Chapter 4
Intersex and cancer

Introduction

4.1 Some intersex conditions present an elevated risk of gonadal cancer (cancer in the tissue that forms testes or ovaries). There are different kinds of cancer, and the main risk in intersex people is presented by what are called type-II germ cell tumours (GCT).[1] Removal of gonadal tissue, called gonadectomy, may be an appropriate treatment to manage the risk. The cancer risks however are complex and in some cases poorly understood. The chance that gonads will develop cancer depends on several variables, and the stage in life at which the risk becomes significant varies depending on the type of intersex (though there is limited information available about this).[2] Removal of gonads in infancy is sometimes recommended in order to nullify the risk of cancer, but this potentially conflicts with the principle of avoiding irreversible surgery on a child unless necessary, to allow the person an opportunity to make their own decisions regarding their medical treatment.[3] In some cases retention of gonads is also desirable to preserve natural hormone production.[4]

4.2 It was reported to the committee that there is a trend toward fewer removals of gonads during infancy as a result of changed approaches to intersex.[5] This is a positive development, but it does mean that more attention now needs to be paid to the health risks – particularly the tumour risk – that may arise from those gonads being retained.

4.3 As was noted in chapter 1, some intersex people are fertile, and others are not. It depends on the type of intersex variation a person has, as well as on the specifics of their case. Removal of gonads in many cases would not be sterilising, because they would not be fertile in the first place. In some cases, however, gonads may be fertile, or may contain tissue that could allow fertility as a result of future advances in

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1 J.W. Oosterhuis and L.H. Looijenga, 'Testicular germ-cell tumours in a broader perspective', *Nature Reviews Cancer*, Vol. 5, 2005, pp 210–222.

2 See also Martine Cools, Arianne Dessens, Stenvert Drop, Jacqueline Hewitt and Gary Warne, Answers to questions on notice, received 27 September 2013.

3 Martine Cools, Stenvert L.S. Drop, Katja P. Wolffenbuttel, J. Wolter Oosterhuis and Leendert H.J. Looijenga, 'Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers', *Endocrine Reviews*, Vol. 27, No. 5, 2006, p. 468.

4 M. Cools, J. Pleskacova, H. Stoop, P. Hoebeke, E. Van Laecke, S.L.S. Drop, J. Lebl, J.W. Oosterhuis, L.H.J. Looijenga, K.P. Wolffenbuttel, and the Mosaicism Collaborative Group, 'Gonadal pathology and tumor risk in relation to clinical characteristics in patients with 45,X/46,XY mosaicism', *Journal of Clinical Endocrinology & Metabolism*, Vol. 96, No. 7, 2011.

5 Australasian Paediatric Endocrine Group, *Submission 88*, p. 2.

medicine. As some decisions to remove gonads are made shortly after birth, this means removal occurs 20 to 40 years before the person might seek to have children – a very long period over which to predict what advances in medicine might occur.

4.4 It is certainly the practice of some specialists to avoid removing potentially fertile tissue wherever possible.[6] This reflects the 2006 Consensus Statement position that 'surgical management of DSD should also consider options that will facilitate the chances of fertility'.[7]

4.5 The main issues raised during the inquiry concerned the estimation of cancer risk, and the way in which medical intervention relies on assessment of those risks. Because there was disagreement amongst participants in the committee's inquiry regarding the levels of cancer risk in intersex people, and appropriate medical responses to those risks, the committee considered in more detail the published research that lies behind this discussion. This chapter explains how cancer risks and diagnostic techniques have been set out in the medical literature. An important part of this discussion involves a table of information that is reproduced in different forms in many publications, and which appeared to be the source of some of the problems that have emerged during debate about gonadectomies in intersex people.

Reviews and clinical recommendations in the medical literature

4.6 Beginning in 2005, a team of researchers largely based in Rotterdam in the Netherlands published a series of articles and reviews regarding the nature, diagnosis and treatment of germ cell tumours in intersex people. Throughout the literature, the discussion is of different 'disorders of sexual development' (DSD), and for consistency of reference to the literature, that terminology will frequently be used in this section of the report. The work of the Dutch team has been pivotal in improving the understanding and management of gonadal cancer in intersex people.

4.7 In 2006, the group published a key review of evidence, titled 'Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers'. This paper assembled evidence from over a hundred studies in the field, and made a number of contributions, including:

- A proposal that both the classification and terminology associated with DSD be revised;
- A synthesis of data, leading to a summary of 'the estimated germ cell tumor prevalence in patients with DSD', according to the type of DSD;
- A new test and diagnostic approach, to reduce over-diagnosis of cancer or cancer risk in some patients;

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6 Disorder of Sex Development multidisciplinary team at Royal Children's Hospital, Melbourne, *Submission 92*, p. 7.

7 Peter A. Lee, Christopher P. Houk, S. Faisal Ahmed, Ieuan A. Hughes et al, 'Consensus Statement on Management of Intersex Disorders', *Paediatrics*, Vol. 118, No. 2, 2006. http://pediatrics.aappublications.org/content/118/2/e488.full#xref-ref-2-1 (accessed 26 July 2013).

