20 September, 2013

Dear Dr Holland,

We write in response to your detailed questions regarding aspects of the clinical features and complications of disorders of sex development (DSD).

We outline our responses to the questions provided by the Senate committee below:

- Is there any published evidence regarding clinical or social outcomes regarding sex assignment and/or gender identity in intersex patients who are not assigned a sex in infancy, and if so, did that research include analysis of the level of support among health professionals and/or family for the assignment / non-assignment decision?

Before we answer your questions, we would like to explain the definitions and terms used in medicine and clinical psychology.

In daily life the term intersex is often loosely used to indicate the diversity among humans with respect to sexuality. The term intersex lacks the specificity needed to be applicable in clinical management and science.

In the past the term intersex has been applied to individuals with gender dysphoria (GD) and patients with a Disorder in Sex Development (DSD). GD refers to being unhappy with the biological sex. Individuals with GD have normally developed sex organs and are biological males or females. They experience an incongruency between their biological sex and the way they experience themselves (psychological sex). GD is considered a medical condition but only when it is severe, long-lasting, causing substantial suffering and significant distress or impairment in social functioning (school, occupational, etc). Despite extensive research, there is no scientific evidence of any underlying biological, psychological or social mechanism leading to GD [4,5]

Disorders of Sex Development (DSD) refers to a group of congenital conditions in which the development of chromosomal, gonadal, and anatomical sex is atypical [6]. Patients with DSD do not have normally developed sex organs; they have no or underdeveloped gonads and/or have partially developed male and female sex characteristics. Biologically, they are neither male nor female. This atypical development started during the embryonic or fetal stage of development. The atypical development of the sex organs has consequences on somatic functioning, health and psychological development. Being congenital conditions, DSD is chronic and cannot be cured. Despite their biological condition, the large majority of patients with DSD experience and identify themselves as females or males. Gender dysphoria is observed in these patients, but severe gender dysphoria with substantial suffering and the wish to change the social gender role, is only seen in a small group of patients [7-18]. However, the number of patients with DSD who changed their social gender role is larger than the population prevalence of gender dysphoria.

Returning to the question: is there any published evidence regarding clinical or social outcomes regarding sex assignment and/or gender identity in intersex patients who are not assigned a sex in infancy, and if so, did that research include analysis of the level of support among health professionals and/or family for the assignment / non-assignment decision?

There is no published evidence regarding clinical of social outcomes in patients with disorders of sex development who are not assigned a sex in infancy. No gender assignment at all is rare as gender is needed in almost all governmental registrations. In many states governmental registration is obligatory and needed to obtain citizenship. Most governmental registrations only allow male or female. Only recently the legal systems of a few countries changed the binary sex registration [19-20]

Worldwide only a few individuals are known who are raised neither boy or girl. As the number of children raised without assigned gender is limited, scientific evaluation of the non assignment on psychological outcome is impossible. In addition, at present, the children known are too young to evaluate the long-term outcome of the non-assignment.

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- Is gender assignment surgery conducted for psychosocial reasons considered a 'therapeutic' procedure?

The definition of the term 'therapeutic' is unclear in respect to this question. Does it mean that the treatment is therapeutic with regard to anatomical correction, with regard to reducing psychosocial harm to the child, or to maximising future sexual function?

In view of this, this is an extremely complex question and is very controversial within the field of DSD.

- Are there any estimates available of the proportion of cases of different kinds of DSD in which gonads are either functional for hormone production or also fertile? If so, can you provide them or advise where they are published?

Referring to the terminology describing the different kinds of DSD as outlined by Houk et al, 2006 (Table 1) we would like to offer a reply which outlines the gonadal function for some specific DSD diagnoses below.

Generally it should be stated that in many DSD disorders number of patients per diagnostic subgroup is limited, with the exception of 45,X Turner syndrome, 47,XXY Klinefelter syndrome, 46,XX congenital adrenal hyperplasia and 46 XY androgen insensitivity, and long term follow up specifically with the objective to document fertility is lacking. However, specialist assessment can provide an indication of gonadal function potential through functional parameters of gonadal function (serum markers of fertility potential and hormone production), imaging (ultrasonography, magnetic resonance imaging) and histology.

