the intent is that hormones and the real-life experience be thoughtfully and recurrently considered over time. In those patients who have already begun the real-life experience prior to being seen, the professional should work closely with them and their families with the thoughtful recurrent consideration of what is happening over time.

Irreversible Interventions. Any surgical intervention should not be carried out prior to adulthood, or prior to a real-life experience of at least two years in the gender role of the sex with which the adolescent identifies. The threshold of 18 should be seen as an eligibility criterion and not an indication in itself for active intervention.

VI. Psychotherapy with Adults

A Basic Observation. Many adults with gender identity disorder find comfortable, effective ways of living that do not involve all the components of the triadic treatment sequence. While some individuals manage to do this on their own, psychotherapy can be very helpful in bringing about the discovery and maturational processes that enable self-comfort.

Psychotherapy is Not an Absolute Requirement for Triadic Therapy. Not every adult gender patient requires psychotherapy in order to proceed with hormone therapy, the real-life experience, hormones, or surgery. Individual programs vary to the extent that they perceive a need for psychotherapy. When the mental health professional's initial assessment leads to a recommendation for psychotherapy, the clinician should specify the goals of treatment, and estimate its frequency and duration. There is no required minimum number of psychotherapy sessions prior to hormone therapy, the real-life experience, or surgery, for three reasons: 1) patients differ widely in their abilities to attain similar goals in a specified time; 2) a minimum number of sessions tends to be construed as a hurdle, which discourages the genuine opportunity for personal growth; 3) the mental health professional can be an important support to the patient throughout all phases of gender transition. Individual programs may set eligibility criteria to some minimum number of sessions or months of psychotherapy.

The mental health professional who conducts the initial evaluation need not be the psychotherapist. If members of a gender team do not do psychotherapy, the psychotherapist should be informed that a letter describing the patient's therapy might be requested so the patient can proceed with the next phase of treatment.

Goals of Psychotherapy. Psychotherapy often provides education about a range of options not previously seriously considered by the patient. It emphasizes the need to set realistic life goals for work and relationships, and it seeks to define and alleviate the patient's conflicts that may have undermined a stable lifestyle.

The Therapeutic Relationship. The establishment of a reliable trusting relationship with the patient is the first step toward successful work as a mental health professional. This is usually accomplished by competent nonjudgmental exploration of the gender issues with the patient during the initial diagnostic evaluation. Other issues may be better dealt with later, after the person feels that the clinician is interested in and understands their gender identity concerns.

Ideally, the clinician's work is with the whole of the person's complexity. The goals of therapy are to help the person to live more comfortably within a gender identity and to deal effectively with non-gender issues. The clinician often attempts to facilitate the capacity to work and to establish or maintain supportive relationships. Even when these initial goals are attained, mental health professionals should discuss the likelihood that no educational, psychotherapeutic, medical, or surgical therapy can permanently eradicate all vestiges of the person's original sex assignment and previous gendered experience.

Processes of Psychotherapy. Psychotherapy is a series of interactive communications between a therapist who is knowledgeable about how people suffer emotionally and how this may be alleviated, and a patient who is experiencing distress. Typically, psychotherapy consists of regularly held 50-minutes sessions. The psychotherapy sessions initiate a developmental process. They enable the patient's history to be appreciated, current dilemmas to be understood, and unrealistic ideas and maladaptive behaviors to be identified. Psychotherapy is not intended to cure the gender identity disorder. Its usual goal is a long-term stable life style with realistic chances for success in relationships, education, work, and gender identity expression. Gender distress often intensifies relationship, work, and educational dilemmas.

The therapist should make clear that it is the patient's right to choose among many options. The patient can experiment over time with alternative approaches. Ideally, psychotherapy is a collaborative effort. The therapist must be certain that the patient understands the concepts of eligibility and readiness, because the therapist and patient must cooperate in defining the patient's problems, and in assessing progress in dealing with them. Collaboration can prevent a stalemate between a therapist who seems needlessly withholding of a recommendation, and a patient who seems too profoundly distrusting to freely share thoughts, feelings, events, and relationships.

Patients may benefit from psychotherapy at every stage of gender evolution. This includes the post-surgical period, when the anatomic obstacles to gender comfort have been removed, but the person may continue to feel a lack of genuine comfort and skill in living in the new gender role.

Options for Gender Adaptation. The activities and processes that are listed below have, in various combinations, helped people to find more personal comfort. These adaptations may evolve spontaneously and during psychotherapy. Finding new gender adaptations does not mean that the person may not in the future elect to pursue hormone therapy, the real-life experience, or genital surgery.

