for patients born between 2012-2016? (UCLA)*

	Had surgery		Did not have surgery		Total	
	N	**%**	**N**	**%**	**N**	**%**
Female	1	10.0	9	90.0	10	100.0
Male	16	38.1	26	61.9	42	100.0

p=0.08

*Fisher's exact test was utilized instead of Pearson's chi-square test because of small sample size.

An analysis of the association between assigned sex and decision to have genetic testing for patients born between 2006-2011 was performed in Table R8. More female patients than male patients had genetic testing performed during this timeframe, however this finding was not statistically significant.

Table R8. Is there an association between sex assignment and decision to have genetic testing for patients born between 2006-2011? (UCLA)

	Had genetic testing		Did not have genetic testing		Total	
	N	**%**	**N**	**%**	**N**	**%**
Female	6	31.6	13	68.4	19	100.0
Male	14	16.9	69	83.1	83	100.0

$X^2(1)=2.12$, p=0.15

An analysis of the association between assigned sex and decision to have genetic testing for patients born between 2012-2016 can be seen performed in Table R9. More male patients than female patients had genetic testing during this timeframe, which differs from the previous timeframe, however this finding was not statistically significant.

Table R9. Is there an association between sex assignment and decision to have genetic testing for patients born between 2012-2016? (UCLA)*

	Had genetic testing		Did not have genetic testing		Total	
	N	**%**	**N**	**%**	**N**	**%**
Female	2	20.0	8	80.0	10	100.0
Male	10	23.8	32	76.2	42	100.0

p=0.32

*Fisher's exact test was utilized instead of Pearson's chi-square test because of small sample size.

DISCUSSION

When a child is born, the first question asked by family, friends, colleagues, and acquaintances is, "Is it a boy or a girl?". For parents of a child born with a DSD, this question can be distressing and anxiety-inducing, because they often do not have the skills or vocabulary to accurately or succinctly put into words their child's condition. In addition, only in some parts of society is it acceptable to have a gender-variant (transgendered) child, and there is not yet a safe place in all of society to accept a sex-atypical infant. The notion of binary sex assignment is so entrenched in society, that the idea of parents answering the question with, "I'm having a baby," and leaving the sex assignment unanswered is not yet an acceptable response to this question.

In 2005, a group of international experts on DSD convened and developed a Consensus Statement on the management of patients with DSD. The resulting recommendations were published in 2006. On the subject of cosmetic surgery in infancy, the guidelines called for a more conservative approach to genital surgery. The goal of this study was to determine whether a decrease in cosmetic genital surgery over time since the Consensus Statement was associated with an increase in genetic diagnostic tools over time. It was hypothesized that there would be a decrease in cosmetic genital surgery and an increase in genetic diagnostic tools. With the help of data abstraction teams at both sites, de-identified data were pulled first from UCI, then from UCLA. Upon retrieval of the first set of data, it was clear that more data were needed from the patients already identified, as data from additional patients, because the complete set of CPT codes was not seen.

The data abstraction team from UCLA agreed to provide additional CPT codes, procedure codes, and all ICD-9 and ICD-10 diagnostic codes, however, due to a change in software used for electronic records, all data requests at UCI were put on hold. In short, the data from UCI provided patients demographic information, incomplete diagnostic data, some genetic testing data, and incomplete surgery data. From the data that were available, no cosmetic genital surgery was performed at UCI, which raised concerns about the accuracy of the UCI data. With a small sample size from UCI (N = 19), it is possible that no surgeries were performed at UCI. The patients born with ambiguous genitalia may have been referred to another hospital in the area, or even to UCLA, where a DSD clinic exists. Because the UCI data did not include any surgery, and the purpose of the study was in part to quantify the surgery rates of patients, the UCI data could not be analyzed with the data from UCLA.

The remaining UCLA data were grouped into eligible and ineligible cases, and divided by timeframe for analysis. Within the cohort, there was a noticeable difference in the number of patients diagnosed in each timeframe, with more patients being diagnosed in between 2006-2011 than in 2012-2016. A portion of the ineligible patients was stratified into two timeframes and quantified to see if a similar pattern arose in comparison to the eligible cohort (Table R1). The number of the excluded patients due to an unspecified abnormality and excluded patients because of unspecified or distal hypospadias also showed a decrease between the timeframes, although not significantly when compared to the eligible patients. There was a similar pattern of increased frequency of diagnoses in the first timeframe compared to the second timeframe. However, there was no significant difference between the time-periods in the frequency of ineligible and eligible diagnoses. The increase in overall diagnoses in the first timeframe may

possibly be attributed to the inception of the UCLA Center for Gender-Based Biology in 2007 [33], a multi-disciplinary clinic which specializes in DSD.

The data were then characterized by the demographic variables of sex assignment, race, diagnoses, and genetic testing. Testing for homogeneity between the time periods with respect to these demographic variables were performed (Table R2 and R3). The distribution of sex assignment across time periods was almost identical, indicating that there was not a change in the frequency of males and females being diagnosed the cohort was homogeneous based on sex assignment. The distribution of race categories was also very similar, and there was no significant change in the number of patients being diagnosed with a DSD across racial groups. For these demographic variables, the eligible cohort was similar across timeframes.

Testing Hypotheses

There was a significant change in the number of patients who had cosmetic genital surgery between the timeframes, showing a decrease over time. However, there was not a statistically significant change in the number of patients who had genetic testing (Table R4 and R5). Therefore, there was no association found between the decrease of cosmetic genital surgery and the decision to have genetic testing. When compared to assigned sex, more female patients than male patients had genetic testing in 2006-2011, but in 2012-2016, more male patients had genetic testing. Males and females were not significantly different in either time-period. The variation in statistical significance in sex assignment and genetic testing across time periods may be due to a small sample size, because of exclusion criteria.

Perhaps some of the patients who were diagnosed with “unspecified congenital anomaly of the genitalia” had some form of genetic testing, but were excluded from this analysis because

of their diagnosis. It is not clear from this ICD-9 code if a patient with this diagnosis has a DSD or not. Without access to the patient's identifiable chart, a full assessment of diagnoses for each patient was not available. The same is true for genetic testing. It is possible that a patient had genetic testing outside UCLA and the results of the testing were available for review by the team treating the patient. Access to the patient's full medical record would be critical to analyzing the impact of a molecular genetic diagnosis to the decision to have surgery in infancy.

Another significant finding in the data is the association between sex assignment and the decision to have genital surgery for patients born between 2006-2011. In the first timeframe, there was a significant difference in the frequency of males who had surgery compared to the females who had surgery. A higher percentage of males had surgery, in comparison to females. In the second timeframe, this same pattern was identified, however was not statistically significant. These data show a uniform pattern to the decrease in surgery over time with respect to sex assignment, and this similarity supports the significance of the decrease in surgery rates overall, reflecting an overall change in practice.