In principle, as for germ cell cancer risk described later, the severity of DSD as well as the type of DSD will determine the degree of functional hormone production or fertility for each individual. In addition, both hormone production and fertility can be affected in varying degrees from mild to severe. More recent reports of fertility in specific forms of DSD have often used newer assisted reproduction technologies.

Some forms of DSD are described below, however as DSD comprise a large group of different disorders, not all forms can be described in this document.

46, XX DSD

- **Congenital adrenal hyperplasia due to 21-hydroxylase deficiency**

This is the most common cause of 46, XX DSD in western societies. The ovaries are 100% functional for oestrogen production, and the ovum population presumed normal**.** However, reduced fertility has been reported as a result of hyperandrogenemia, the outcomes of feminising genital surgery, and decreased sexual function.

- **46 XX testicular DSD**

This is a rare genetic condition of 46,XX phenotypic males who have presence of hormonally functioning testes. There is limited literature exploring this condition, and its etiology remains poorly understood. There is currently no clinical guidance available for fertility clinicians to follow when treating this condition.

Sex chromosome DSD	46,XY-DSD	46,XX-DSD
47,XXY (Klinefelter syndrome and variants)	Disorders of gonadal (testicular) development	Disorders of gonadal (ovarian) development
45,X (Turner syndrome and variants)	1. Complete or partial gonadal dysgenesis	1. Gonadal dysgenesis
45,X/46,XY (mixed gonadal dysgenesis)	2. Ovotesticular DSD	2. Ovotesticular DSD
46,XX/46,XY (chimerism)	3. Gonadal regression	3. Testicular DSD
	Disorders in androgen synthesis or action	Androgen excess
	1. Disorders of androgen synthesis a. LH receptor mutations b. Smith-Lemli-Opitz syndrome c. Steroidogenic acute regulatory protein mutations d. Cholesterol side-chain cleavage e. 3 β-hydroxysteroid dehydrogenase 2 f. 17 β-hydroxysteroid dehydrogenase g. 5 α-reductase 2	1. Fetal a. 3 β-hydroxysteroid dehydrogenase 2 b. 21-hydroxylase c. P450 oxidoreductase d. 11 β-hydroxylase e. Glucocorticoid receptor mutations
	2. Disorders of androgen action a. Androgen insensitivity syndrome b. Drugs and environmental modulators	2. Fetoplacental a. Aromatase deficiency b. Oxidoreductase deficiency
		3. Maternal a. Maternal virilizing tumours b. androgenic drugs
	Other	Other
	1. Syndromic associations of male genital development (e.g. cloacal anomalies, Robinow, Aarskog)	1. Syndromic associations (e.g. cloacal anomalies)
	2. Persistent Müllerian duct syndrome	2. Müllerian agenesis/hypoplasia
	3. Vanishing testis syndrome	3. Uterine abnormalities
	4. Isolated hypospadias	4. Vaginal atresis
	5. Congenital hypogonadotropic hypogonadism	5. Labial adhesions
	6. Cryptorchidism	
	7. Environmental influences	
Adapted from		

Table 1: Houk CP, Hughes IA, Ahmed SF, Lee PA; Writing Committee for the International Intersex Consensus Conference Participants. Summary of consensus statement on intersex disorders and their management. International Intersex Consensus Conference. Pediatrics. 2006 Aug;118(2):753-7.

46, XY DSD

As shown in Table 1 various DSD disorders are shared under the umbrella of 46, XY DSD. Generally these disorders are characterized by either incomplete development of testicular tissue (46, XY gonadal dysgenesis) resulting in deficient hormone production and often in lacking spermatogenesis (however, with rare exceptions as discussed below) or by in principle normal gonadal development but deficient androgen synthesis or action. As androgens play a pivotal role intra-testicularly the end-result is deficient spermatogenesis.