- A new classification model for patient risk, based on morphology and histology; and
- A table ('the 2006 table') that set out a 'summary of the risk of germ cell malignancy in the various forms of DSD, subdivided into high, intermediate, low and possibly no risk' including a column describing 'action needed'.[8]

4.8 It was this table and its subsequent incarnations that featured regularly thereafter in publications, including in submissions to the current inquiry. The 2006 table is reproduced in full, below:

8 Martine Cools, Stenvert L.S. Drop, Katja P. Wolffenbuttel, J. Wolter Oosterhuis and Leendert H.J. Looijenga, 'Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers', *Endocrine Reviews*, Vol. 27, No. 5, 2006, pp 468–484.

TABLE 7. Summary of the risk of germ cell malignancy in the various forms of DSD, subdivided into high, intermediate, low, and possibly no risk

Risk group	Disorder	Risk (%)	Action needed	No. of studies	No. of patients
High	GD[1](+Y)[2]intra-abd	15–35	Gonadectomy[3]	12	>350
	PAIS nonscrotal	15	Gonadectomy[3]	3	80
	Frasier	60	Gonadectomy[3]	1	15
	Denys-Drash (+Y)	40	Gonadectomy[3]	1	5
Intermediate	Turner (+Y)	12	Gonadectomy[3]	11	43
	17β-HSD	28	Watchful waiting and possible biopsy	2	7
Low	CAIS	0.8	Biopsy[4] and possible irrad/gonadectomy	3	120
	Ovotest. DSD	3	Testicular tissue removal in case of ♀ rearing?	3	426
	Turner (−Y[5])	1	None	11	557
Unknown[6]	5α-Reductase	0	Unresolved	1	3
	Leydig cell hypoplasia	0	Unresolved	1	2
	GD (+Y)[2] scrotal	Unknown	Biopsy[4] and irrad?	0	0
	PAIS scrotal gonad	Unknown	Biopsy[4] and irrad?	0	0

Recommended actions are indicated, as well as the number of studies and patients included in the survey. In case of PAIS, 17β-HSD, and ovotestis, the decision regarding gonadectomy is largely determined by sex of rearing. Relevant data from the recently published study by Hannema *et al*. (107) are not included in this table because it is at present unclear to us to what extent patient series from this study show overlap with patient series from a previously published study by the same group (117). Intra-abd, Intraabdominal located gonad; nonscrotal, nonscrotally located gonad; scrotal, scrotally located gonad; irrad, local irradiation with 18 Gy; ovotest. DSD, formally ovotestis (true hermaphrodite).

1 GD (including not further specified, 46XY, 46X/46XY, mixed, partial, complete).

2 GBY region positive, including the TSPY gene.

3 At time of diagnosis.

4 At puberty, allowing investigation of at least 30 seminiferous tubules, preferential diagnosis based on OCT3/4 immunohistochemistry.

5 PCR detection of Y-chromosomal sequences (in particular the GBY region) is implicated if a marker is identified by karyotyping.

6 Based on current knowledge (single study including limited number of patients, or no studies reported at all).

4.9 A version of this table also appeared in the 2006 'Consensus Statement on management of intersex disorders' (discussed in chapter 2). There are however some significant differences between the versions of the table. Compared to the table above, in the 2006 Consensus Statement version of the table:[9]

9 Peter A. Lee, Christopher P. Houk, S. Faisal Ahmed, Ieuan A. Hughes et al, 'Consensus Statement on Management of Intersex Disorders', *Paediatrics*, Vol. 118, No. 2, 2006, p. 493.

- Two of the disorders – gonadal dysgenesis (GBY region positive, including the TSPY gene) with scrotally located gonad; and partial androgen insensitivity syndrome with scrotally located gonad – have been moved from the 'unknown' or 'possibly no' risk category, and placed in the 'intermediate risk' group;
- The 'unknown' risk category is re-titled 'no(?)' risk;
- In the case of partial androgen insensitivity syndrome (PAIS) with non-scrotally located gonad, it appears one of the three studies used to provide an estimate has been omitted, reducing the number of patients from 80 to 24, and significantly increasing the estimated risk, from 15 per cent to 50 per cent;
- In the case of complete androgen insensitivity syndrome (CAIS), it also appears one of the three studies used to provide an estimate has been omitted, reducing the number of patients from 120 to 55, and increasing the estimated risk, from 0.8 per cent to 2 per cent;
- The main footnote, with its explanation for recommended action in the case of PAIS, 17β-HSD, and ovotestis, is omitted;
- The proposed action for CAIS is changed from 'Biopsy and possible irrad/gonadectomy' to 'Biopsy and ???';
- The proposed action for Ovotesticular DSD is changed from 'Testicular tissue removal in case of ♀ rearing?' to ' Testicular tissue removal?'; and
- The last two footnotes are omitted.