Activities:

Biological Males:

1. Cross-dressing: unobtrusively with undergarments; unisexually; or in a feminine fashion;
2. Changing the body through: hair removal through electrolysis or body waxing; minor plastic cosmetic surgical procedures;
3. Increasing grooming, wardrobe, and vocal expression skills.

Biological Females:

1. Cross-dressing: unobtrusively with undergarments, unisexually, or in a masculine fashion;
2. Changing the body through breast binding, weight lifting, applying theatrical facial hair;

3. Padding underpants or wearing a penile prosthesis.

Both Genders:

1. Learning about transgender phenomena from: support groups and gender networks, communication with peers via the Internet, studying these Standards of Care, relevant lay and professional literatures about legal rights pertaining to work, relationships, and public cross-dressing;
2. Involvement in recreational activities of the desired gender;
3. Episodic cross-gender living.

Processes:

1. Acceptance of personal homosexual or bisexual fantasies and behaviors (orientation) as distinct from gender identity and gender role aspirations;
2. Acceptance of the need to maintain a job, provide for the emotional needs of children, honor a spousal commitment, or not to distress a family member as currently having a higher priority than the personal wish for constant cross-gender expression;
3. Integration of male and female gender awareness into daily living;
4. Identification of the triggers for increased cross-gender yearnings and effectively attending to them; for instance, developing better self-protective, self-assertive, and vocational skills to advance at work and resolve interpersonal struggles to strengthen key relationships.

VII. Requirements for Hormone Therapy for Adults

Reasons for Hormone Therapy. Cross-sex hormonal treatments play an important role in the anatomical and psychological gender transition process for properly selected adults with gender identity disorders. Hormones are often medically necessary for successful living in the new gender. They improve the quality of life and limit psychiatric co-morbidity, which often accompanies lack of treatment. When physicians administer androgens to biologic females and estrogens, progesterone, and testosterone-blocking agents to biologic males, patients feel and appear more like members of their preferred gender.

Eligibility Criteria. The administration of hormones is not to be lightly undertaken because of their medical and social risks. Three criteria exist.

1. Age 18 years;
2. Demonstrable knowledge of what hormones medically can and cannot do and their social benefits and risks;
3. Either:
   a. A documented real-life experience of at least three months prior to the administration of hormones; or
   b. A period of psychotherapy of a duration specified by the mental health professional after the initial evaluation (usually a minimum of three months).

In selected circumstances, it can be acceptable to provide hormones to patients who have not fulfilled criterion 3 – for example, to facilitate the provision of monitored therapy using hormones of known quality, as an alternative to black-market or unsupervised hormone use.

Readiness Criteria. Three criteria exist:

1. The patient has had further consolidation of gender identity during the real-life experience or psychotherapy;
2. The patient has made some progress in mastering other identified problems leading to improving or continuing stable mental health (this implies satisfactory control of problems such as sociopathy, substance abuse, psychosis and suicidality;
3. The patient is likely to take hormones in a responsible manner.

Can Hormones Be Given To Those Who Do Not Want Surgery or a Real-life Experience? Yes, but after diagnosis and psychotherapy with a qualified mental health professional following minimal standards listed above. Hormone therapy can provide significant comfort to gender patients who do not wish to cross live or undergo surgery, or who are unable to do so. In some patients, hormone therapy alone may provide sufficient symptomatic relief to obviate the need for cross living or surgery.

Hormone Therapy and Medical Care for Incarcerated Persons. Persons who are receiving treatment for gender identity disorders should continue to receive appropriate treatment following these Standards of Care after incarceration. For example, those who are receiving psychotherapy and/or cross-sex hormonal treatments should be allowed to continue this medically necessary treatment to prevent or limit emotional lability, undesired regression of hormonally-induced physical effects and the sense of desperation that may lead to depression, anxiety and suicidality. Prisoners who are subject to rapid withdrawal of cross-sex hormones are particularly at risk for psychiatric symptoms and self-injurious behaviors. Medical monitoring of hormonal treatment as described in these Standards should also be provided. Housing for transgendered prisoners should take into account their transition status and their personal safety.

VIII. Effects of Hormone Therapy in Adults

The maximum physical effects of hormones may not be evident until two years of continuous treatment. Heredity limits the tissue response to hormones and this cannot be overcome by increasing dosage. The degree of effects actually attained varies from patient to patient.

