1 Introduction: Changing Landscapes

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What's in a name? *A rose by any other* ***name*** *would smell as sweet.*

Ref Romeo and Juliet. Shakespeare

To open a book with an uncertainty regarding what term and title to use sounds like a poor start. Yet, to put this uncertainty and challenge upfront highlights exactly the issues that this book wishes to tackle.

The cluster of conditions collected under the expression Disorders|Divergences|Differences of Sex Development (DSD), Conditions Associated with Reproductive Development (CARD), Intersex and Variations in Sex Characteristics (VSC) consist of those associated with atypical genetic, phenotypic or hormonal makeup.

Where possible, each individual condition has its own specific or diagnostic term, which attempts to describe the difference or variation in a recognisable, defined way. This serves to enable advancement and achievement of understanding and optimal health care—so that we can share knowledge and experience, and thereby, we are all speaking the same language.

The challenge lies in the 'umbrella' expression or terminology. It is this expression which is fraught with difficulties, as two of the key umbrella expressions (DSD and intersex) are not directly interchangeable, and an individual who may have a condition that falls under a medical DSD classification (e.g. Turner syndrome) may identify with one term but not the other, or indeed neither.

There are also challenges in deciding which conditions or variations should be included and excluded under a given umbrella expression, as well as what care is required to provide optimal outcomes for affected babies, infants, young people and adults.

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The word disorder has been avoided here—yet it does remain in the title of this book. This has been done, partly to reflect the relationship with the first edition, now several years old, and partly because, although we recognise that times have changed and the terminology is changing, to date, there is no consensus on a new term. At the time of writing, this is still the umbrella term most commonly used and recognised in the medical literature. We do acknowledge that it is not a universally accepted term and is perceived by many as having unnecessarily 'pathologising' connotations. For this reason, we have adjusted the title to Disorders|Differences of Sex Development, and we will use the abbreviation 'DSD' throughout the book to allow scope for readers to use or infer their preferred term. As clinicians, we rarely use any umbrella term in our clinical interactions with an individual or family.

This book acknowledges that there are different 'ways of knowing' (Lundberg 2017). Its contents may provide information that not everyone wants or needs to know or understand. For others, this book may only provide an overview and a background to understanding and knowing about DSD.

For families and people with DSD, knowing and understanding their respective conditions as well as about the related challenges and controversies is an important stepping stone to knowing oneself or one's child's condition and subsequently towards gaining optimal health outcomes.

The information in this book is the result of knowledge, collected and shared, as well as our different perspectives of knowing based on our different backgrounds as health clinicians. The evidence and knowledge comes from a clinical team that has grown and changed and learnt together and learnt from our patients, as we have provided care to people with DSD for over 30 years. Taking this multidisciplinary skill set, we hope to continue to learn and further develop our knowledge of DSD into the future. While the information provided here is current at the time of writing, it will undoubtedly also change with improvements in our understanding and knowledge in years to come.

1.1 Background

1.1.1 Terminology

In 2005, there was an international consensus meeting that endeavoured to establish some consistency in definitions of various conditions in order to lay the groundwork for international research and guidelines for care in this field (Chicago consensus statement—Hughes et al. 2006). Previously, the management and long-term outcomes of people with this cluster of diagnoses had been poorly studied, as work in this area was challenged by a lack of consistency in terminology to enable accurate comparisons between clinicians and researchers in different cities and countries. Additionally, there were challenges associated with old terminology that were not only confusing but also insensitive to those people with these conditions.

At the Chicago consensus meeting, the 'Disorders of Sex Development' classification system was proposed and thereafter adopted in the medical literature as an umbrella expression to define 'congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical.' There was also a reclassification of the variety of conditions that are encompassed by this label to enable collaboration and more effective comparison internationally with all researchers and clinicians using a common language and classification. Affected individuals and advocates were, and continue to be, vital in the push for more research and long-term follow-up. This classification could be considered a medical or even genetic classification system. This is true as the development of a structured descriptive classification system that allows similar data to be collected, and comparison to improve outcomes was one of the aims of the meeting. Moreover, it was recognised that more accurate data on malignancy risks would be useful for those

trying to contribute to ensuring the best possible health outcomes.