The decrease in cosmetic genital surgery is a significant finding. It shows that more parents are either waiting until their child with DSD is older, when they can have a more autonomous choice to surgically alter their bodies, or that parents and the patients with DSD are choosing to forgo surgery altogether. One physician who specializes in DSD has noticed the decrease in surgery rates as well. Dr. Eric Vilain, whose work with patients with DSD was featured in Nature in 2016, says that in his experience, more parents are now choosing to delay surgery [34]. The motivating factors for choosing to delay surgery has not yet been systematically researched. One possible factor is the increased attention DSD has gotten in the media. In particular, there was a lawsuit brought against the Medical University of South

Carolina over a cosmetic genital surgery performed on an infant born with a DSD. The patient, referred to as M.C. in the lawsuit, had a feminizing genital surgery performed in 2006, when he was 16 months old, and was assigned female by his medical team. M.C.'s birth parents had put him up for adoption at birth, and at the time of the surgery, M.C. was a ward of the state. When M.C. became older, he identified as male. In 2014, his adoptive parents filed a lawsuit against the doctors who performed the surgery during M.C.'s infancy, charging that the doctors committed medical malpractice by failing to obtain adequate informed consent before performing the surgery [35]. This case garnered national media attention.

The United Nations has made public statements on the surgical treatment of DSD, starting as early as 2011. In a 2013 report, the United Nations special rapporteur on torture noted:

> Children who are born with atypical sex characteristics are often subject to irreversible sex assignment, involuntary sterilization, involuntary genital normalizing surgery, performed without their informed consent, or that of their parents, 'in an attempt to fix their sex,' leaving them with permanent, irreversible infertility and causing severe mental suffering [36].

This attention given to the cosmetic genital surgery of infants with DSD is likely to influence the decision-making of parents and may be the explanation for the decrease in surgery rates across this timeframe; however, the influence of media on parental choices would be difficult to quantify.

The current diagnostic trend for patients with DSD is to perform imaging studies, endocrine testing, and metabolic testing to search for additional phenotypic features that may allow the clinician to narrow the single gene testing that could explain the phenotype. Chromosomal microarray is also used to help diagnose the DSD, however it is not as effective for detecting smaller genetic deletions and duplications. Many patients still do not receive a

clinical diagnosis even after these diagnostic tests are completed. Exome sequencing is advantageous because all genes known to be involved in sex development can be analyzed, and newly discovered genes can be included in analysis. As exome sequencing continues to decrease in cost and turnaround time, more DSD patients will have access to this type of genetic testing in hopes of finding a definitive diagnosis. Once more patients receive definitive diagnoses, it will become easier to provide more practical guidelines based on the unique molecular diagnoses of children with DSD, rather than grouping the guidelines together for all types of DSD.

Limitations of the study

Because this study was a retrospective chart review, there are some limitations. The most important limitation was not having IRB-approved access to the complete patient medical record. Having this access would have provided definitive diagnoses and lab reports of genetic testing if performed at a different institution. The patient data were retrieved from an electronic medical record warehouse, which does not include patients born prior to 2006. If this study had access to medical records prior to 2006, a more robust analysis could have been conducted showing changes in the 10 years before the Consensus Statement was issued compared to the 10 years after the Consensus Statement was published. Additionally, the study was limited to analysis at one site, in part because the data from UCI was incomplete, A retrospective chart review conducted at multiple institutions (including sites that do not have a DSD clinic) may allow for a more generalizable pattern regarding surgery rates and genetic testing.

Areas for future research

Future research should include an IRB-approved study of the complete patient medical record, with access to doctor's notes on severity of the ambiguity of the genitalia, which may or may not influence a parent's decision to have surgery. In addition, parental comprehension of DSD, genetics, and sex differentiation may provide some insight into health literacy and improved health outcomes. For physicians who are involved in the care team of the patient with DSD, the following research is essential: the comfort level with discussing gender and sex issues, and feasibility and support for alternative approaches to sex-atypical patients. This research may provide insight into the quality of support received by parents when they are informed their newborn has a DSD.

Conclusion

This study investigated the rates of cosmetic genital surgery in infants diagnosed with DSDs since the Consensus Statement was published in 2006. It was hypothesized that a decrease in the rate of surgery would be associated with an increase in genetic testing. There was a statistically significant drop in the rate of surgery, but the increase in genetic testing for patients with DSD was not statistically meaningful. With IRB-approved full access to medical charts of patients with DSD, the sample size would increase, and more informative data might arise.

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Appendix A: Inclusion criteria

Original inclusion criteria used at UCI: List of ICD-9 and ICD-10 Codes, CPT Codes, Procedure Codes

ICD-9	**ICD_Description**
255.2	Adrenogenital disorders
259.52	Partial androgen insensitivity
752.0	Congenital anomalies of ovaries
752.4	Anomalies of cervix, vagina, and external female genitalia
752.40	Congenital malformation of female genitalia, unspecified
752.45	Vaginal agenesis
752.49	Other anomalies of cervix, vagina, and external female genitalia
752.64	Micropenis
752.65	Hidden penis
752.69	Other penile anomalies
752.7	Indeterminate sex and pseudohermaphroditism
752.9	Unspecified Congenital anomaly of genital organs
752.90	Congenital malformation of female genitalia, unspecified
752.89	Other specified anomalies of genital organs
758.6	Gonadal dysgenesis
758.81	Other conditions due to sex chromosome abnormality
V13.61	Hypospadias
ICD-10	**ICD_Description**
E34.5	Androgen insensitivity syndrome
E34.50	Androgen insensitivity syndrome, unspecified
E34.51	Complete androgen insensitivity syndrome
E34.52	Partial androgen insensitivity syndrome
N89.5	Stricture and atresia of vagina
N90.6	Hypertrophy of vulva
N90.60	Unspecified hypertrophy of vulva
N90.61	Childhood asymmetric labium majus enlargement
Q53	Undescended and ectopic testicle
Q53.0	Ectopic testis
Q53.00	Ectopic testis, unspecified
Q53.01	Ectopic testis, unilateral
Q53.02	Ectopic testes, bilateral
Q53.1	Undescended testicle, unilateral
Q53.10	Unspecified undescended testicle, unilateral
Q53.11	Abdominal testis, unilateral
Q53.12	Ectopic perineal testis, unilateral
Q53.2	Undescended testicle, bilateral
Q53.20	Undescended testicle, unspecified, bilateral