Desired Effects of Hormones. Biologic males treated with estrogens can realistically expect treatment to result in: breast growth, some redistribution of body fat to approximate a female body habitus, decreased upper body strength, softening of skin, decrease in body hair, slowing or stopping the loss of scalp hair, decreased fertility and testicular size, and less frequent, less firm erections. Most of these changes are reversible, although breast enlargement will not completely reverse after discontinuation of treatment.

Biologic females treated with testosterone can expect the following permanent changes: a deepening of the voice, clitoral enlargement, mild breast atrophy, increased facial and body hair and male pattern baldness. Reversible changes include increased upper body strength, weight gain, increased social and sexual interest and arousability, and decreased hip fat.

Potential Negative Medical Side Effects. Patients with medical problems or otherwise at risk for cardiovascular disease may be more likely to experience serious or fatal consequences of cross-sex hormonal treatments. For example, cigarette smoking, obesity, advanced age, heart disease, hypertension, clotting abnormalities, malignancy, and some endocrine abnormalities may increase side effects and risks for hormonal treatment. Therefore, some patients may not be able to tolerate cross-sex hormones. However, hormones can provide health benefits as well as risks. Risk-benefit ratios should be considered collaboratively by the patient and prescribing physician.

Side effects in biologic males treated with estrogens and progestins may include increased propensity to blood clotting (venous thrombosis with a risk of fatal pulmonary embolism), development of benign pituitary prolactinomas, infertility, weight gain, emotional lability, liver disease, gallstone formation, somnolence, hypertension, and diabetes mellitus.

Side effects in biologic females treated with testosterone may include infertility, acne, emotional lability, increases in sexual desire, shift of lipid profiles to male patterns which increase the risk of cardiovascular disease, and the potential to develop benign and malignant liver tumors and hepatic dysfunction.

The Prescribing Physician's Responsibilities. Hormones are to be prescribed by a physician, and should not be administered without adequate psychological and medical assessment before and during treatment. Patients who do not understand the eligibility and readiness requirements and who are unaware of the SOC should be informed of them. This may be a good indication for a referral to a mental health professional experienced with gender identity disorders.
The physician providing hormonal treatment and medical monitoring need not be a specialist in endocrinology, but should become well-versed in the relevant medical and psychological aspects of treating persons with gender identity disorders.

After a thorough medical history, physical examination, and laboratory examination, the physician should again review the likely effects and side effects of hormone treatment, including the potential for serious, life-threatening consequences. The patient must have the capacity to appreciate the risks and benefits of treatment, have his/her questions answered, and agree to medical monitoring of treatment. The medical record must contain a written informed consent document reflecting a discussion of the risks and benefits of hormone therapy.

Physicians have a wide latitude in what hormone preparations they may prescribe and what routes of administration they may select for individual patients. Viable options include oral, injectable, and transdermal delivery systems. The use of transdermal estrogen patches should be considered for males over 40 years of age or those with clotting abnormalities or a history of venous thrombosis. Transdermal testosterone is useful in females who do not want to take injections. In the absence of any other medical, surgical, or psychiatric conditions, basic medical monitoring should include: serial physical examinations relevant to treatment effects and side effects, vital sign measurements before and during treatment, weight measurements, and laboratory assessment. Gender patients, whether on hormones or not, should be screened for pelvic malignancies as are other persons.

For those receiving estrogens, the minimum laboratory assessment should consist of a pretreatment free testosterone level, fasting glucose, liver function tests, and complete blood count with reassessment at 6 and 12 months and annually thereafter. A pretreatment prolactin level should be obtained and repeated at 1, 2, and 3 years. If hyperprolactemia does not occur during this time, no further measurements are necessary. Biologic males undergoing estrogen treatment should be monitored for breast cancer and encouraged to engage in routine self-examination. As they age, they should be monitored for prostatic cancer.

For those receiving androgens, the minimum laboratory assessment should consist of pretreatment liver function tests and complete blood count with reassessment at 6 months, 12 months, and yearly thereafter. Yearly palpation of the liver should be considered. Females who have undergone mastectomies and who have a family history of breast cancer should be monitored for this disease.

Physicians may provide their patients with a brief written statement indicating that the person is under medical supervision, which includes cross-sex hormone therapy. During the early phases of hormone treatment, the patient may be encouraged to carry this statement at all times to help prevent difficulties with the police and other authorities.

Reductions in Hormone Doses After Gonadectomy. Estrogen doses in post-orchiectomy patients can often be reduced by 1/3 to ½ and still maintain feminization. Reductions in testosterone doses post-oophorectomy should be considered, taking into account the risks of osteoporosis. Lifelong maintenance treatment is usually required in all gender patients.