The medical terms 'condition' and 'diagnosis' are not intended as negative expressions or descriptions. One can have hair or eye colour as a description, or a diagnosis of heart or kidney conditions, without there being any intention that the term 'diagnosis' is negative. It is simply a description. One should not be judged for any of these differences. For some people with a 'diagnosis' such as a heart condition, treatment may be recommended, whereas for others, no intervention or specific care is required, or potentially, some monitoring for possible future risks. Likewise, the expression of having a condition or diagnosis related to the field that this book focuses on does not mean that it is a problem; again, it is simply a description.

Since 2006, there has been ongoing debate regarding the most appropriate language with some affected individuals, advocates or clinicians preferring alternative expressions. We acknowledge this, and in using the term DSD, we intend no offence to those who do not identify with this descriptor.

This debate is challenging, as clinicians would rarely use the umbrella expression in the setting of individual patient care. Additionally, it is our experience that affected individuals and their families when asked (e.g. CAH support group meeting Melbourne 2016, MRKH support group Melbourne 2018, (Mortimer 2017)) report that they would prefer the expressions that describe their exact diagnosis and very infrequently would they prefer the expressions intersex or disorder of sex development. Yet for many affected individuals and advocacy groups, 'intersex' is the preferred expression/term (see Darlington statement 2017). A European/UK study specifically undertaken to explore how young people affected by these diagnoses, their parents and focus groups of people with no previous knowledge or experience with these diagnoses or understanding of the different terms found that none preferred DSD; the focus group participants preferred 'intersex' and affected young people and their families preferred descriptive terms (Lundberg et al. 2018). Likewise, in a study undertaken by DSD-life, 45% of participants agreed that DSD applied to their medical condition and 43% considered 'intersex' a bad term; however, almost one-third disagreed that DSD applied to them (Bennecke and De Vries 2016). Recent Australian research also reported broad acceptance of the term 'intersex' amongst affected individuals, with 60% comfortable to use the word in some way to self-describe themselves; of the same cohort, only 3% of respondents reported using the term DSD (Jones et al. 2016). This research also reported that affected individuals preferred words specifically describing their own diagnosis when talking with friends and family and when accessing medical services. In our experience, it is rare for either umbrella term (DSD or intersex) to be used in clinical consultations or in conversations with an affected individual. Thus, although DSD may be used in medical literature, actual clinical practice aligns with the preferences of affected individuals.

In many public and political settings, the expression 'intersex' has become the standard term and has been incorporated into the ambit of the sexuality and gender diverse LGBT grouping, to make LGBTI.

'Disorders', as defined in a medical sense in the Oxford dictionary, refer to a disruption of normal function, a lack of order or regular arrangement. Hence, people may have disorders of metabolism or metabolic disorders, disorders of growth/growth disorders, genetic disorders, bleeding disorders and many others. Importantly, it is not the people who are disordered nor are they less of an individual because of their specific disorder. This issue with language is more pronounced in English than some other languages. In the English language, the expression '*I am cold*' can be confusing, as it could mean *I am cold/freezing* or that I am a cold (distant and potentially unpleasant) person. In other languages, for example, German, this confusion does not exist, as the sentence structure precludes this confusion, so that '*Mir ist kalt*' (I feel cold [e.g. due to weather]) is quite different from '*Ich bin kalt*' (I am a cold person). Yet, it is worth noting that, even in Germany, the debate regarding DSD terminology exists.

Definitions and meanings change over time. Given that this book is about sex development, a simple example relates to colours and dichotomous sex stereotypes. From the mid-1900s, colours have been increasingly used to denote gender, with girls/females being linked to pink and often clothed in pink (with the stereotypical presumption that they have a preference for this colour), whereas boys/males have been linked to the colour blue (Del Giudice 2012). Prior to this, the gender coding of pink and blue was inconsistent and not used in such a gender-dimorphic manner to masculinity and femininity (Paoletti 1997).