Q53.21	Abdominal testis, bilateral
Q53.22	Ectopic perineal testis, bilateral
Q53.9	Undescended testicle, unspecified
Q54.0	Hypospadias, balanic
Q54.1	Hypospadias, penile
Q54.2	Hypospadias, penoscrotal
Q54.3	Hypospadias, perineal
Q54.4	Congenital chordee
Q54.8	Other hypospadias
Q54.9	Hypospadias, unspecified
Q55	Other congenital malformations of male genital organs
Q55.0	Other congenital malformations of male genital organs
Q55.1	Hypoplasia of testis and scrotum
Q55.2	Other and unspecified congenital malformations of testis and scrotum
Q55.20	Unspecified congenital malformations of testis and scrotum
Q55.21	Polyorchism
Q55.22	Retractile testis
Q55.23	Scrotal transposition
Q55.29	Other congenital malformations of testis and scrotum
Q55.4	Other congenital malformations of vas deferens, epididymis, seminal vesicles and prostate
Q55.5	Congenital absence and aplasia of penis
Q55.6	Other congenital malformations of penis
Q55.62	Hypoplasia of penis
Q55.64	Hidden penis
Q55.69	Other congenital malformation of penis
Q56	Indeterminate sex and pseudohermaphroditism
Q56.0	Hermaphroditism, not elsewhere classified
Q56.1	Male pseudohermaphroditism, not elsewhere classified
Q56.2	Female pseudohermaphroditism, not elsewhere classified
Q56.3	Pseudohermaphroditism, unspecified
Q56.4	Indeterminate sex, unspecified
Q97.3	Female with 46, XY karyotype
Q97.8	Other specified sex chromosome abnormalities, female phenotype
Q97.9	Sex chromosome abnormality, female phenotype, unspecified
Q98.3	Other male with 46, XX karyotype
Q99.0	Chimera 46, XX/46, XY
Q99.1	46, XX true hermaphrodite
CPT Code	**CPT Code_Description**
00920	Anesthesia for procedures on male genitalia

00932	Anesthesia for procedures on male genitalia; complete amputation of penis
00934	Anesthesia for procedures on male genitalia; radical amputation of penis with bilateral inguinal lymphadenectomy
00938	Anesthesia for procedures on male genitalia; radical amputation of penis with bilateral inguinal and iliac lymphadenectomy
55899	Unlisted procedure male genital system
55970	Intersex surgery male female
55980	Intersex surgery female male
56805	Clitoroplasty intersex state
57335	Vaginoplasty intersex state
58999	Unlisted procedure female genital system nonobstetrical
76870	US scrotum and contents
81228	Cytogenomic constitutional microarray analysis
81229	Cytogenomic constitutional microarray analysis; SNP
81400	MOPATH PROCEDURE LEVEL 1
81401	MOPATH PROCEDURE LEVEL 2
81402	MOPATH PROCEDURE LEVEL 3
81403	MOPATH PROCEDURE LEVEL 4
81404	MOPATH PROCEDURE LEVEL 5
81405	MOPATH PROCEDURE LEVEL 6
81406	MOPATH PROCEDURE LEVEL 7
81407	MOPATH PROCEDURE LEVEL 8
81408	Tier 2 Molecular pathology procedures
81415	Exome sequence analysis
81416	Exome; sequence analysis
81417	Exome; re-evaluation of previously obtained exome sequence
81425	Genome sequence analysis
81426	Genome sequence analysis each comparator genome
81427	Genome re-evaluation
81479	UNLISTED MOLECULAR PATHOLOGY
88261	Chromosome analysis; count 5 cells, 1 karyotype, with banding
88262	Chromosome analysis; count 15-20 cells, 2 karyotypes, with banding
88263	Chromosome analysis; count 45 cells for mosaicism, 2 karyotypes, with banding
88264	Chromosome analysis, analyze 20-25 cells
88267	Chromosome analysis, amniotic fluid or chorionic villus, count 15 cells, 1 karyotype, with banding
88269	Chromosome analysis, in situ for amniotic fluid cells, count cells from 6-12 colonies, 1 karyotype
88280	Chromosome analysis; additional karyotypes, each study

ICD-Procedure Codes	ICD_Description
86.04	Drainage of genitalia skin with drainage device, external approach
86.09	Division of genitalia skin, external approach
86.11	Drainage of genitalia skin, external approach, diagnostic
86.22	Excision of genitalia skin, external approach
86.28	Extraction of genitalia skin, external approach
86.3	Destruction of genitalia skin, external approach
86.59	Repair genitalia skin, external approach
86.63	Replacement of genitalia skin with autologous tissue substitute, full thickness, external approach
86.64	Release genitalia skin, external approach
86.67	Replacement of genitalia skin with nonautologous tissue substitute, full thickness, external approach
86.69	Replacement of genitalia skin with autologous tissue substitute, partial thickness, external
86.74	Transfer genitalia skin, external approach
86.84	Release genitalia skin, external approach
86.89	Reattachment of genitalia skin, external approach

Appendix B: Timeline for data

- 6/29/17: Data requested from UCI Enterprise Data and Analytics Team. Per UCI Enterprise Data and Analytics Team, OMOP scripts were created from the ICD-9 and ICD-10 variables to pull the data.

- 8/15/17: OMOP scripts created at UCI were provided to the UCLA CTSI Biomedical Informatics Program. Scripts were altered and only included the following ICD-9 and ICD-10 codes to identify patients:
    - ICD-9
        - 752.40 - Congenital malformation of female genitalia, unspecified
        - 752.7 - Indeterminate sex and pseudohermaphroditism
        - 752.9 - Unspecified Congenital anomaly of genital organs
        - 758.6 – Gonadal dysgenesis
        - 758.81 - Other conditions due to sex chromosome abnormality
    - ICD-10
        - Q54.8 – Other hypospadias
        - Q56.0 - Hermaphroditism, not elsewhere classified
        - Q56.1 - Male pseudohermaphroditism, not elsewhere classified
        - Q56.2 - Female pseudohermaphroditism
        - Q56.3 - Pseudohermaphroditism, unspecified
        - Q56.4 - Indeterminate sex, unspecified
        - Q96.3 - Mosaicism 45,X/46,XX or XY
        - Q97.3 - Female with 46,XY karyotype
        - Q97.8 - Other specified sex chromosome abnormalities, female phenotype
        - Q97.9 - Sex chromosome abnormality, female phenotype, unspecified
        - Q98.3 - Other male with 46,XX karyotype
        - Q99.0 - Chimera 46,XX/46,XY
        - Q99.1 - 46,XX true hermaphrodite

- 8/21/17: Received data from UCI Enterprise Data and Analytics Team. 347 patients were identified.

- 9/1/17: Received data from UCLA CTSI Biomedical Informatics Program. 178 patients were identified.

- 10/15/17: Requested all CPT codes and procedure codes for 178 patients from UCLA CTSI Biomedical Informatics Program.

- 10/20/17: Received all CPT codes and procedure codes for 178 patients from UCLA. Requested the same information from UCI Enterprise Data and Analytics Team. Due to a scheduled live EPIC launch at UCI, the UCI Enterprise Data and Analytics Team were no longer able to provide any more data.