The Misuse of Hormones. Some individuals obtain hormones without prescription from friends, family members, and pharmacies in other countries. Medically unmonitored hormone use can expose the person to greater medical risk. Persons taking medically monitored hormones have been known to take additional doses of illicitly obtained hormones without their physician's knowledge. Mental health professionals and prescribing physicians should make an effort to encourage compliance with recommended dosages, in order to limit morbidity. It is ethical for physicians to discontinue treatment of patients who do not comply with prescribed treatment regimens.

Other Potential Benefits of Hormones. Hormonal treatment, when medically tolerated, should precede any genital surgical interventions. Satisfaction with the hormone's effects consolidates the person's identity as a member of the preferred sex and gender and further adds to the conviction to proceed. Dissatisfaction with hormonal effects may signal ambivalence about proceeding to surgical interventions. In biologic males, hormones alone often generate adequate breast development, precluding the need for augmentation mammaplasty. Some patients who receive hormonal treatment will not desire genital or other surgical interventions.

The Use of Antiandrogens and Sequential Therapy. Antiandrogens can be used as adjunctive treatments in biologic males receiving estrogens, though they are not always necessary to achieve feminization. In some patients, antiandrogens may more profoundly suppress the production of testosterone, enabling a lower dose of estrogen to be used when adverse estrogen side effects are anticipated.

Feminization does not require sequential therapy. Attempts to mimic the menstrual cycle by prescribing interrupted estrogen therapy or substituting progesterone for estrogen during part of the month are not necessary to achieve feminization.

Informed Consent. Hormonal treatment should be provided only to those who are legally able to provide informed consent. This includes persons who have been declared by a court to be emancipated minors and incarcerated persons who are considered competent to participate in their medical decisions. For adolescents, informed consent needs to include the minor patient's assent and the written informed consent of a parent or legal guardian.

Reproductive Options. Informed consent implies that the patient understands that hormone administration limits fertility and that the removal of sexual organs prevents the capacity to reproduce. Cases are known of persons who have received hormone therapy and sex reassignment surgery who later regretted their inability to parent genetically related children. The mental health professional recommending hormone therapy, and the physician prescribing such therapy, should discuss reproductive options with the patient prior to starting hormone therapy. Biologic males, especially those who have not already reproduced, should be informed about sperm preservation options, and encouraged to consider banking sperm prior to hormone therapy. Biologic females do not presently have readily available options for gamete preservation, other than cryopreservation of fertilized embryos. However, they should be informed about reproductive issues, including this option. As other options become available, these should be presented.

IX. The Real-Life Experience

The act of fully adopting a new or evolving gender role or gender presentation in everyday life is known as the real-life experience. The real-life experience is essential to the transition to the gender role that is congruent with the patient's gender identity. Since changing one's gender presentation has immediate profound personal and social consequences, the decision to do so should be preceded by an awareness of what the familial, vocational, interpersonal, educational, economic, and legal consequences are likely to be. Professionals have a responsibility to discuss these predictable consequences with their patients. Change of gender role and presentation can be an important factor in employment discrimination, divorce, marital problems, and the restriction or loss of visitation rights with children. These represent external reality issues that must be confronted for success in the new gender presentation. These consequences may be quite different from what the patient imagined prior to undertaking the real-life experiences. However, not all changes are negative.

Parameters of the Real-Life Experience. When clinicians assess the quality of a person's real-life experience in the desired gender, the following abilities are reviewed:

1. To maintain full or part-time employment;
2. To function as a student;
3. To function in community-based volunteer activity;
4. To undertake some combination of items 1-3;
5. To acquire a (legal) gender-identity-appropriate first name;

6. To provide documentation that persons other than the therapist know that the patient functions in the desired gender role.

Real-Life Experience versus Real-Life Test. Although professionals may recommend living in the desired gender, the decision as to when and how to begin the real-life experience remains the person's responsibility. Some begin the real-life experience and decide that this often imagined life direction is not in their best interest. Professionals sometimes construe the real-life experience as the real-life test of the ultimate diagnosis. If patients prosper in the preferred gender, they are confirmed as "transsexual," but if they decided against continuing, they "must not have been." This reasoning is a confusion of the forces that enable successful adaptation with the presence of a gender identity disorder. The real-life experience tests the person's resolve, the capacity to function in the preferred gender, and the adequacy of social, economic, and psychological supports. It assists both the patient and the mental health professional in their judgments about how to proceed. Diagnosis, although always open for reconsideration, precedes a recommendation for patients to embark on the real-life experience. When the patient is successful in the real-life experience, both the mental health professional and the patient gain confidence about undertaking further steps.