The origins of our words are clearly very old, and thus, it is not surprising that the meanings and significance change. English dictionaries tell us that the word 'sex' came from *sexe* (from middle French, 1382), which comes from the Latin *sexus* (gender), derived from *seco, secare* ('divide, cut') in the concept of 'half' of the race. 'Sex' tends to refer to biological differences, and historically, there was male sex and other, or male and a second sex.

In contrast, the expression 'gender' comes from *gendre* (old French), which is derived from Latin *genus* (gender) birth, family, nation. 'Gender' tends to refer to cultural or social aspects of sex.

Historically, the concept of a people who do not fit the dichotomous male/female sex and gender extends well back into Mesopotamian mythology. Inscribed upon a stone tablet from the second millennium BC (Sumer—pre Babylon), there is a myth about the creation of a type of human who is neither man nor woman. The goddess Ninmah fashions a being with 'no male organ and no female organ', for whom there is a position in society—'to stand before the king.' In an Akkadian myth, the goddess of birth establishes a third category of people, which includes demons who steal infants, women who are unable to give birth and priestesses who are prohibited from bearing children (Murray and Roscoe 1997).

In India's three ancient spiritual traditions—Hinduism (Wilhelm 2004), Jainism (Zwilling and Sweet 1996) and Buddhism (Jackson 1996), there is also reference to a third gender. In the Buddhist Vinaya (codified around the second century BC), there were four main categories: male, female, people of dual sexual nature and people of various sexual natures (Jackson 1996; Gyatso 2003).

A 'third sex' known as Hijra (in Hindi हिजड़, in Urdu ہجڑ) exists in India, Pakistan and Bangladesh. These people are mostly men dressed as women, although they are not trying to pass as female. Less than 10% are thought to have a DSD. Although this population has been held up as an example that these societies tolerate non-dichotomous sexuality, it is worth noting that the Hijra hold a very low social status, with a very defined function in society. They appear at weddings and births to bring good luck; refusing their presence will bring bad luck (Khan et al. 2009).

Sexuality is defined as *how* people experience the erotic and express themselves as sexual beings. Again, this has changed over time. In ancient Egypt and Greece, homosexuality was well described and accepted, with evidence from the tomb of Niankhkhnum and Khnumhotep, as well as in Homer's The Iliad. In Persia (1500s–1700s), homosexuality was well accepted in public (with the existence of erotic poems, and male prostitution houses that paid taxes). During the Renaissance, in northern Italy, same-sex love was widespread, although authorities were prosecuting individuals. In the mid-1800s, in European culture, homosexuality was a crime and considered an abnormality that required treatment. Nowadays, in many places, homosexuality is recognised and accepted, including having all the relevant legal rights (many of which were previously denied). The Royal College of Psychiatry considered 'Sexual orientation biological in nature' in 2014, and homosexuality was removed from DSM in 1973 (Bayer 1981). But there are many countries today where sadly homosexuality is still not tolerated or is considered an abnormality. As a general principle, broader societal awareness and acknowledgement of diversity is very important in ensuring its acceptance.

1.1.2 Recent History of DSD

From a more recent historical perspective, a number of important developments that have impacted significantly on the clinical management of individuals with DSD occurred in the 1980s and 1990s.

Patient advocacy groups were first established in the late 1980s and early 1990s and became vocal, establishing a 'contested collaboration' (Kessler 1998; Davis 2015). Some patient advocacy groups took a high-profile approach (Intersex Society of North America (now named Accord Alliance), Organisation Intersex International), appearing at conferences and challenging the attending clinicians. Important limitations in clinical care such as a lack of robust outcome studies and insufficient psychological support were thus increasingly brought to the attention of the clinicians. Unfortunately, in many countries, the ongoing lack of funding for comprehensive prospective patient databases to support high-quality research means that longitudinally acquired data on medium- and long-term outcomes are still relatively limited.