4.10 There were two main effects of these changes. First, they increased the apparent level of cancer risk of some intersex conditions. Second, they removed explanation of the table's content regarding links between the preferred course of action and the chosen sex of rearing, but without removing or modifying the courses of action based on those explanations.

4.11 A 2007 paper by the research team, titled 'Tumor risk in disorders of sex development',[10] contained a table substantively identical to that in the 2006 consensus statement. The table (as reproduced in one of the committee's submissions) is reproduced below:

10 Leendert H.J. Looijenga, Remko Hersmus, J. Walter Oosterhuis, Martine Cools, Stenvert L.S. Drop and Katja P. Wolffenbuttel, 'Tumor risk in disorders of sex development (DSD)', *Best Practice & Research Clinical Endocrinology & Metabolism*, Vol. 21, No. 3, 2007, pp 480–495.

Risk group	Disorder	Malignancy risk (%)	Recommended action	Studies (n)	Patients (n)
High	GD[a] (+Y)[b] intra-abdominal	15–35	Gonadectomy[c]	12	>350
	PAIS non-scrotal	50	Gonadectomy[c]	2	24
	Frasier	60	Gonadectomy[c]	1	15
	Denys–Drash (+Y)	40	Gonadectomy[c]	1	5
Intermediate	Turner (+Y)	12	Gonadectomy[c]	11	43
	17β-HSD	28	Monitor	2	7
	GD (+Y)[c]	Unknown	Biopsy[d] and irradiation?	0	0
	PAIS scrotal gonad	Unknown	Biopsy[d] and irradiation?	0	0
Low	CAIS	2	Biopsy[d] and ???	2	55
	Ovotestis DSD	3	Testis tissue removal?	3	426
	Turner (– Y)	1	None	11	557
No (?)	5α-reductase	0	Unresolved	1	3
	Leydig cell hypoplasia	0	Unresolved	2	

CAIS, complete androgen insensitivity syndrome; 17β-HSD, 17β-hydroxysteroid dehydrogenase deficiency; PAIS, partial androgen insensitivity syndrome.
[a] Gonadal dysgenesis (including not further specified, 46XY, 46X/46XY, mixed, partial, complete).
[b] GBY region positive, including the *TSPY* gene.
[c] At time of diagnosis.
[d] At puberty, allowing investigation of at least 30 seminiferous tubules, with diagnosis preferably based on OCT3/4 immunohistochemistry.

Source: APEG, *Submission 88*, citing Leendert H.J. Looijenga, Remko Hersmus, J. Walter Oosterhuis, Martine Cools, Stenvert L.S. Drop and Katja P. Wolffenbuttel, 'Tumor risk in disorders of sex development (DSD)', *Best Practice & Research Clinical Endocrinology & Metabolism*, Vol. 21, No. 3, 2007, p. 491.

4.12 The 2006 and 2007 papers from the Dutch research team, and the 2006 Consensus Statement, contain no information regarding the omission of one study from the sample, or accounting for the other changes.

4.13 The team of researchers responsible for the 2007 paper were cautious in their presentation of the information. They stated that the application of a combination of diagnostic techniques presented by them 'might *in future* be used to develop a decision tree for optimal management of patients with DSD' (emphasis added).[11] The authors concluded that 'patients with DSD can be classified into high, intermediate, low or unknown risk groups for type-II germ-cell tumors'.[12] They qualified the classification, however, by noting that there are some intersex conditions for which no or insufficient data is available (including 5α-reductase deficiency and Leydig-cell hypoplasia), and by indicating that:

> This first attempt to estimate the risk of the individual patient with DSD developing a type-II germ-cell tumor must be tested using additional cases

11 Leendert H.J. Looijenga, Remko Hersmus, J. Walter Oosterhuis, Martine Cools, Stenvert L.S. Drop and Katja P. Wolffenbuttel, 'Tumor risk in disorders of sex development (DSD)', *Best Practice & Research Clinical Endocrinology & Metabolism*, Vol. 21, No. 3, 2007, p. 480.

12 Leendert H.J. Looijenga, Remko Hersmus, J. Walter Oosterhuis, Martine Cools, Stenvert L.S. Drop and Katja P. Wolffenbuttel, 'Tumor risk in disorders of sex development (DSD)', *Best Practice & Research Clinical Endocrinology & Metabolism*, Vol. 21, No. 3, 2007, p. 491.