Removal of Beard and other Unwanted Hair for the Male to Female Patient. Beard density is not significantly slowed by cross-sex hormone administration. Facial hair removal via electrolysis is a generally safe, time-consuming process that often facilitates the real-life experience for biologic males. Side effects include discomfort during and immediately after the procedure and less frequently hypo-or hyper pigmentation, scarring, and folliculitis. Formal medical approval for hair removal is not necessary; electrolysis may be begun whenever the patient deems it prudent. It is usually recommended prior to commencing the real-life experience, because the beard must grow out to visible lengths to be removed. Many patients will require two years of regular treatments to effectively eradicate their facial hair. Hair removal by laser is a new alternative approach, but experience with it is limited.

X. Surgery

Sex Reassignment is Effective and Medically Indicated in Severe GID. In persons diagnosed with transsexualism or profound GID, sex reassignment surgery, along with hormone therapy and real-life experience, is a treatment that has proven to be effective. Such a therapeutic regimen, when prescribed or recommended by qualified practitioners, is medically indicated and medically necessary. Sex reassignment is not "experimental," "investigational," "elective," "cosmetic," or optional in any meaningful sense. It constitutes very effective and appropriate treatment for transsexualism or profound GID.

How to Deal with Ethical Questions Concerning Sex Reassignment Surgery. Many persons, including some medical professionals, object on ethical grounds to surgery for GID. In ordinary surgical practice, pathological tissues are removed in order to restore disturbed functions, or alterations are made to body features to improve the patient's self image. Among those who object to sex reassignment surgery, these conditions are not thought to present when surgery is performed for persons with gender identity disorders. It is important that professionals dealing

with patients with gender identity disorders feel comfortable about altering anatomically normal structures. In order to understand how surgery can alleviate the psychological discomfort of patients diagnosed with gender identity disorders, professionals need to listen to these patients discuss their life histories and dilemmas. The resistance against performing surgery on the ethical basis of "above all do no harm" should be respected, discussed, and met with the opportunity to learn from patients themselves about the psychological distress of having profound gender identity disorder.

It is unethical to deny availability or eligibility for sex reassignment surgeries or hormone therapy solely on the basis of blood seropositivity for blood-borne infections such as HIV, or hepatitis B or C, etc.

The Surgeon's Relationship with the Physician Prescribing Hormones and the Mental Health Professional. The surgeon is not merely a technician hired to perform a procedure. The surgeon is part of the team of clinicians participating in a long-term treatment process. The patient often feels an immense positive regard for the surgeon, which ideally will enable long-term follow-up care. Because of his or her responsibility to the patient, the surgeon must understand the diagnosis that has led to the recommendation for genital surgery. Surgeons should have a chance to speak at length with their patients to satisfy themselves that the patient is likely to benefit from the procedures. Ideally, the surgeon should have a close working relationship with the other professionals who have been actively involved in the patient's psychological and medical care. This is best accomplished by belonging to an interdisciplinary team of professionals who specialize in gender identity disorders. Such gender teams do not exist everywhere, however. At the very least, the surgeon needs to be assured that the mental health professional and physician prescribing hormones are reputable professionals with specialized experience with gender identity disorders. This is often reflected in the quality of the documentation letters. Since fictitious and falsified letters have occasionally been presented, surgeons should personally communicate with at least one of the mental health professionals to verify the authenticity of their letters.

Prior to performing any surgical procedures, the surgeon should have all medical conditions appropriately monitored and the effects of the hormonal treatment upon the liver and other organ systems investigated. This can be done alone or in conjunction with medical colleagues. Since pre-existing conditions may complicate genital reconstructive surgeries, surgeons must also be competent in urological diagnosis. The medical record should contain written informed consent for the particular surgery to be performed.

XI. Breast Surgery

Breast augmentation and removal are common operations, easily obtainable by the general public for a variety of indications. Reasons for these operations range from cosmetic indications to cancer. Although breast appearance is definitely important as a secondary sex characteristic, breast size or presence are not involved in the legal definitions of sex and gender and are not important for reproduction. The performance of breast operations should be considered with the

same reservations as beginning hormonal therapy. Both produce relatively irreversible changes to the body.