- **Androgen insensitivity syndromes (complete or partial)**

The hormonal function of the testis is fully intact. As a consequence at the time of puberty and thereafter androgens are produced. However depending on the remaining function of the androgen receptor the increased serum levels of androgens will result in no androgen

effects at all (CAIS) or in some effects (PAIS). It is of specific interest to note that in girls with complete AIS the increased levels of androgens are converted to estrogens. Therefore, as a practical clinical consequence these girls undergo spontaneous puberty in the sense of breast development, however lacking pubic hair development and merarche.

Patients with the severe form CAIS are infertile; however most recently a case report describes fertility in a patient with moderate partial androgen insensitivity following high dose testosterone treatment and intracytoplasmic sperm injection.

- **Testosterone biosynthesis disorders**

These disorders are rare and large series with long-term follow up are lacking. Depending on the specific enzymatic insufficiency the synthesis of testosterone is disturbed. As a result the androgen dependent genital development at birth is insufficient and pubertal male development will be also insufficient. However in some disorders such as 17BHSD androgen synthesis during puberty is rather increased as a result of a bypassing pathway. A practical consequence is that a patient with 17BHSD raised as a girl will virilise during puberty. Fertility has not been reported.

- **5 alpha reductase deficiency type II**

This disorder is strictly speaking not a testosterone biosynthesis disorder as testosterone synthesis by the testis is intact. However the critical conversion of testosterone to dihydro-testosterone is deficient resulting incomplete development of the male external genitalia. Importantly, fertility (fatherhood) has been described.

- **46,XY gonadal dysgenesis**

These are rare syndromes and generally the same applies as stated for chromosomal DSD gonadal dysgenesis and 46,XX testicular DSD i.e these disorders are characterized by incomplete development of gonadal (testicular) tissue resulting in varying degrees of deficient hormone production and often in lacking spermatogenesis. However exceptions have been reported recently. NR5A1 (SF-1) mutations have been found to be associated with 46,XY disorders of sex development but also with 46,XX primary ovarian insufficiency.

Mixed sex chromosome DSD

Mixed sex chromosome DSD is characterized by gonadal dysgenesis, implying that full development of functional ovarian or testicular tissue has been lacking or deficient. This becomes clinically evident at the time of puberty when hormonal activity of the dysgenetic gonads (androgen and/or estrogen production) will induce signs of secondary sex characteristics (breast development; pubic hair; phallic enlargement).

Generally there is a varying degree of infertility as normal spermatogenesis and ovum development is lacking, which may be suggested by abnormal levels of serum markers at the time of puberty (AMH, InhB).

- **Turner syndrome**

Turner syndrome (TS) affects 1 in 2000 liveborn females, and is associated with partial or complete loss of one X chromosome in a 46,XX fetus or of loss of a Y chromosome in a 46,XY fetus, resulting in monosomy of the X chromosome. It is characterized by ovarian failure, which occurs prior to puberty in most cases. Mosaicism is thought to account for much of the variability in phenotype, including the degree of ovarian dysfunction. Women with TS and a mosaic karyotype containing a Y chromosome, e.g. 45,X/46,XY, usually have complete gonadal dysgenesis and streak gonads. In these gonads, which are unlikely to have potential for fertility or significant hormone production, the risk of germ cell malignancy is 10-15% due to presence of Y chromosomal material.

Spontaneous puberty occurs in 15-30% of girls with TS, and 2-5% experience menarche. Approximately 2-5% of women with TS are able to conceive.

- **Ovotesticular DSD**

This term covers a wide spectrum of gonadal dysgenesis characterized by the presence of both testicular and ovarian tissue in one or both gonads. The chromosomal background is very heterogeneous as mosaicism, 46,XX and 46XY has been described. The hormonal production depends largely on the functionality of the testicular and ovarian components of the gonads.