> in which proper criteria are used for classifying patients in the different DSD entities…[13]

4.14 In 2009, researchers Professor Gary Warne and Dr Jacqueline Hewitt published a paper in the Medical Journal of Australia, titled 'Disorders of sex development: current understanding and continuing controversy'. Based on the 2007 results in Looijenga et al, Warne and Hewitt stated, regarding risks of cancer:

> In any DSD associated with a Y chromosome, there is an increased risk of germ cell cancer, especially when the testes are intraabdominal (the risk of seminoma in partial androgen insensitivity is 50% for an intra-abdominal testis) or when there is gonadal dysgenesis.[14]

4.15 In relation to clinical management of those children in whom testes are retained, Warne and Hewitt continued:

> The trend for surgeons to recommend male-sex rearing for greater numbers of children with DSD could also mean greater reluctance to remove testes that pose a significant risk of cancer on the grounds that physiologically useful hormone secretion might be retained. It is therefore imperative that a risk management strategy be prepared for each patient. This would mandate:
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> • educating parents and patients about risk;
>
> • removing all intra-abdominal gonads that cannot be brought down into the scrotum;
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> • regular clinical and ultrasound surveillance of scrotal gonads with removal of any that contain suspicious lumps;
>
> • biopsy of testes after the onset of puberty, looking for early signs of malignant change; and
>
> • effective communication between paediatric and adult care providers at the time of transition.[15]

4.16 In 2009, the Dutch team published another review paper that incorporated a table similar to that published in 2006, with the larger number of studies for CAIS and

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13 Leendert H.J. Looijenga, Remko Hersmus, J. Walter Oosterhuis, Martine Cools, Stenvert L.S. Drop and Katja P. Wolffenbuttel, 'Tumor risk in disorders of sex development (DSD)', *Best Practice & Research Clinical Endocrinology & Metabolism*, Vol. 21, No. 3, 2007, p. 490.

14 Garry L. Warne and Jacqueline K. Hewitt, 'Disorders of sex development: current understanding and continuing controversy', *Medical Journal of Australia*, Vol. 190, No. 11, p. 612.

15 Garry L. Warne and Jacqueline K. Hewitt, 'Disorders of sex development: current understanding and continuing controversy', *Medical Journal of Australia*, Vol. 190, No. 11, pp 612–13.

PAIS (3 in each case rather than 2), and repeating the lower risk estimates of their 2006 publication.[16]

4.17 In 2010, the Dutch research team (in a publication with a Czech lead author, J. Pleskacova) published a further paper in the field, somewhat confusingly carrying the same title as the 2007 article. The 2010 publication did not carry a version of the same table, but did contain a similar, smaller table summarising the prevalence of GCT in DSD patients. This table was as follows:

Table 1. Prevalence of type II GCT in various forms of DSD

Risk	Type of DSD	Prevalence %
High	GD in general	12*
	46,XY GD	30
	Frasier syndrome	60
	Denys-Drash syndrome	40
	45,X/46,XY GD	15–40
Intermediate	PAIS	15
	17β-hydroxysteroid dehydrogenase deficiency	17
Low	CAIS	0.8
	Ovotesticular DSD	2.6
Unknown	5α-reductase deficiency	?
	Leydig cell hypoplasia	?

GD = Gonadal dysgenesis; PAIS = partial androgen insensitivity syndrome; CAIS = complete androgen insensitivity syndrome.
* Might reach more than 30%, if gonadectomy has not been performed.

4.18 Notably, the estimates of prevalence for two key disorders, PAIS and CAIS, reflect again the lower estimates in the 2006 publication, which is cited as the principal source for the table.[17] The team of researchers concluded that:

> Presently available tools allow us to assess gonadal tissue of DSD patients and identify gonads at risk for GCT development, i.e. gonads containing dysplastic cells or noninvasive neoplasia. This ability together with precise diagnosis of DSD cases based on molecular-genetic methods may facilitate a more accurate estimation of the tumor risk in various forms of DSD. With that knowledge we might be able to preserve gonads in selected patients.[18]

16 Martine Cools, Leendert H.J. Looijenga, Katja P. Wolffenbuttel, and Sten L.S. Drop, 'Disorders of sex development: update on the genetic background, terminology and risk for the development of germ cell tumors', *World Journal of Pediatrics*, Vol. 5, No. 2, 2009, pp 93–102.

17 J. Pleskacova, R. Hersmus, J.W. Oosterhuis, B.A. Setyawati, S.M. Faradz, M. Cools, K.P. Wolffenbuttel, J. Lebl, S.L. Drop, and L.H. Looijenga, 'Tumor Risk in Disorders of Sex Development', *Sexual Development*, Vol. 4, No. 4–5, 2010, p. 7 (online version).

18 J. Pleskacova, R. Hersmus, J.W. Oosterhuis, B.A. Setyawati, S.M. Faradz, M. Cools, K.P. Wolffenbuttel, J. Lebl, S.L. Drop, and L.H. Looijenga, 'Tumor Risk in Disorders of Sex Development', *Sexual Development*, Vol. 4, No. 4–5, 2010, pp 259–269.