- 11/2/17: Requested the following additional variables from UCLA CTSI Biomedical Informatics Program:
    - ICD-9
        - 255.2 – Adrenogenital disorders
        - 259.52 - Partial androgen insensitivity
        - 752.45 - Vaginal agenesis
        - 752.49 - Other anomalies of cervix, vagina, and external female genitalia
        - 752.61 - Hypospadias
        - 752.62 - Epispadias
        - 752.64 - Micropenis
        - 752.69 - Other penile anomalies
        - 752.81 – Scrotal Transposition
        - 752.89 - Other specified anomalies of genital organs
        - V13.61 - Personal history of (corrected) hypospadias

    - ICD-10
        - E25.0 - Congenital adrenogenital disorders associated with enzyme deficiency
        - E25.8 - Other adrenogenital disorders
        - E25.9 - Adrenogenital disorder, unspecified
        - E34.52 Partial androgen insensitivity
        - Q52.0 - Congenital absence of vagina
        - Q52.4 - Other congenital malformations of vagina
        - Q52.5 - Fusion of labia
        - Q52.6 - Congenital malformation of clitoris
        - Q52.70 - Unspecified congenital malformations of vulva
        - Q52.71 - Congenital absence of vulva
        - Q52.79 - Other congenital malformations of vulva
        - Q52.8 - Other specified congenital malformations of female genitalia
        - Q52.9 - Congenital malformation of female genitalia, unspecified
        - Q54.0 – Hypospadias, Balanic
        - Q54.1 - Hypospadias, penile
        - Q54.2 – Hypospadias, penoscrotal
        - Q54.3 – Hypospadias, perineal
        - Q54.9 – Hypospadias, unspecified
        - Q55.23 – Scrotal transposition
        - Q55.5 - Congenital absence and aplasia of penis
        - Q55.62 – Hypoplasia of penis
        - Q55.69 - Other congenital malformation of penis
        - Q55.8 - Other specified congenital malformations of male genital organs
        - Q55.9 - Congenital malformation of male genital organ, unspecified
        - Q64.0 - Epispadias
        - Z87.710 - Personal history of (corrected) hypospadias
- 11/13/17 Received data from UCLA, contained 1,169 additional participants.

- Total number of UCLA participants = 1,347 eligible and non-eligible.

- Total number of UCI participants = 347 eligible and non-eligible.

Appendix C: Study Protocol Narrative

PROTOCOL NARRATIVE FOR EXEMPT RESEARCH

University of California, Irvine
Institutional Review Board
Version: January 2010

HS#: 2017-3562
For IRB Office Use Only

Lead Researcher Name: Beatriz Menendez
Study Title: Rates of cosmetic surgery in children born with disorders of sexual development

NON-TECHNICAL SUMMARY

Provide a non-technical summary of the proposed research project. The summary should include a brief statement of the **purpose of the research** and a brief description of the **procedure(s) involving human subjects**. ***This summary should not exceed ¼ page.***

Disorders of sex development (DSDs) are defined as congenital conditions within which the development of chromosomal, gonadal and anatomic sex is atypical. A portion of infants born with DSDs present with ambiguous genitalia, where cosmetic surgery has often been utilized to align the genitalia with the assigned sex. This research study will examine the rates of surgery among infants with DSDs, and try to identify associations between the composition of the medical team and diagnostic techniques with the decision to have surgery performed. The data will be collected with the help of information specialists from three sites within the University of California hospital system: University of California, Irvine; University of California, Los Angeles, and University of California, San Diego. The data will be de-identified before being sent to this study's research team. The de-identified data will then be coded, quantified and analyzed to obtain results for this study. None of the patients will be contacted directly and no protected health information will be collected. De-identified data will not link to subject identifiable data. De-identified data will only be sent from UCLA and UCSD to the study team.

SECTION 1: PURPOSE OF THE RESEARCH

1. Describe the **purpose of the research** project and state the **overall objectives, specific aims, hypotheses** (or research question) and **scientific or scholarly rationale** for performing the study.
2. Clearly identify the **primary outcome(s) and key factor(s) of interest**, as applicable.

Controversy exists regarding the timing of cosmetic surgery for patients with DSDs. A debate exists on whether cosmetic surgery to create more "normal appearing" genitalia is in the child's best interest. Some studies have noted adults with DSDs attributing damaging early surgery to poor sexual function[1,2], and incorrect gender assignment, raising objections to early cosmetic surgery[3,4,5]. Other

studies have shown that early intervention results in minimal impairment in quality of life or gender development and that it relieves parental stress[6,7].

In 2006, the American Academy of Pediatrics issued a consensus statement on the management of DSDs. This statement provided guidelines for the management of DSDs[8]. Indications and timing of surgery were not detailed. These guidelines suggest that evidence for surgery performed for cosmetic reasons in the first year of life is lacking, and recommend that surgery involving genitoplasty be postponed until puberty, when the child with DSD can be involved in decision making, and the gender of the child is more firmly established. Based on this recommendation and the lack of specific guidelines for surgery in the early stages of life, there should be a trend of decreased amount of cosmetic surgeries in the first year of life of children born with DSDs since the year 2006.

Many factors may influence a parent's choice to have cosmetic surgery on their infant born with a DSD. One concern brought up at the Chicago consensus was that each child born with a DSD should have a multidisciplinary team that is responsible for developing a plan for optimal clinical management, diagnosis, gender assignment and treatment options before making any recommendations. Ideally, the multidisciplinary team consists of pediatric subspecialists in endocrinology, surgery, and/or urology, psychology/psychiatry, gynecology, genetics/genetic counselors and neonatology. Surgical decisions are now made within the context of a team and all members of the team, not just specialist surgeons, may be called upon to discuss choices for surgery with parents. If the model of multidisciplinary practice was not utilized for the patient, does that affect the diagnostic approach and treatment decision on early cosmetic surgery on an infant? Is there a correlation between number of pediatric specialists involved during the first year of life of a newborn with a DSD and the decision to have cosmetic surgery?
An increased number of specialists in the multidisciplinary team may lead to an increase in the endocrine, cytogenetic and molecular genetic testing performed on the child, depending on the make-up of the multidisciplinary team. Considerable progress has been made with understanding the genetic basis of human sexual development[9]. Yet a specific molecular diagnosis is identified in only 50% of cases of DSD. Increased testing may also lead to an increase in a diagnosis of the DSD with a specific gene alteration. Once a parent is given a diagnosis, they may be able to understand how their child was born with ambiguous genitalia, and put an end to the "diagnostic odyssey" that many parents suffer when they do not have an explanation for their child's condition. Having a diagnosis may ease a parent's discomfort and anxiety, which in turn can help alleviate a parent's dissatisfaction with the appearance of their child's genitalia, and thus decrease the number of surgeries performed.