In the late 1990s, John Colapinto publicised the long-term outcome of the life of David Reimer following a disastrous surgical accident, whereby he suffered irreparable damage to his penis when cauterising equipment malfunctioned during a circumcision at the age of 8 months in Canada in 1966 (Colapinto 1997, 2000, 2001). At the age of 22 months, David Reimer's parents were advised to raise 'John' (one of twin boys) as 'Joan' following the recommendations of Dr. John Money, a renowned psychologist at the time, based at John Hopkins University. Money's theory of gender identity development, which was then increasingly popular, claimed that gender was a societal construct that was malleable; hence, nurture rather than nature determined gender identity (Money 1985). Thus, appropriate nurturing and 'corrective'/feminising surgery (orchidectomy and feminising genitoplasty) were recommended to reinforce the gender role. As children, David (Joan) and his twin brother were not told that they were both born boys; nor did they know the story of David's surgeries. Money regularly presented this 'John/Joan' case as a success story in academic settings, which led to both dissemination of and increased support for the theory, hence potentially influencing medical/surgical decisions in the management of children with DSD where sex of rearing was uncertain in infancy. Sadly, this was despite there reportedly being evidence when David (Joan) was as young as 6 years old that he was increasingly unhappy with his female sex assignment (Diamond and Sigmundson 1997). He went on to have pubertal induction with oestrogen, but on learning his personal history as an adolescent, he transitioned to living as a male with the name David. In allowing his story to be told publically in the late 1990s, a number of issues relating to his care were highlighted, not only in relation to apparent inaccuracies in Dr. Money's theory and reporting of the case, but also in relation to the importance of open disclosure and optimal information sharing in clinical settings and decision-making. While David's path arose from an acquired injury rather than a congenital DSD, there were many similarities and implications for care pathways in DSD, which is why it is included here.

Furthermore, in the 1990s, there were several publications regarding gender change from female to male in classical CAH (Warne 1992; Meyer-Bahlburg et al. 1996). These cases additionally highlighted that future gender identity was beyond the control of managing clinicians and emphasised the need for awareness amongst all parties (family and clinicians) that, while sex assignment can occur at birth, gender cannot be known by anyone other than a given individual.

From the early 2000s, along with the increasing recognition of the role of patient advocacy and a desire to review management strategies and long-term outcomes, these events culminated in the 2005 Chicago meeting, the changed definition and terminology, as well as recommendations in relation to management of various conditions (Hughes et al. 2006). Management guidelines continue to be revised and evolve as knowledge also improves (Ahmed et al. 2016; Lee et al. 2016; Cools et al. 2018). While the terminology remains

contentious, since the introduction of the medical DSD classification system, there has been a significant increase in DSD-related scientific publications and DSD-specific international meetings and conferences, all of which will serve to further advance knowledge in the field. In tandem with this, our understanding of the underlying genetic variants that may be associated with different DSD has also increased exponentially. These will be discussed further in Chap. 2.

1.1.3 Clinical Definition of DSD

If the challenge regarding definitions is now extended to the clinical definition of DSD, further problems arise. There are a number of diagnoses for which there is ongoing debate as to whether they belong under the DSD umbrella. In particular, this applies to structural anomalies such as bladder exstrophy and cloacal anomalies. Hypospadias, in its more severe forms, is increasingly recognised as a DSD, with specific genetic testing allowing recognition of variations in hormone production and androgen receptor sensitivity. But should the less severe forms of hypospadias be considered a DSD? In line with the decision to stay with the terminology of 'DSD' that arose at the Chicago meeting, this book will encompass those conditions that were accepted at that consensus meeting (Table 1.1).

Table 1.1 Summary of new terminology

Title	Previous terminology
Disorders of sex development	Intersex
46,XY DSD	Male pseudohermaphrodite Under-virilised male Under-masculinised male
46,XX DSD	Female pseudohermaphrodite Virilised female Masculinised female
Ovo-testicular DSD	True hermaphrodite
46,XY complete gonadal dysgenesis	XY female XY sex reversal
46,XX testicular DSD	XX male XX sex reversal

Adapted from Hughes et al. (2007)

1.1.4 Incidence of DSD

The incidence of DSD is clearly influenced by which definition is used. A few incidences of the common forms of DSD are shown in Table 1.2. Many estimates of the relative proportion of the different diagnoses have used the selection criteria as ambiguous genitalia. Few papers have used the Chicago definition. A study at The Royal Children's Hospital in Melbourne attempted to utilise the Chicago definition but limited the cohort to children aged up to 10 years. This means that adolescents presenting with lack of pubertal development and girls with primary amenorrhoea were not identified in this cohort (Table 1.2).