The approach for male-to-female patients is different than for female-to-male patients. For female-to-male patients, a mastectomy procedure is usually the first surgery performed for success in gender presentation as a man; and for some patients it is the only surgery undertaken. When the amount of breast tissue removed requires skin removal, a scar will result and the patient should be so informed. Female-to-male patients may have surgery at the same time they begin hormones. For male-to-female patients, augmentation mammoplasty may be performed if the physician prescribing hormones and the surgeon have documented that breast enlargement after undergoing hormone treatment for 18 months is not sufficient for comfort in the social gender role.

XII. Genital Surgery

Eligibility Criteria. These minimum eligibility criteria for various genital surgeries equally apply to biologic males and females seeking genital surgery. They are:

1. Legal age of majority in the patient's nation;
2. Usually 12 months of continuous hormonal therapy for those without a medical contraindication (see below, "Can Surgery Be Performed Without Hormones and the Real-life Experience");
3. 12 months of successful continuous full time real-life experience. Periods of returning to the original gender may indicate ambivalence about proceeding and generally should not be used to fulfill this criterion;
4. If required by the mental health professional, regular responsible participation in psychotherapy throughout the real-life experience at a frequency determined jointly by the patient and the mental health professional. Psychotherapy per se is not an absolute eligibility criterion for surgery;
5. Demonstrable knowledge of the cost, required lengths of hospitalizations, likely complications, and post surgical rehabilitation requirements of various surgical approaches;
6. Awareness of different competent surgeons.

Readiness Criteria. The readiness criteria include:

1. Demonstrable progress in consolidating one's gender identity;
2. Demonstrable progress in dealing with work, family, and interpersonal issues resulting in a significantly better state of mental health; this implies satisfactory control of problems such as sociopathy, substance abuse, psychosis, suicidality, for instance).

Can Surgery Be Provided Without Hormones and the Real-life Experience? Individuals cannot receive genital surgery without meeting the eligibility criteria. Genital surgery is a treatment for a diagnosed gender identity disorder, and should undertaken only after careful evaluation. Genital surgery is not a right that must be granted upon request. The SOC provide for an individual approach for every patient; but this does not mean that the general guidelines, which specify treatment consisting of diagnostic evaluation, possible psychotherapy, hormones,

and real-life experience, can be ignored. However, if a person has lived convincingly as a member of the preferred gender for a long period of time and is assessed to be a psychologically healthy after a requisite period of psychotherapy, there is no inherent reason that he or she must take hormones prior to genital surgery.

Conditions under which Surgery May Occur. Genital surgical treatments for persons with a diagnosis of gender identity disorder are not merely another set of elective procedures. Typical elective procedures only involve a private mutually consenting contract between a patient and a surgeon. Genital surgeries for individuals diagnosed as having GID are to be undertaken only after a comprehensive evaluation by a qualified mental health professional. Genital surgery may be performed once written documentation that a comprehensive evaluation has occurred and that the person has met the eligibility and readiness criteria. By following this procedure, the mental health professional, the surgeon and the patient share responsibility of the decision to make irreversible changes to the body.

Requirements for the Surgeon Performing Genital Reconstruction. The surgeon should be a urologist, gynecologist, plastic surgeon or general surgeon, and Board-Certified as such by a nationally known and reputable association. The surgeon should have specialized competence in genital reconstructive techniques as indicated by documented supervised training with a more experienced surgeon. Even experienced surgeons in this field must be willing to have their therapeutic skills reviewed by their peers. Surgeons should attend professional meetings where new techniques are presented.

Ideally, the surgeon should be knowledgeable about more than one of the surgical techniques for genital reconstruction so that he or she, in consultation with the patient, will be able to choose the ideal technique for the individual patient. When surgeons are skilled in a single technique, they should so inform their patients and refer those who do not want or are unsuitable for this procedure to another surgeon.

Genital Surgery for the Male-to-Female Patient. Genital surgical procedures may include orchiectomy, penectomy, vaginoplasty, clitoroplasty, and labiaplasty. These procedures require skilled surgery and postoperative care. Techniques include penile skin inversion, pedicled rectosigmoid transplant, or free skin graft to line the neovagina. Sexual sensation is an important objective in vaginoplasty, along with creation of a functional vagina and acceptable cosmesis.

Other Surgery for the Male-to-Female Patient. Other surgeries that may be performed to assist feminization include reduction thyroid chondroplasty, suction-assisted lipoplasty of the waist, rhinoplasty, facial bone reduction, face-lift, and blepharoplasty. These do not require letters of recommendation from mental health professionals.
There are concerns about the safety and effectiveness of voice modification surgery and more follow-up research should be done prior to widespread use of this procedure. In order to protect their vocal cords, patients who elect this procedure should do so after all other surgeries requiring general anesthesia with intubation are completed.