4.19 The Dutch team published two papers in 2011. Neither included a table of data equivalent to that found in earlier publications. One of the 2011 papers related only to one subset of DSD: 45,X / 46,XY mosaicism.[19] The other focussed on 'tumor risk in relation to the gonadal differentiation pattern and the phenotypic presentation of the patient'.[20] The papers do not directly discuss the risks associated with CAIS or PAIS, but do indicate the developing understanding of the relationship between tumour risk and the location and nature of gonadal tissue, concluding 'tumor risk is most pronounced in immature and/or poorly differentiated gonadal tissue and can be – at least in part – predicted from the presence of specific immunohistochemical markers'.[21]

Discussion during the committee inquiry of the medical research

4.20 APEG made a submission to the committee's inquiry that reproduced the table from the 2007 paper, described above. APEG's position in its submission was:

> In high-risk groups the recommendation is to remove the gonads before the individual develops cancer, which can occur in childhood. It would be negligent to expose these children to cancer by leaving the testes/ovaries in when the high risk is known…[and] The recommendation of Warne and Hewitt, and in the current medical literature, is for preventative surgical removal only in the high-risk and intermediate-risk cancer group…[22]

4.21 The Disorder of Sex Development multidisciplinary team at Royal Children's Hospital, Melbourne (RCH) also discussed the risk of cancer. It reported a number of figures, including the 50 per cent figure that appeared in Warne and Hewitt's 2009 paper, again citing the Dutch team's 2007 publication as the source:

> XY Complete gonadal dysgenesis. Individuals with this condition may have both the external physical appearances of a girl and a uterus, and will most likely identify as female. If [their] gonads are intra-abdominal, there is 15-30% risk of malignancy occurring by the time the young woman reaches her mid 20's…
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> Partial androgen insensitivity syndrome (PAIS)…There is a considerable spectrum – with some people being born with almost normal male external genitalia, and others having almost normal female genitalia (but all will

19 M. Cools, J. Pleskacova, H. Stoop, P. Hoebeke, E. Van Laecke, S.L.S. Drop, J. Lebl, J.W. Oosterhuis, L.H.J. Looijenga, K.P. Wolffenbuttel, and the Mosaicism Collaborative Group, 'Gonadal pathology and tumorrisk in relation to clinical characteristics in patients with 45,X/46,XY mosaicism', *Journal of Clinical Endocrinology & Metabolism*, Vol. 96, No. 7, 2011, pp E1171–E1180.

20 M. Cools, K.P. Wolffenbuttel, S.L.S. Drop, J.W. Oosterhuis and L.H.J. Looijenga, 'Gonadal development and tumor formation at the crossroads of male and female sex determination', *Sexual Development*, Vol. 5, 2011, p. 177.

21 M. Cools, K.P. Wolffenbuttel, S.L.S. Drop, J.W. Oosterhuis and L.H.J. Looijenga, 'Gonadal development and tumor formation at the crossroads of male and female sex determination', *Sexual Development*, Vol. 5, 2011, p. 178.

22 Australasian Paediatric Endocrine Group, *Submission 88*, pp 3–4.

> have no uterus). If the testes are undescended and inside the abdomen, the cancer risk of the testes is reported to be 50%.[23]

4.22 It should be noted that the 2007 paper cited by the Melbourne team claimed only to summarise major findings from other papers, and referred the reader to the 2006 paper and the Consensus Statement for details.[24] Of these, only the 2006 paper discusses risk for individual types of intersex in detail, and gives a reported cancer risk for PAIS of 15 per cent rather than 50.[25] The 15 per cent figure is likewise reproduced in 2009 and 2010 papers from the same team.[26]

4.23 In its submission, OII commented on the 2009 Warne and Hewitt paper. OII said:

> Warne and Hewitt's assertion regarding the percentage risk of malignancy in internal gonads strongly imply a general, across the board, risk of 50%. This is considerably different from research elsewhere, suggesting either sampling bias, or a hitherto unknown cancer hot spot…
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> …
>
> The protocol described by Warne and Hewitt means that the testes of all people with CAIS, and very many with PAIS, are removed in infancy. Alternative views are numerous, including international expert Katrina Karkazis or, in the case of AIS specifically, by Quigley *et al* Batch *et al*, Crouch. The AISSG UK summarise some of the research in this field, showing sampling bias in many studies, and far lower risks for most intersex people with internal gonads, albeit risks that increase with age.[27]

4.24 OII's submission went on to cite some of that research, which gives differing rates of cancer risk for different types of intersex condition.[28] The two studies mentioned by OII that were published in medical journals (Quigley *et al* and Batch *et al*) pre-date the work of the Dutch team (and others), who were able to draw on new diagnostic techniques and larger sample sizes.

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23 Disorder of Sex Development multidisciplinary team at Royal Children's Hospital, Melbourne, *Submission 92*, pp 3–4.

24 Leendert H.J. Looijenga, Remko Hersmus, J. Walter Oosterhuis, Martine Cools, Stenvert L.S. Drop and Katja P. Wolffenbuttel, 'Tumor risk in disorders of sex development (DSD)', *Best Practice & Research Clinical Endocrinology & Metabolism*, Vol. 21, No. 3, 2007, p. 490.

25 Martine Cools, Stenvert L.S. Drop, Katja P. Wolffenbuttel, J. Wolter Oosterhuis and Leendert H.J. Looijenga, 'Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers', *Endocrine Reviews*, Vol. 27, No. 5, 2006, p. 471.