Beyond acknowledging the challenges in terminology, definitions and incidence of these conditions, this discussion is not the primary purpose of this book. This book aims to explore the challenges of providing optimal care in situations where outcomes are often uncertain.

1.1.5 Clinical Care: Historical Perspective and Changes Over Time

History has a place to play here, as what is known in medical and psychological spheres has changed over time, and thus, what care is possible has changed rapidly in recent decades. This is important, as a comparison of care provided 30 or 40 years ago will reflect significantly different knowledge.

The first report of a female with congenital adrenal hyperplasia (CAH) is thought to be from 1865 (De Crecchio 1865). Although the association between altered function of the adrenal gland and excessive sex steroid production ('adrenogenital syndrome') was understood in the early twentieth century, it was not until 1950 that the successful use of cortisone as a therapeutic intervention to alleviate excess ACTH stimulation was first reported. The endocrine basis of congenital adrenal hyperplasia (CAH) was only discovered in 1953 by Lawson Wilkins, an endocrinologist in Baltimore (Wilkins 1965). Further advances in

Table 1.2 Diagnostic breakdown of reported DSD cohorts

Authors	Country	Cohort size	Study population	Common diagnoses
Parisi et al. (2007)	United States	250	Children with DSD assessed by hospital gender team (excluding Klinefelter, Turner and multiple congenital abnormality patients)	CAH 14% AIS 10% MGD 8%
Thyen et al. (2006)	Germany	80	Infants with ambiguous genitalia	CAH 18% AIS 16% MGD 9%
Al Agha et al. (2001)	Australia	51	Infants with ambiguous genitalia	CAH 31% AIS 10% MGD 6%
Bhullar et al. (2011)	Melbourne	199	All children aged 0–10 years identified with DSD using consensus statement	Perineal hypospadias 34% CAH 22% Exstrophy 14%
Joshi et al. (2006)	India	109	Infants with ambiguous genitalia	CAH 28% AIS 15% 5ARD 12%

CAH congenital adrenal hyperplasia, *AIS* androgen insensitivity syndrome, *MGD* mixed gonadal dysgenesis, *5ARD* 5α-reductase deficiency

genetics and classification of different enzyme deficiencies followed in the 1960s. Synthetic glucocorticoid and mineralocorticoid medications have been available since the 1950s; however, these medications are still not readily accessible in some parts of the world. Thus, even survival for a child with salt-losing 21-hydroxylase deficiency congenital adrenal hyperplasia (CAH) is a relatively recent expectation, and even today in some parts of the world, the mortality of affected children, particularly boys with severe salt-wasting CAH, remains high (see Chap. 22). In some parts of the world, the essential hormonal treatment is available only on the black market, thus compromising health and increasing mortality and morbidity.

Vaginal agenesis was recognised in ancient Greek times with endeavours to create a vagina dating back to 460 BC by Hippocrates (Goldwyn 1977). Today, there are a number of different techniques of creating a vagina, including approaches that require no surgery, yet we still do not know which approach results in the best long-term outcomes (McQuillan and Grover 2014a, b).

The capacity to provide hormone replacement therapy for people with non-functioning ovaries or testes to allow the development of secondary sexual characteristics and, importantly, provide the necessary protection for bone and cardiovascular health became available only in the last few decades.

Children with bladder and cloacal exstrophy still die in many parts of the world due to lack of access to the necessary complex surgery.

The first surgery for CAH was undertaken in the late 1950s. Open disclosure to patients and their families began in the Royal Children's Hospital and some other places in the 1980s, although in many places, this may not be still happening. Previously, this full disclosure and explanation regarding the underlying diagnosis and previous interventions (if relevant) was not given, in the misguided belief that knowing might be more painful or difficult. Clearly, evidence and experience have shown that this approach was not appropriate.

Over the last decade, psychosocial support for DSD has been recognised to be an essential aspect of medical care. Testimony from cohorts of adults who have been treated as infants and children without these supports and resources has highlighted their importance.