Genital Surgery for the Female-to-Male Patient. Genital surgical procedures may include hysterectomy, salpingo-oophorectomy, vaginectomy, metoidioplasty, scrotoplasty, urethroplasty, placement of testicular prostheses, and phalloplasty. Current operative techniques for

phalloplasty are varied. The choice of techniques may be restricted by anatomical or surgical considerations. If the objectives of phalloplasty are a neophallus of good appearance, standing micturition, sexual sensation, and/or coital ability, the patient should be clearly informed that there are several separate stages of surgery and frequent technical difficulties which may require additional operations. Even metoidioplasty, which in theory is a one-stage procedure for construction of a microphallus, often requires more than one surgery. The plethora of techniques for penis construction indicates that further technical development is necessary.

Other Surgery for the Female-to-Male Patient. Other surgeries that may be performed to assist masculinization include liposuction to reduce fat in hips, thighs and buttocks.

XIII. Post-Transition Follow-up

Long-term postoperative follow-up is encouraged in that it is one of the factors associated with a good psychosocial outcome. Follow-up is important to the patient's subsequent anatomic and medical health and to the surgeon's knowledge about the benefits and limitations of surgery. Long-term follow-up with the surgeon is recommended in all patients to ensure an optimal surgical outcome. Surgeons who operate on patients who are coming from long distances should include personal follow-up in their care plan and attempt to ensure affordable, local, long-term aftercare in the patient's geographic region. Postoperative patients may also sometimes exclude themselves from follow-up with the physician prescribing hormones, not recognizing that these physicians are best able to prevent, diagnose and treat possible long term medical conditions that are unique to hormonally and surgically treated patients. Postoperative patients should undergo regular medical screening according to recommended guidelines for their age. The need for follow-up extends to the mental health professional, who having spent a longer period of time with the patient than any other professional, is in an excellent position to assist in any post-operative adjustment difficulties.

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LEADING ARTICLE

Consensus statement on management of intersex disorders

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1ST ONLINE

Management of intersex disorders

The birth of an intersex child prompts a long term management strategy that involves a myriad of professionals working with the family. It is estimated that genital anomalies occur in 1 in 4500 births. There has been progress in diagnosis, surgical techniques, understanding psychosocial issues, and recognising and accepting the place of patient advocacy. The Lawson Wilkins Pediatric Endocrine Society (LWPES) and the European Society for Paediatric Endocrinology (ESPE) considered it timely to review the management of intersex disorders from a broad perspective, to review data on longer term outcome, and to formulate proposals for future studies. The methodology comprised establishing several working groups whose membership was drawn from 50 international experts in the field. The groups prepared prior written responses to a defined set of questions resulting from an evidence based review of published reports. At a subsequent gathering of participants, a framework for a consensus document was agreed. This paper constitutes its final form.

NOMENCLATURE AND DEFINITIONS

Advances in identification of molecular genetic causes of abnormal sex with heightened awareness of ethical issues and patient advocacy concerns necessitate a re-examination of nomenclature.[1] Terms such as intersex, pseudohermaphroditism, hermaphroditism, sex reversal, and gender based diagnostic labels are particularly controversial. These terms are perceived as potentially pejorative by patients,[2] and can be confusing to practitioners and parents alike. The term "disorders of sex development" (DSD) is proposed, as defined by congenital conditions in which development of chromosomal, gonadal, or anatomical sex is atypical.

The proposed changes in terminology are summarised in table 1. A modern lexicon is needed to integrate progress in molecular genetic aspects of sex development. As outcome data in individuals with DSD are limited, it is essential to employ precision when applying definitions and diagnostic labels.[3 4] It is also appropriate to use terminology that is sensitive to the concerns of patients. The ideal nomenclature should be sufficiently flexible to incorporate new information yet robust enough to maintain a consistent framework. Terms should be descriptive and reflect genetic aetiology when available, and accommodate the spectrum of phenotypical variation. Clinicians and scientists must value its use and it must be understandable to patients and their families. An example of how the proposed nomenclature could be applied in a classification of DSD is shown in table 2.

Psychosexual development is traditionally conceptualised as three components. Gender identity refers to a person's self representation as male or female (with the caveat that some individuals may not identify exclusively with either). Gender role (sex-typical behaviours) describes the psychological characteristics that are sexually dimorphic within the general population, such as toy preferences and physical aggression. Sexual orientation refers to the direction(s) of erotic interest (heterosexual, bisexual, homosexual) and includes behaviour, fantasies, and attractions. Psychosexual development is influenced by multiple factors such as exposure to androgens, sex chromosome genes, and brain structure, as well as social circumstance and family dynamics.