26 Martine Cools, Leendert H.J. Looijenga, Katja P. Wolffenbuttel, and Sten L.S. Drop, 'Disorders of sex development: update on the genetic background, terminology and risk for the development of germ cell tumors', *World Journal of Pediatrics*, Vol. 5, No. 2, 2009, p. 100; J. Pleskacova, R. Hersmus, J.W. Oosterhuis, B.A. Setyawati, S.M. Faradz, M. Cools, K.P. Wolffenbuttel, J. Lebl, S.L. Drop, and L.H. Looijenga, 'Tumor Risk in Disorders of Sex Development', *Sexual Development*, Vol. 4, No. 4–5, 2010, p. 7 (online version).

27 Organisation Intersex International Australia, *Submission 23*, p. 8.

28 Organisation Intersex International Australia, *Submission 23*, pp 8–9.

4.25 Professor Warne and Dr Hewitt were co-authors (with others) of the APEG submission. That submission responded to evidence from OII, stating:

> The Senate has unfortunately received misleading information in submissions on this issue. We are concerned that some of the information presented appears to have been either misunderstood, or misrepresented in error, leading to inaccurate conclusions. Some authors have misunderstood the difference between high-risk and low-risk cancer groups within DSD, and in particular, one submission incorrectly implied that the cancer risk for a diagnosis in the highest-risk group ('PAIS with non-scrotal/intra-abdominal testes') was quoted by Warne and Hewitt as being the cancer risk for a diagnosis in the low-risk group ('CAIS'), as outlined in Table 2. The implication is that testes or ovaries are being removed from patients with diagnoses at low-risk of cancer, such as CAIS, however this is incorrect.[29]

4.26 Subsequent submissions appear to indicate that there is some common ground,[30] in recognising that cancer risk in some intersex people, especially those with CAIS or ovotesticular DSD, does not warrant prophylactic removal of testes.[31] At the same time, OII, quoting other medical research,[32] maintained that testes are still being removed from low-risk individuals (though presumably not by those specialists who do not support the practice, such as Warne and Hewitt, or the team at RCH Melbourne).[33] The committee received no evidence on the numbers of gonadectomies being performed where surgery was based on cancer risk.

4.27 The committee wrote to authors of the published research, seeking clarification of the variation in the estimated cancer risk or prevalence between different studies. In responding, the group of medical experts noted:

> 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 [germ cell tumour], 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

29 Australasian Paediatric Endocrine Group, *Submission 88*, p. 3.

30 See Organisation Intersex International Australia, *Submission 23.3 (30 June)*, pp 5–6.

31 See, for example, Disorder of Sex Development multidisciplinary team at Royal Children's Hospital, Melbourne, *Submission 92*, p. 4.

32 Organisation Intersex International Australia, *Submission 23.3 (30 June)*, p. 6, citing soon-to-be published research: Nakhal et al, *Radiology*, Vol. 268, 2013 (in press).

33 For the RCH Melbourne team's position, see *Submission 92*, p. 4.

> from the studies presented later, focusing primarily on tumor risk and in which the clinical emphasis is less elaborated.[34]

Discussion

4.28 The committee identified two related issues in the discussion of intersex and cancer risk:

- The complexity and diversity of cancer risk can become oversimplified, potentially elevating the perceived or communicated risk. Alternative monitoring options may be overlooked.
- The committee is concerned that other matters such as 'sex of rearing' or 'likelihood of gender dysphoria' are interpolated into the discussion of cancer risk. This confusion between treatment options to manage cancer risk and treatment options to manage intersex could undermine confidence in the neutrality of those advocating for surgical interventions.

Simplifying complexity

4.29 One of the difficulties faced by the committee and others when considering this literature is that the application of labels such as 'low risk' or 'high risk' appears to be masking some of the variation between individual intersex conditions. There are also serious questions to be raised about what constitutes 'high risk', and why it is that cases facing an 'intermediate risk' should be subject to prophylactic gonadectomy in infancy.

4.30 As cited above, the APEG submission stated that 'The recommendation of Warne and Hewitt, and in the current medical literature, is for preventative surgical removal only in the high-risk and intermediate-risk cancer group'. However the detail is more complex. In intermediate risk cases, the published literature has recommended gonadectomy only in some cases. For others, there is no definite recommendation.[35]

4.31 The summary classification of intersex conditions by cancer risk may also mask the importance of considering the circumstances of individual cases. There is great genotypic and phenotypic diversity among intersex people, even within a single category of intersex condition, and the literature suggests that these specific circumstances have a bearing on the cancer risk. As Dr Cools pointed out:

> 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… any

34 Martine Cools, Arianne Dessens, Stenvert Drop, Jacqueline Hewitt and Gary Warne, answers to questions on notice (received 27 September 2013).