This study has three objectives: 1) To quantify the temporal trend of the surgeries performed on infants with DSDs within the first year of life, between the years 2006-2016, 2) To identify if there is an association with the surgery trend and the number of specialists in the multidiscliplinary care team of the infant, and 3) To identify if there is an association with the surgery trend and the number of patients who received a molecular diagnosis via genetic testing.

Citations

1. Callens N, De Cuypere G, Van Hoeke E, T'Sjoen G, Monstrey S, Cools M, Hoebeke P. Sexual quality of life after hormonal and surgical treatment, including phalloplasty, in men with micropenis: A review. J Sex Med. 2013;10:2890-2903.
2. Nordenskjold A, Holmdahl G, Frisen L, Falhammar H, Filipsson H, Thoren M, Janson PO, Hagenfeldt K. Type of mutation and surgical procedure affect long-term quality of life for women with congenital adrenal hyperplasia. J Clin Endocrinol Metab. 2008;93(2):380-386.
3. Diamond M, Garland J. Evidence regarding cosmetic and medically unnecessary surgery on infants. Journal of Pediatric Urology. 2014;10:2-7.
4. Kon AA. Ethical issues in decision-making for infants with disorders of sex development. Horm Metab Res 2015;

47:340-343.
5. Schultzman K, Brinkmann L, Schacht M, Richter-Appelt H. Psychological distress, self-harming behavior, and suicidal tendencies in adults with disorders of sex development. Arch Sex Behav. 2009;38:16-33.
6. Crawford JM, Warne G, Grover S, Southwell BR, Hutson JM. Results from a pediatric surgical centre justify early intervention in disorders of sex development. Journal of Pediatric Surgery 2009;44:413-416.
7. Mouriquand P, Caldamone A, Malone P, Frank JD, Hoebeke P. The EPSU/SPU standpoint on the surgical management of disorders of sex development (DSD). Journal of Pediatric Urology. 2013;10:8-10.
8. Lee PA, Houk CP, Ahmed SF, Hughes IA. Consensus statement on management of intersex disorders. Pediatrics 2006;118:e488.
9. Barseghyan H, Delot E, Vilain E. New genomic technologies: An aid for diagnosis of disorders of sex development. Horm Metab Res. 2015;47:312-320.

SECTION 2: ROLES AND EXPERTISE OF THE STUDY TEAM

List all study team members below.

1. Identify each **member's position** (e.g., Associate Professor, graduate or undergraduate student) and **department**, and describe his or her **qualifications, level of training and expertise.** Include information about relevant licenses/medical privileges, as applicable.
2. Describe each team member's **specific role and responsibility** on the study.
3. **Faculty Sponsors** - list as Co-Researchers and describe their role on the project; include oversight responsibilities for the research study.
4. Explain who will have **access to subject identifiable data**.
5. Indicate who will be **involved in recruitment, informed consent process, research procedures/interventions, and analysis of data.**

Lead Researcher:
Beatriz Menendez, BA
Graduate student in Genetic Counseling in the Department of Pediatrics, Division of Genetic and Genomic Medicine. BA in anthropology from Grinnell College. bmenende@uci.edu (312)636-6950.
Will be collecting de-identified data and performing data analysis.

Co-Researcher(s):

M. Anne Spence, PhD
Professor, Division of Genetic and Genomic Medicine, Department of Pediatrics, UCI;
maspence@uci.edu
-Thesis Mentor, will aid in analysis of data

June-Anne Gold, MD
Associate Professor, Division of Genetic and Genomic Medicine, Department of Pediatrics, UCI;
goldj@uci.edu
-Thesis Mentor, will aid in analysis of data

Kathryn Osann, PhD, MPH
Adjunct Professor, Division of Hematology-Oncology, Department of Medicine, UCI;

kosann@uci.edu -Thesis Mentor, will aid in analysis of data
Research Personnel: none

IMPORTANT TIME SAVER: If requesting Exempt Registration under Category 4 ONLY, complete the non-technical summary, Sections 1-2 and Sections 10-11.

SECTION 3: EXEMPT CATEGORY JUSTIFICATION

If you are requesting Exempt Registration per Category(ies) 1-3 or 5, provide **a brief justification** for why the research **meets each applicable Exempt category**. ***Note:*** *Research involving prisoners is not eligible for Exempt Registration. Also, research involving children may only be Exempt under Category 1; or under Category 2 if the research involves only educational tests or observation without direct interaction by the researchers.*
<Type here>

SECTION 4: RESEARCH METHODOLOGY/STUDY PROCEDURES FOR EXEMPTION

A. Study Design and Procedures

1. Provide a detailed chronological description of all **study activities** (e.g., pilot testing, recruitment, screening, intervention/interaction/data collection, and follow-up) and **procedures**.
    a. Indicate how much **time will be required of the subjects**, per visit and in total for the study.
    b. Indicate the **setting** where each **procedure will take place**/be administered (e.g. via telephone, sent via email, online, classroom). ***Note:*** *If any of the procedures will take place at off-campus location (e.g., educational institutions, businesses, organizations, etc)* ***Letters of Permission*** *are required.*
    c. If a procedure will be completed more than once (e.g., pre and post survey), indicate **how many times** and the **time span** between administrations.
2. If study procedures include collecting **photographs, or audio/video recording**, specify whether any subject identifiable will be collected and describe which identifiers will, if any.
3. Describe how the **subject's privacy will be protected** during the research procedures. ***Note****: This is not the same as confidentiality (see the Privacy and Confidentiality web page).*
4. Be sure to submit **data collection instruments** for review with your e-IRB Application (e.g., measures, questionnaires, interview questions, observational tool, etc.). ***Note:*** *If the instrument is still being developed, submit a draft with this application. The final version of the data collection*

instrument must be submitted to the IRB via an eMOD request before you begin data collection.
<Type here>

IMPORTANT TIME SAVER: Complete Part B ONLY if you are requesting permission to review student academic records.