This disorder has attracted specific attention in the past as it was claimed that selective gonadal surgery would enable the preservation of one of the components (mostly the ovarian component). However, in a recent report and subsequent discussion it was stated that no fertility has been observed.

- **Persistent Müllerian Duct Syndrome**

In this rare syndrome testicular function is fully intact. Boys undergo normal puberty. However due to persistence of Mullerian structures the internal genital anatomy is disrupted precluding production of fertile sperm. Collection of sperm cells and ICCI procedures are currently available in specialized centres.

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- The committee understands that the risk of germ cell tumour (GCT) development varies according to the person's age / stage of development. Is this correct? If so, is it directly related to which DSD a person may have?

- Have there been any substantive studies published presenting either new diagnostic techniques for, or new statistics on, type-II GCTs in DSD patients since the series of papers by Cools *et al* (2006 – 2011)?

The risk of GCT development varies undoubtedly according to which DSD a person has. However, in view of the very low incidence of most DSD conditions, and given the fact that gonadectomy has been performed prophylactically at an early age in many cases, it is currently impossible to obtain correct estimates of this risk for every DSD condition.

In general, it can be said that the risk is much higher in conditions in which the gonad has not fully differentiated into a testis or an ovary, *i.e*. conditions in which the global cellular organization of the gonad – at a microscopic level – is atypical, or in which germ cells and possibly also other cell types have not reached the maturation stage that is typical for the patient's age. From the above can be derived that any statement about tumor risk on an individual basis is an estimate and is possible only after thorough diagnostic investigations, most often including gonadal biopsy taking and specialized immunohistochemical analysis, which needs expert surgical manipulation and centralization of material, with specialist analysis.

New histological and genetic techniques are continuously being developed for the diagnosis and cancer risk stratification of patients with DSD. These techniques are not available at all centres, and may be known only to those with a subspecialist interest in the area. For this reason expert specialist care and analysis of biological material is required, along with multidisciplinary case discussion by an expert group.

However, generally spoken, it can be argued on the basis of these and other findings, that tumor risk is high and grossly independent of age in individuals with 46,XY gonadal dysgenesis and 45,X/46,XY individuals with atypical looking genitalia, and is lower in individuals with 46,XY disorders of testosterone synthesis or action and perhaps also in 45,X/46,XY individuals with typically-looking male or female genitalia.

Apart from the type of DSD which a person has, the GCT risk is also affected by the severity of the form of DSD. For example, mild forms of DSD have a lower cancer risk than more severe forms, but unusually complete androgen insensitivity carries a very low risk.

- The committee is aware of a significant literature on the risk of development of GCTs in DSD patients, but has not identified evidence regarding the health outcomes for those who develop type-II GCT. Is there any quantitative data available on health outcomes (eg. 5-year mortality; change in fertility status) for

  DSD patients diagnosed with type-II GCT, with or without treatment?

  The general population diagnosed with type-II GCT, with or without treatment?

Carcinoma-in-situ testis and gonadoblastoma are early forms of germ cell cancer in which there is no invasion of surrounding tissue by the pre-malignant tumour cells. It is currently thought that all carcinoma-in-situ cells and 50% of gonadoblastoma cells will eventually undergo malignant transformation (1). As these tumours are pre-malignant, curative treatment involves surgical resection only.

Malignant germ cell tumours can arise purely from the primordial germ cell (spermatozoa or oocyte precursor) lineage and or represent pluripotential differentiation along various lineages, including teratoma, choriocarcinoma, and yolk-sac carcinoma and embryonal carcinoma. Tumours arising purely from the primordial germ cell are sensitive to adjuvant

radiotherapy following surgical resection, and tumours which represent pluripotential differentiation are sensitive to chemotherapy.

Tumour staging allows stratification of good and poor risk patients. The overall five-year survival rate for good risk patients with modern cancer treatment is now 90-95%, however late tumour recurrence is reported (2). Poor risk occurs in 10-25%, and is associated with high serum tumour markers, metastases, and mediastinal non-seminomatous tumours (3). The five-year survival rate for poor risk patients is 60-70% (4). In the past, without treatment metastatic germ cell cancers were usually fatal, with mortality by 18 months.