35 See, for example, Leendert H.J. Looijenga, Remko Hersmus, J.Walter Oosterhuis, Martine Cools, Stenvert L.S. Drop and Katja P. Wolffenbuttel, 'Tumor risk in disorders of sex development (DSD)', *Best Practice & Research Clinical Endocrinology & Metabolism*, Vol. 21, No. 3, 2007, p. 491.

> 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[36] analysis, which needs expert surgical manipulation and centralization of material, with specialist analysis.[37]

4.32 There are, for example, some types of intersex that are generally classed as at high risk of gonadal cancer, but in which the published research papers indicate that the risk of tumour development depends on the morphology and histology in the individual case.[38] These include people with dysgenetic testes or with 'undervirilising' conditions such as PAIS. For these intersex people, and others, a number of specific factors can be examined in the individual that will influence whether they or not they are at high risk of developing tumours.[39] As the Dutch team concluded in one of its most recent papers:

> Tumor risk is most pronounced in immature and/or poorly differentiated gonadal tissue and can be – at least in part – predicted from the presence of specific immunohistochemical markers. This increase in knowledge has modified our clinical approach to the DSD patient, resulting in an individualized management with regard to tumor risk.[40]

4.33 It is also the case that the authors of the published research continue to repeat their cautions that the estimates and diagnostic models are only preliminary, and are in need of further empirical validation.[41] In these circumstances, the quoting of some of the risk estimates, particularly the higher ones relating to PAIS and 17β-HSD, appears not necessarily to be based on strong evidence. Quoting some of these summary estimates has the potential to hinder the process of objectively assessing individual patient risk, and of ensuring that cancer-related treatment considerations are kept

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36 Histochemistry is the study of the chemistry of organic tissue through observing chemical reactions. Immunohistochemistry studies the reaction patterns associated with the antibodies produced by the immune system. Immunohistochemistry is widely used to detect specific structures in tissues and in the diagnosis of abnormal cells such as those found in tumours.

37 Martine Cools, Arianne Dessens, Stenvert Drop, Jacqueline Hewitt and Gary Warne, answers to questions on notice (received 27 September 2013), emphasis in original.

38 Martine Cools, Stenvert L.S. Drop, Katja P. Wolffenbuttel, J. Wolter Oosterhuis and Leendert H.J. Looijenga, 'Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers', *Endocrine Reviews*, Vol. 27, No. 5, 2006, p. 479.

39 See also Martine Cools, Arianne Dessens, Stenvert Drop, Jacqueline Hewitt and Gary Warne, answers to questions on notice (received 27 September 2013).

40 M. Cools, K.P. Wolffenbuttel, S.L.S. Drop, J.W. Oosterhuis and L.H.J. Looijenga, 'Gonadal development and tumor formation at the crossroads of male and female sex determination', *Sexual Development*, Vol. 5, 2011, p. 178.

41 See, for example, Martine Cools, Leendert H.J. Looijenga, Katja P. Wolffenbuttel, and Sten L.S. Drop, 'Disorders of sex development: update on the genetic background, terminology and risk for the development of germ cell tumors', *World Journal of Pediatrics*, Vol. 5, No. 2, 2009, p. 100.

visibly separate from other factors (such as urogenital corrective surgery, or normalising treatments).

Action to manage cancer versus action to manage intersex

4.34 The committee concluded that one of the causes of disquiet regarding the management of cancer risk is that some of the published literature does not adequately distinguish between the appropriate clinical course of action regarding an intersex person's risk of cancer, and the appropriate clinical course of action to manage a person's intersex condition itself.

4.35 The footnotes to the 2006 table, missing from other later versions, encapsulate this problem. The 2006 table had notes making it clear that the recommended actions did not arise solely from the cancer risk associated with a variety of intersex, but took account of other factors such as the proposed sex of rearing of the child. This clarity was lost once such notes were omitted. By far the most serious omission was in the case of the 2006 Consensus Statement, because of its broad scope and considerable influence.

4.36 In answering the committee's questions about the communication of cancer risk in the literature, Dr Cools and others argued that the 2006 paper discusses the risks in a 'broader context' that is 'different from the studies presented later, focusing primarily on tumor risk'.[42] The balance of evidence does not support this. The paper that they describe as having a 'broader context' is specifically titled 'germ cell tumours in the intersex gonad', and its abstract refers solely to tumour risk and developments in the field in relation to this. The one apparent exception within that paper – the authors' development of an alternative classification schema for intersex – is itself 'proposed as a tool *to refine our insight in the prevalence of germ cell tumors* in specific diagnostic groups'.[43] Within that paper the table is headed 'summary of the risk of germ cell malignancy in the various forms of DSD, subdivided into high, intermediate, low, and possibly no risk', contradicting the argument that the paper is discussing treatment in a broader context compared to later papers, where the table has a very similar title in all cases. Furthermore, if this explanation was correct, then the 2006 Consensus Statement – which definitely does have a far broader context than any of the individual research papers – should have the additional explanations included, yet it does not. Furthermore, the 2006 Consensus Statement explicitly describes the 'recommended actions' in the table as being 'recommendations for management' of the risk of tumour development, not management of the person's intersex condition generally.[44] This does not appear consistent with the explanations offered in the 2006

42 Martine Cools, Arianne Dessens, Stenvert Drop, Jacqueline Hewitt and Garry Warne, answer to questions on notice, (received 27 September 2013), p. 9.