B. Student Academic Records Review

1. Specify the **types/source of records/data** that will be reviewed by selecting the appropriate bracket(s) below. 2. If you will **manually extract research** data from academic records, upload a **Data Extraction Sheet** when you submit your e-IRB application (i.e. the document used to record the information). **Note:** The application will be considered incomplete until this is submitted.
[ ] School Records (specify): <Type here> **[ ]** Individual level data from an established data repository (specify): <Type here> **[ ]** Other (specify): <Type here>
3. Specify how the **records/data will be obtained**, and whether the data are **publicly available**. 4. Submit a copy of the **School or School District Permission Letter** to access the academic records with your e-IRB Application. ***Note:*** *Since official student records will be accessed for research purposes, the letter of permission must address how Title 34 of the Code of Federal Regulations Part 99 -* ***Family Educational Rights and Privacy Act*** *(FERPA) applies to this research.*
<Type here>
5. Specify how the **data are identified** when they are made available to the study team. Please indicate by marking the appropriate bracket(s) below.
i) **[ ]** No Identifier (i.e., neither the researcher nor the source providing the data can identify a student based upon information provided with the data) ii) **[ ]** Indirect Identifier* (i.e., an assigned code will be kept which could be used by the investigator or the source providing data to identify a student, such as a tracking code used by the source.) iii) **[ ]** Direct Identifier (i.e., student name, address, social security number, academic record number, etc. will be attached to data)

***If ii is checked above,** specify whether the study team will be given access to the code.

[ ] Yes, the study team will have access to the link between the tracking code and subject identities.

[ ] No, the study team will not have access to the link between the code and subject identities.

SECTION 5: SUBJECTS

A. Number of Subjects

1. Indicate the maximum number of subjects to be **recruited/consented** on this UCI protocol. This is the number of potential subjects you may recruit in order to get your sample—not just the number who actually participate in the study.
2. For studies where multiple groups of subjects will be evaluated, please **provide a breakdown per group** (e.g., controls vs. experimental subjects; children vs. adults).
3. For **Mail/Internet surveys** include the number of people directly solicited.
4. For **academic records review**, specify the maximum number of records that will be reviewed to compile the data necessary to address the research question or the maximum number of individuals that will comprise the dataset.

<Type here>

B. Subject Populations

1. Describe the **characteristics** of the proposed subject population. At a minimum include information about the age and gender of the study population.
2. Describe **different subject groups** (e.g., students and teachers) **separately**.

<Type here>

SECTION 6: RECRUITMENT METHODS AND PROCESS

A. Recruitment Methods

Please check **all** applicable recruitment methods that apply to the study. Place an "**X**" in the bracket **[ ]** next to the recruitment method.

[ ] UCI IRB approved advertisements, flyers, notices, and/or media will be used to recruit subjects.

Submit advertisements for IRB approval.

- Passive Recruitment - Potential subjects initiate contact with the study team.
- ***Complete Question 6B - Explain where recruitment materials will be posted.***

[ ] The study team will recruit potential subjects who are unknown to them (e.g., convenience sampling, use of social networks, direct approach in public situations, random digit dialing, etc.)

- Active Recruitment – Researchers contact potential subjects.
- ***Complete Question 6B.***

[ ] The UCI Social Sciences human subject pool will be used. ***Submit the Social Science Human Subject Pool Recruitment Advertisement for IRB approval.***

- Passive Recruitment - Potential subjects initiate contact with the study team.
- ***Skip to Section 7.***

[ ] Study team members will contact potential subjects who have provided permission to be contacted for participation in future research studies.

- Active Recruitment – Researchers contact potential subjects.
- ***Complete Question 6B – Explain when and how these individuals granted permission for future contact; provide the IRB protocol numbers, if applicable.***

[ ] Study team members will approach their own patients, students, employees for participation in the study.

- Active Recruitment – Researchers contact potential subjects.
- ***Complete Question 6B.***

[ ] Other Methods: <Type here>

- ***Complete Question 6B.***

B. Recruitment Process

1. Based on the methods checked above, describe and provide **details of the recruitment process** (i.e. when, where, by whom and how potential subjects will be approached).
2. If you will recruit by **mail, e-mail, or phone**, explain how potential subjects' **contact information will be obtained**.
3. If active recruitment methods will be used, explain how the individual's **privacy will be protected**. ***Note****: This is not the same as confidentiality (see the Privacy and Confidentiality web page).*

<Type here>

SECTION 7: INFORMED CONSENT PROCESS

1. If there will be contact with subjects*, then specify **how consent will be obtained** and **describe the specific steps** for obtaining informed consent (e.g. a study information sheet used to obtain verbal consent, an introductory paragraph included on the data collection instrument, a telephone script used, etc.).
2. Include information about **when and where** consent will take place and the **length of time** subjects will be given to decide whether they wish to participate.
3. If study team members will approach their own patients, students, or employees for participation in the study, then explain what precautions will be taken to **minimize potential undue influence or coercion**, and **how compromised objectivity will be avoided**.
4. If children are involved in this study, please describe the **parental permission** process and the **child assent** process.
5. Be sure to **submit the consent/assent document(s)** with your e-IRB Application.
6. If this study involves the creation, use, or disclosure of Protected Health Information (PHI), specify the process for **obtaining HIPAA Authorization**.

****Note:** *Mail/Internet surveys constitute subject contact.*

Check all that apply:

[ ] N/A – There will be no direct subject contact. No consent process will take place. ***Explain why consent is not required.***

[ ] Written (signed) consent will not be obtained - Informed consent, parental permission and/or child assent will be obtained from subjects, as applicable. ***Explain how this will be obtained.***

[ ] Written (signed) informed consent will be obtained – Signed informed consent, parental permission, and/or assent will be obtained from subjects, as applicable. ***Describe the informed consent process.*** ***Note:*** *Signed informed consent is infrequently required when conducting Exempt research.*

<Type here>

7. **Non-English Speaking Participants:** In order to consent subjects who are unable to read and speak English, the English version of the consent form must be translated into appropriate languages once IRB approval is granted.

Check all that apply:

[ ] Not applicable - Only individuals who can read and speak English are eligible for this study.

[ ] The English version of the consent form will be translated into appropriate languages for non-English speaking subjects once IRB approval is granted. An interpreter will be involved in the consenting process. ***Note:*** *The IRB must officially stamp the translated consent forms*.

SECTION 8: PARTICIPANT COMPENSATION

1. If subjects will be compensated for their participation, provide detailed information about the **amount and the method/terms of payment** (e.g., money; check; extra credit; gift certificate).
2. Describe the **schedule of compensation** (e.g., at end of study; after each session/visit).

Note: *Compensation should be offered on a prorated basis when the research involves multiple sessions.*

[ ] No compensation will be provided to subjects.

OR

<Type here>

SECTION 9: CONFIDENTIALITY OF RESEARCH DATA

1. Explain how the collected data will be **identified**.

[ ] No subject identifiers are obtained.
[ ] Names and other subject identifying information are obtained but are not shared with anyone except the study staff
[ ] Names and other subject identifying information are obtained and potentially used in publications/presentations. ***Note****: This may require written consent.*
[ ] Other (specify): <Type here>

2. Explain the manner in which the **data will be stored.**

Note: *If the research data includes subject identifiable information the storage devices or research files must be encrypted. Avoid storing subject identifiable data on portable devices (such as laptop computers, digital cameras, portable hard drives including flash drives, USB memory sticks, iPods or similar storage devices) as these devices are particularly susceptible to loss or theft. [For guidance on the use of cloud services, please review the UCI OIT policy.]*

[ ] Anonymous or de-identified data only (i.e., no code key)
[ ] Coded data with the code key kept in separate location. Key destroyed upon completion of the research or (specify):
[ ] Coded data with the code key kept in separate location. Key maintained beyond the completion of the research.