At present there is no data comparing germ cell tumour outcome between patients who have an underlying DSD and those who do not.

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- In the notes to Table 7 in Cools *et al* 2006, it is stated: 'In case of PAIS, 17β-HSD, and ovotestis, the decision regarding gonadectomy is largely determined by sex of rearing'. Does this mean that, in these cases, they were stating that the rate of GCT risk is not the primary determinant of the clinical decision on whether to conduct a gonadectomy?

In any individual with a DSD condition, the decision to perform gonadectomy is reached by weighing benefits and risks of various issues, such as risk for GCC, sex of rearing, estimated capacity of the gonad to produce hormones in accordance with or opposite to sex of rearing and/or (developing) gender identity, likelihood of gender dysphoria later in life, etc.

The statement 'In case of PAIS, 17β-HSD, and ovotestis, the decision regarding gonadectomy is largely determined by sex of rearing' should be interpreted in this broader and clinically oriented context, which is different from the studies presented later, focusing primarily on tumor risk and in which the clinical emphasis is less elaborated.

In some centres gonadectomy is not performed at an early age for reasons of sex of rearing and is only considered for GCT risk. Gonadectomy for reasons of sex of rearing is deferred until the young person can be involved in the decision. However, at other centres sex of rearing may be a factor considered for consideration of early gonadectomy.

- Cools *et al* 2006 propose a model classification of patients directly related to their risk of tumour development (Figure 7). In this model, it appears that the histology of cases with either undervirilisation or GD with testicular dysgenesis determines whether or not they are high or low risk for GCT, and that the position of testes (scrotal, inguinal or intra-abdominal) is not the critical factor. Is this a correct understanding of the model? Is there subsequent published research supporting or rejecting this model?

Our current understanding is that the original position of the gonad and possibly also age at orchidopexy may be an additional element in determining the ultimate risk for GCC development, specifically in cases with undervirilization. However, to our knowledge, there is no research available that directly addresses this question.

- Cools *et al* 2006 provide a summary of risk of germ cell malignancy in their paper (see esp. Table 7). What exactly do the percentages, quoted here and elsewhere, represent? Are they estimates of the lifetime risk of acquiring a type-II GCT? If not, what risk are the figures reporting?
- There are a number of differences between the tabulated summary risk data in Cools *et al* 2006, the 2006 'consensus statement', Looijenga *et al* 2007 and Pleskacova *et al* 2010 that do not appear to be explained by the article texts. There is, in particular, variation in the number of studies, and assessed risks, associated with CAIS and PAIS; and a statement included in the 2006 research, that 'In case of PAIS, 17β-HSD, and ovotestis, the decision regarding gonadectomy is largely determined by sex of rearing' is omitted in other versions of the same table. Are you able to explain any of these variations?

It should be emphasized that risk estimates should not be interpreted as incidence or prevalence numbers, which can only be obtained for some frequently occurring conditions within a given population, e.g prevalence of type I diabetes.

Risk estimates for GCC in DSD conditions are largely derived from extrapolation and meta-analysis of available, historical data, obtained by previous researchers. Risk estimates for GCC may vary according to which series have been included in the analysis, which is largely dependent on the specific research question that has been addressed in the different papers. The 2006 paper (Cools et al, Endocrine Reviews 2006) discusses the risk for GCC in this broader context.

Yours sincerely (in alphabetical order),

Martine Cools

Paediatric Endocrinologist, Ghent University Hospital, Ghent, Belgium

Senior Clinical Investigator Ghent University and Flanders Research Foundation, Belgium

Arianne Dessens

Stenvert Drop

Jacqueline Hewitt

Professor Garry Warne

Honorary Visiting Endocrinologist, Royal Children's Hospital Melbourne

Esteemed Honorary Fellow, Murdoch Children's Research Institute

Honorary Professorial Associate, University of Melbourne