Therefore, over time, evolution in medical understanding and interventions have allowed

gradual improvements in the understanding of, and care across, a number of diagnoses. However, there have been many areas where proposed therapeutic interventions have been subsequently shown over time not to result in the desired outcome. Surgical interventions in particular have been the subject of increased debate and with increased recognition of the potential for adverse outcomes in this regard, approaches have changed in recent years and continue to evolve (Hrabovszky and Hutson 2002). The practice of early genital surgery and sex assignment has shifted in recent decades. For example, in the late twentieth and early twenty-first centuries, in boys with partial androgen insensitivity syndrome (PAIS), where a female sex of rearing was assigned based on genital appearance at birth and predictions of little further virilisation of appearance in puberty, interventions such as removal of testes in childhood were commonly undertaken. It is now recognised that this intervention can lead to harm and many affected individuals who had such surgery in childhood are deeply unhappy that this occurred. Prior to 1990, 35% of those with 46,XY DSD diagnosed as PAIS, variations of gonadal development or androgen biosynthesis were assigned male, compared to 68% after 1999 (Kolesinska et al. 2014). Various factors contribute to this trend, including shifting cultural and societal views, improved surgical reconstruction techniques and better understanding about the potential fertility, oncogenic risk and adult gender identity in this cohort. Gender dysphoria is not uncommon in individuals with PAIS, but this is regardless of sex assigned and not convincingly influenced by such surgery. While malignancy risk is higher in intra-abdominal gonads in those with PAIS, this risk is low pre-puberty; hence, removal of gonads is now recognised to be more appropriately considered at an age when the individual can be involved in this decision for themselves (see Chap. 7). Deferring such surgery also allows for potential effects of endogenous hormone production in puberty and an individual's own gender identity to be established.

In contrast, those conditions where there are gonads with Y genetic material but the gonads are non-functioning (i.e. with no fertility potential and no hormone production), there can be a malignancy risk of up to 30%, even in childhood. Hence, removal of these gonads is considered important to prevent cancer.

Other surgeries performed in individuals with DSD are also the subject of much debate. Feminising genitoplasty for girls with CAH is a case in point, with opinions on this intervention ranging from support in those with significant virilisation (Prader stage 3+) due to the high incidence of satisfaction with outcomes (e.g. RCH follow-up studies (Lean et al. 2005, 2007; Crawford et al. 2009)) to opinions that it should not be performed in infancy (Creighton et al. 2001) but rather deferred until the girl herself is old enough to be involved in the decision.

1.1.6 Human Rights and DSD: Where to from Here?

Internationally, in recent years, human rights agencies and UN treaty bodies, agencies and special rapporteurs have increasingly called on Member States to strengthen protections for the human rights of people born with variations in sex characteristics (e.g. San Francisco 2005, Germany 2012, Switzerland 2012). In 2013, the UN Human Rights Council called upon all states to repeal laws allowing 'intrusive and irreversible treatments for children with intersex variations'. Such interventions included genital surgery and involuntary sterilisation without the free and informed consent of the person concerned (UNHRC 2013). In 2016, a group of UN and international human rights experts published a statement on Intersex Awareness Day (26 October) that sought for governments to prohibit medical procedures on intersex infants, children and adolescents without 'the full, free and informed consent of the person concerned (http://www.ohchr.org/EN/NewsEvents/Pages/DisplayNews.aspx?NewsID=20739&LangID=E).

It is clear therefore that there is growing impetus for change in this space in recent years. Rulings such as those from the UN where people with intersex variations who have experienced so-called 'normalising' surgery or treatment have

been recognised as 'victims of abuses and mistreatment', and where medical interventions have been labelled 'harmful practices,' may understandably be confronting for clinicians and surgeons who have offered such interventions with best intentions for optimal outcomes. Nonetheless, although not universal, suboptimal historical outcomes cannot be ignored and the lived experience of affected individuals has both changed practices and greatly increased awareness of the need to continually scrutinise all interventions undertaken. However, it remains the case today that the life-course and outcomes of a given individual with some DSD (such as PAIS or androgen biosynthetic variations) can be very difficult to predict in infancy or childhood, and decisions that may result in future regret are, and will likely remain, difficult to fully eliminate. It should be noted that this may indeed be the case whether a decision to intervene or to defer intervention is made. Deferring intervention, particularly where outcomes in relation to this are unknown (and should not automatically be presumed to be better), is as much a decision as opting to intervene.