[ ] Data includes subject identifiable information. ***Note**: If electronic record/file, encryption software is required.*

3. Explain **how long subject identifiable research data** will be **retained.** The data may include a code with a separate code key or the data may include subject identifiers (hard copy documents, computer files, recordings, biospecimens)

[ ] Not applicable – No subject identifiers will be collected.
[ ] Research records will be retained for seven years after all children enrolled in the study reach the age of majority [age 18 in California] as this study includes children.
[ ] Destroy once data collection is completed
[ ] Destroy after publication/presentation
[ ] Maintain indefinitely for future research
[ ] Maintain for future research (specify time frame, e.g., 3 months, etc.): <Type here>
[ ] Other (specify): <Type here>

OR

<Type here>

4. If audio or video recordings will be collected, specify the **timeframe for the transcription and/or destruction of the audio and video recordings.**
5. If photographs will be collected, specify the **timeframe destruction of photographs**

[ ] Not applicable – No audio/video recordings or photographs will be collected.
[ ] Audio or video recordings transcribed; specify time frame: <Type here>
[ ] Audio or video recordings destroyed; specify time frame: <Type here>
[ ] Audio or video recordings maintained indefinitely
[ ] Photographs destroyed; specify time frame: <Type here>
[ ] Photographs maintained indefinitely

IMPORTANT TIME SAVER: ONLY COMPLETE Sections 10-11 if you are requesting Exempt Registration under Category 4. OTHERWISE STOP, YOU HAVE COMPLETED THE PROTOCOL NARRATIVE.

***Note:** If you will not have access to subject identifiers or the code key that links ID numbers and subject identifiers, this activity may not constitute human subjects research. You should submit a Request for Determination of Non-Human Subjects Research.*

SECTION 10: BIOSPECIMENS/CHARTS/RECORDS/DATASETS

A. Exempt Category 4 Eligibility

1. Will investigators have **interaction or intervention** with subjects? **[ ] YES [X] NO**

2. Will investigators collect information that does not currently exist? (i.e., biospecimens that are **not currently on the shelf** or information from records that does **not already exist as of the date of submission of this protocol**)? **[ ] YES [X] NO**

3. Will investigators collect **subject identifiers** or have access to a **code key** linking subjects' identities to the data or biospecimens?
[ ] YES [X] NO

***Note**: If you answer YES to any of the above three questions, your protocol does not qualify as Exempt research under Category 4. If another Exempt category does not apply complete the Protocol Narrative for Expedited/Full Committee Research.*

B. Number of Biospecimens/Charts/Records/Datasets

Specify the **maximum number of records or biospecimens that will be reviewed/analyzed** to compile the data necessary to address the research question **or the maximum number of individuals that will comprise the dataset**.
The maximum number of individuals that will comprise the dataset from all sites is 500.

IMPORTANT TIME SAVER: Complete Part C ONLY if you are requesting permission to study biospecimens.

C. Description of Biospecimens

1. Specify the **type(s) of human biospecimens** that will be studied:
<Type here>
2. Specify the **source of the biospecimens and** whether the biospecimens were originally **collected solely for research purposes**. 3. If the biospecimens were originally collected for research purposes, please **submit a copy of the IRB Approval Notice and Consent Form for the original collection** of these specimens with the e-IRB Application.
<Type here>
4. Specify how the **biospecimens are identified** when they are made available to the study team. Please indicate by marking the appropriate bracket(s) below.

i)	**[ ]** No Identifier	(i.e., neither the researcher nor the source providing the data can identify a subject based upon information provided with the biospecimens.)
ii)	**[ ]** Indirect Identifier	(i.e., an assigned code will be kept which could be used by the investigator or the source providing biospecimens to identify a subject, such as a tracking code used by the source.)
iii)	**[ ]** Direct Identifier**	(i.e., subject name, address, social security number, medical record number, etc. will be attached to biospecimens)

If ii is checked above, specify whether the study team will be given access to the key code.

[ ] Yes, the study team will have access to the code key linking the code and subject identities**

[ ] No, the study team will not have access to the code key linking the code and subject identities

***Note:** If direct identifiers will be used or the study team will have access to the code key, the research does not qualify for Exempt Registration under Category 4. If another Exempt category does not apply complete the Protocol Narrative for Expedited/Full Committee Research.*

IMPORTANT TIME SAVER: Complete Part D ONLY if you are requesting permission to study existing data, charts, or records.

D. Description of Charts/Records/Datasets

1. Specify the **types/sources of records/data** that will be reviewed by selecting the appropriate box below (e.g., census, medical).
2. Please be sure to submit a copy of the **Data Extraction Sheet** that will be used to collect the data for this study (i.e. the document used to record the information) with the e-IRB Application.

***Note:** If direct identifiers will be collected on the data abstraction sheet (e.g., medical record number, name), or the study team will have access to the code key linking the code to the subjects' identities, the research does not qualify for Exempt Registration. STOP completing this form and complete the Protocol Narrative for Expedited or Full Committee Review.*

[X] UCI Medical Records
[ ] Individual level data from an established data bank or repository (specify): <Type here>
[ ] Publicly available information (i.e. DMV, US Census)
[ ] NCI SEER (Surveillance Epidemiology and End Results)
[ ] Data Sets not including any of the 18 Protected Health Identifiers
[X] Other (specify): Medical records from UCLA and UCSD

3. Provide a description of **how** the appropriate **records/data** for study will be **provided** to the study team. (e.g. the Investigator will ask the Medical Records Department to provide specific charts and/or de-identified data; the Investigator will review his/her own charts and abstract data directly

from those charts; the Investigator will be provided an already existing, de-identified data set, etc.)

The investigator will contact a member of the Enterprise Data and Analytics team in Information Services at UC Irvine Health, and submit the data collection form to them. The Information Services technician will collect the data specified on the data collection form, using ICD-9 and CPT codes.

A similar contact person in Information Services will be contacted at UCLA and UCSD.

4. Specify whether the information is **publicly available**.
5. Explain whether the data was originally collected **solely for research purposes**.
6. If the records/data were originally collected for research purposes, please **submit a copy of the IRB Approval Notice and Consent Form for the original collection** of this information with the e-IRB Application.

The data being collected is not publicly available. The data will come from clinical medical charts of patients seen at a UC medical system. The data has not been previously collected solely for research purposes.