43 Martine Cools, Stenvert L. S. Drop, Katja P. Wolffenbuttel, J. Wolter Oosterhuis and Leendert H. J. Looijenga, 'Germ cell tumors in the intersex gonad: old paths, new directions, moving frontiers', *Endocrine Reviews*, Vol. 27, No. 5, 2006, p. 468, emphasis added.

paper and elsewhere. Finally, the experts' answer to the committee's question argued that the explanations are included in the 2006 paper because of its 'clinically oriented context', yet the 2007 paper, which lacks the explanations, is even more explicitly clinically oriented, appearing in the journal 'Best Practice and Research Clinical Endocrinology and Metabolism', where each section of the article concludes with 'practice points' for clinicians.[45]

4.37 Dr Cools and her Dutch team have sought to advance the scientific understanding and estimation of cancer risk in intersex individuals, and have done so with considerable success. This was intended to provide better information about one key factor in intersex medical decision-making (assessing the patient's cancer risk). Instead, because of the incorporation of a table column listing 'recommended actions' based in part on consideration of other factors such as sex of rearing but with that explanation frequently omitted (most importantly from the 2006 Consensus Statement), the information risks being interpreted as a guide to clinical action *on the grounds of* cancer risk, which it is not.

4.38 This detail is important. There is considerable debate, some of it outlined in the previous chapter, about the merits of performing surgery at different ages. Intersex organisations, regulators, courts and other decision-makers are closely scrutinising, and sometimes relying on, this medical literature to inform this extremely important discussion taking place in the broader community, beyond just the medical professions. To allow this debate to take place transparently and with the confidence of the intersex community, it is essential that the different reasons for medical treatment, and the attendant risks, are characterised separately. Otherwise, decision-making becomes opaque to families, courts, regulators, support groups, and even to external clinicians. This will undermine confidence, in turn prompting calls for blanket bans on particular medical procedures, removing clinicians from decision-making processes. The committee would see these as undesirable outcomes.

Conclusion

4.39 The committee is aware of a risk, not directly discussed by witnesses to the inquiry, that clinical intervention pathways stated to be based on probabilities of cancer risk may be encapsulating treatment decisions based on other factors, such as the desire to conduct normalising surgery. This kind of encapsulation of factors under a single reason is evident in the published tables discussed in this chapter. This might happen because of the distinction made by Australian courts between 'therapeutic' and 'non-therapeutic' medical intervention. Treating cancer may be regarded as unambiguously therapeutic treatment, while normalising surgery may not. Thus

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44 Peter A. Lee, Christopher P. Houk, S. Faisal Ahmed, Ieuan A. Hughes et al, 'Consensus Statement on Management of Intersex Disorders', Paediatrics, Vol. 118, No. 2, 2006. http://pediatrics.aappublications.org/content/118/2/e488.full#xref-ref-2-1 (accessed 26 July 2013).

45 Leendert H.J. Looijenga, Remko Hersmus, J. Walter Oosterhuis, Martine Cools, Stenvert L.S. Drop and Katja P. Wolffenbuttel, 'Tumor risk in disorders of sex development (DSD)', *Best Practice & Research Clinical Endocrinology & Metabolism*, Vol. 21, No. 3, 2007, pp 480–495.

basing a decision on cancer risk might avoid the need for court oversight in a way that a decision based on other factors might not. The committee is disturbed by the possible implications of this.

4.40 If the distinction between therapeutic and non-therapeutic treatment were to be retained, then the committee would draw attention to an example used in Queensland legislation relating to guardianship and the circumstances in which a court should be involved in decisions. The example suggests that decision-makers may need to distinguish between treatment of cancer, and treatment *for the possible risk of* cancer.

> If the child *has cancer* affecting the reproductive system and, without the health care, the cancer is likely to cause serious or irreversible damage to the child's physical health, the health care is not sterilisation.[46]

4.41 An implication of the example is that a treatment for the *risk of* cancer may *not* fall into the category of treatments that do not require authorisation.

4.42 The committee shares others' concerns, however, outlined in the next chapter, regarding the current way in which decision-making occurs for intersex people who are unable to make the decisions for themselves (generally children), including concerns about the distinction between therapeutic and non-therapeutic treatment. The committee does not favour the status quo. Chapter 3 and this chapter have both outlined how complex and contentious is some of the information that supports medical treatment of intersex people.

Recommendation 5

4.43 In light of the complex and contentious nature of the medical treatment of intersex people who are unable to make decisions for their own treatment, the committee recommends that oversight of these decisions is required.

4.44 The next chapter considers what such a system of oversight should look like.

46 *Guardianship and Administration Act 2000 (Qld)*, s. 80B (Example), emphasis added.