How best to progress to ensure ongoing improvement to maximising optimal outcomes for affected individuals not surprisingly remains the subject of much debate. Clinically, there has been a significant shift over the last decade towards optimising care through management in specialised multidisciplinary teams, using a clinical ethics framework (see Chap. 15 for detailed discussion). A clinical ethics framework incorporates key concerns from the human rights field, but framed in a way that gives room for nuanced considerations of the circumstances of each individual child. Human rights discourse has a tendency to be black-and-white, implying that one approach is always the right thing for every individual. It works best for civil and political rights, which can reasonably be seen to transcend individual difference. In contrast, the principle-based approach of clinical ethics aims to better acknowledge the complexity of seeking to promote each individual's well-being in their specific circumstances. There are multiple aspects of a person's well-being, and the clinical ethics framework allows for structured ethical consideration of these in decision-making for each individual.

Many individual DSD or variations are very uncommon, hence infrequently encountered even in large tertiary clinical centres. This, along with the many uncertainties in outcomes, means that decisions in relation to care are often highly complex and need to be taken in the context of current knowledge, with open discussion of the uncertainties and controversies in approaches, while being individualised for a given child and family's unique circumstances.

Approaches to these difficult issues vary internationally. In 2015, Malta became the first country to institute a legal ban to prohibit deferrable interventions or surgery. Groups in other countries are also seeking legal frameworks. For example, in March 2017, Australian and Aotearoa/New Zealand intersex organisations and independent advocates issued a joint consensus statement (Darlington Statement 2017) calling for the criminalisation of deferrable medical interventions and the development of human rights-based lifetime standards of care. This statement also declared, however, that the Family Court system (in Australia) has 'failed to adequately consider the human rights and autonomy of children born with variations of sex characteristics'; hence, oversight in this setting is not thought to be optimal (nor likely feasible). An alternative put forward in place of the Court was an 'independent effective human rights-based oversight mechanism/s consisting of human rights experts, clinicians and intersex-led community organisations'.

Deferring decisions about surgery until an age when an individual may develop the capacity to be involved in decisions relating to their own care fits in with rights-based considerations such as autonomy and bodily integrity. However, the effects of deferring such decisions on the overall well-being of the child and future adult are not known. There are currently no data to support the hypothesis that such a management plan will invariably have preferable outcomes to interventions performed earlier, with informed parental consent on the child's behalf. As surgical prac-

tices and techniques have evolved (albeit to varying extents internationally), regulating to put a blanket ban on all surgery in infancy on the basis of sub-optimal outcomes using historical evidence from outdated surgical practices, is argued to not be a sound approach.

There is, however, some agreed ethical ground. Perhaps one of the most notable advances in recent decades is much greater involvement of parents of young children and older children themselves in decision-making. As part of best practice, clinicians discuss with parents and older children both what is known and not known about the child's particular condition and introduce some of the existing controversies in relation to potential management. Awareness of and openness to change over time (e.g., in future, gender identity relative to assigned sex in infancy) are increasingly promoted. Parents' and adolescents' decision-making and consent to any intervention is arguably much better informed than it has been in the past.

We do not presume to give final answers to these difficult issues in this book, but rather raise them to highlight the many changes that are occurring in the current context in which children and adolescents with DSD are managed. Like all ethical issues, good ethics depends on good facts. Recent and ongoing scientific advances such as the generation of international/multicentre registries (e.g. iDSD, iCAH and the DSD Translational Research Network) and ongoing strides in our understanding of the genetics relating to DSD will increasingly allow the collection of higher quality prospectively acquired data in very specific conditions, to optimally inform progress in this regard. Good ethics also depends on sustained reflection and deliberation on the values underpinning decision-making, recognition of pluralism about values in our communities and awareness of the limits of one's own perspective. So we can expect good ethics to lead to further debate and further change over time.

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