7. Specify how the **data is identified** when it is **recorded** by the study team. Please indicate by marking the appropriate bracket(s) below.

i)	**[ ]** No Identifier	(i.e., neither the researcher nor the source providing the data can identify a subject based upon information provided with the data)
ii)	**[X]** Indirect Identifier	(i.e., an assigned code will be kept which could be used by the investigator or the source providing data to identify a subject, such as a tracking code used by the source.)
iii)	**[ ]** Direct Identifier**	(i.e., subject name, address, social security number, medical record number, etc. will be attached to data)

If ii is checked above, specify whether the study team will be given access to the code.

[ ] Yes, the study team will have access to the link between the tracking code and subject identities.**

[X] No, the study team will not have access to the link between the code and subject identities.

***Note:** Unless the information is publicly available, if direct identifiers will be used, or the study team will have access to the code key linking the code to the subjects' identities, the research does not qualify for Exempt Registration. STOP completing this form and instead complete the Protocol Narrative for Expedited or Full Committee Review.*

SECTION 11: RESEARCH METHODOLOGY/STUDY PROCEDURES

A. Study Design and Procedures

1. Provide a detailed chronological description of all **study procedures**. Describe how the **subject's privacy will be protected** during the research procedures (i.e., during data extraction procedures). *[For guidance on the use of cloud services, please review the UCI OIT policy.]*
Study procedures: The investigator will provide IRB approval to the Information Services team, fill out a data extraction request, and submit the data collection form to the Information Services team. The Information Services team will submit the de-identified data to the study team. No protected health identifiers will be requested. The study team will not have direct access to patient medical records or charts.

Appendix D: UCI IRB Approval

CONFIRMATION OF EXEMPT RESEARCH REGISTRATION

June 27, 2017

BEATRIZ MENENDEZ
DEPARTMENT OF PEDIATRICS, DIVISION OF GENETIC AND GENOMIC MEDICINE

RE: HS# 2017-3562 *Rates of cosmetic surgery in children born with disorders of sexual development*

The human subjects research project referenced above has been adminsitratively registered with the UC Irvine Institutional Review Board (UCI IRB) as Exempt from Federal regulations in accordance with 45 CFR 46.101. This exemption is limited to the described activities in the registered UCI IRB Protocol Narrative and extends to the performance of such activities at the sites identified in your UCI IRB Protocol Application. Informed consent from subjects must be obtained unless otherwise indicated below. UCI IRB conditions for the conduct of this research are included on the attached sheet.

Information provided to prospective subjects to obtain their informed consent should, at a minimum, consists of the following information: the subject is being asked to participate in research, what his/her participation will involve, all foreseeable risks and benefits, the extent to which privacy and confidentiality will be protected, that participation in research is voluntary and the subject may refuse to participate or withdraw at any time without prejudice.

Questions concerning registration of this study may be directed to the UC Irvine Office of Research, 141 Innovation Drive, Suite 250, Irvine CA 92697-7600; 949-824-0665 (biomedical committee) or 949-824-6662 (social-behavioral committee).

Level of Review: Administrative Review, Category 4

Cristobal Barrios, MD
Vice Chair, Institutional Review Board
Registration valid from 06/27/2017 to 06/26/2022
UCI (FWA) 00004071, Approved: January 31, 2003

Determinations as Conditions of Exemption:

Study Status:

1. Retrospective Review of Records from 01-01-2006 through 12-31-2016
2. Receiving De-Identified Data from UCLA and UCSD

Informed Consent Requirements:

3. Informed Consent Not required
4. Assent Not Required
5. Waiver of UC HIPAA Research Authorization Granted

APPROVAL CONDITIONS FOR ALL UCI HUMAN RESEARCH PROTOCOLS

UCI RESEARCH POLICIES:
All individuals engaged in human-subjects research are responsible for compliance with all applicable UCI Research Policies. The Lead Researcher (and Faculty Sponsor, if applicable) of the study is ultimately responsible for assuring all study team members adhere to applicable policies for the conduct of human-subjects research.

LEAD RESEARCHER RECORDKEEPING RESPONSIBILITIES:
Lead Researchers are responsible for the retention of protocol–related records. The following web pages should be reviewed for more information about the Lead Researcher's recordkeeping responsibilities for the preparation and maintenance of research files: Lead Researcher Recordkeeping Responsibilities and Preparation and Maintenance of a Research Audit File.

PROTOCOL EXPIRATION:
The UCI IRB expiration date is provided on the exempt registration letter. All exempt protocols are registered for a maximum period of five years. If the study will continue beyond five years, a new Application for IRB review is required. No annual continuing renewals are required.

MODIFICATIONS & AMENDMENTS:
Per federal regulations, once a human research study has received IRB approval, any subsequent changes to the study must be reviewed and approved by the IRB prior to implementation *except when necessary to avoid an immediate, apparent hazard to a* subject. Accordingly, no changes are permissible (*unless to avoid an immediate, apparent hazard to a subject*) to the approved protocol or the approved, stamped consent form without the prior review and approval of the UCI IRB. All changes (e.g., a change in procedure, number of subjects, personnel, study locations, new recruitment materials, study instruments, etc.) must be prospectively reviewed and approved by the IRB before they are implemented.

APPROVED VERSIONS OF CONSENT DOCUMENTS, INCLUDING STUDY INFORMATION SHEETS:
Unless a waiver of informed consent is granted by the IRB, the consent documents (consent form; study information sheet) with the UCI IRB approval stamp must be used for consenting all human subjects enrolled in this study. Only the current approved version of the consent documents may be used to consent subjects. Approved consent documents are not to be used beyond the expiration date provided on the IRB approval letter. Current consent documents are available on the IRB Document Depot.

UNANTICIPATED PROBLEMS REPORTING:
In accordance with Federal regulations and HRP policies, only internal (where UCI serves as the IRB of record), Unanticipated Problems must be reported to the UCI IRB. Unanticipated Problems should also be reported to the UCI IRB when UCI is relying on an external IRB, and the incident occurred at UCI or the incident occurred at an offsite location on a study conducted by a UCI LR. Unanticipated Problems must be submitted to the IRB via the Unanticipated Problems (UP) Report within 5 business days upon the Lead Researcher's (LR) knowledge of the event. For additional information visit the updated HPR webpage on Unanticipated Problems.

CHANGES IN FINANCIAL INTEREST:
Any changes in the financial relationship between the study sponsor and any of the investigators on the study and/or any new potential conflicts of interest must be reported immediately to the UCI Conflict of Interest Oversight Committee (COIOC). If these changes affect the conduct of the study or result in a change in the text of the currently-approved informed consent document, these changes must also be reported to the UCI IRB via a modification request. Research subject to COIOC oversight is not eligible for Extended IRB Approval.

CLOSING REPORT:
A closing report should be filed with the UCI IRB when the research concludes. Visit the HRP webpage Closing a Protocol for complete details.