Gender dissatisfaction denotes unhappiness with assigned sex. Causes of gender dissatisfaction are poorly understood, even among individuals without DSD. Gender dissatisfaction occurs more frequently in individuals with DSD than in the general population, but is difficult to predict from karyotype, prenatal androgen exposure, degree of genital virilisation, or assigned gender.[5-7] Prenatal androgen exposure is clearly associated with other aspects of psychosexual development.[8 9] There are dose related effects on childhood play behaviour in girls with congenital adrenal hyperplasia (CAH), whereby those with the more severe mutations and marked genital virilisation play more with boys' toys.[10] Prenatal androgen exposure is also associated with other psychological characteristics such as maternal interest and sexual orientation. It is important to emphasise the separability of sex-typical behaviour, sexual orientation, and gender identity. Thus homosexual orientation (relative to sex of rearing) or strong cross-sex interest in an individual with DSD is *not* an indication of incorrect gender assignment. Understanding variations in psychosexual development in individuals with DSD requires reference to studies in non-human species that show marked but complex effects of androgens on sex differentiation of the brain and on behaviour. Outcomes can be influenced by timing, dose, and type of androgen exposure, receptor availability, and modification by the social environment.[11-14]

Data from rodent studies suggest that sex chromosome genes may also influence brain structure and behaviour directly.[15 16] However, studies in individuals with complete androgen insensitivity syndrome (CAIS) do not indicate a behavioural role for Y chromosome genes, although data are limited.[17] Sex differences in brain structures have been identified across species, some of which coincide with pubertal onset, perhaps suggesting hormonal responsivity.[18-20] The limbic system and hypothalamus, both playing a role in reproduction, show sex differences in specific nuclei but it is not clear when these differences emerge. Interpretation of sex differences is complicated by the effect of cell death and synaptic pruning on normal maturation and by effects of experience on the brain. Structure of the brain is not currently useful for gender assignment.

INVESTIGATION AND MANAGEMENT OF DSD

General concepts of care

Optimal clinical management of individuals with DSD[21] should comprise the following:

- gender assignment must be avoided before expert evaluation in newborns;

Abbreviations: CAH, congenital adrenal hyperplasia; CAIS, complete androgen insensitivity syndrome; DSD, disorders of sex development; ESPE, European Society for Paediatric Endocrinology; LWPES, Lawson Wilkins Pediatric Endocrine Society; MGD, mixed gonadal dysgenesis; PAIS, partial androgen insensitivity syndrome

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- evaluation and long term management must be carried out at a centre with an experienced multidisciplinary team;
- all individuals should receive a gender assignment;
- open communication with patients and families is essential and participation in decision making is encouraged;
- patient and family concerns should be respected and addressed in strict confidence.

The initial contact with the parents of a child with a DSD is important, as first impressions from these encounters often persist. A key point to emphasise is that the DSD child has the potential to become a well adjusted, functional member of society. While privacy needs to be respected, DSD is not shameful. It should be explained to the parents that the best course of action may not initially be clear, but the health care team will work with the family to reach the best possible set of decisions in the circumstances. The health care team should discuss with the parents what information to share in the early stages with family members and friends. Parents need to be informed about sexual development, and web based information may be helpful, provided the content and focus of the information is balanced and sound (http://www.sickkids.ca/childphysiology/cpwp/genital/genitalintro.html).

Ample time and opportunity should be made for continued discussion with review of information previously provided.[1]

Table 1 Proposed revised nomenclature

Previous	Proposed
Intersex	**Disorders of sex development** (DSD)
Male pseudohermaphrodite Undervirilisation of an XY male Undermasculinisation of an XY male	46,XY DSD
Female pseudohermaphrodite Overvirilisation of an XX female Masculinisation of an XX female	46,XX DSD
True hermaphrodite	Ovotesticular DSD
XX male or XX sex reversal	46,XX testicular DSD
XY sex reversal	46,XY complete gonadal dysgenesis

The multidisciplinary team

Optimal care for children with DSD requires an experienced multidisciplinary team which is generally found in tertiary care centres. Ideally, the team includes paediatric subspecialists in endocrinology, surgery or urology or both, psychology/psychiatry, gynaecology, genetics, neonatology, and, if available, social work, nursing, and medical ethics.[22] Core composition will vary according to DSD type, local resources, developmental context, and location. Ongoing communication with the family primary care physician is essential.[23]

The team has a responsibility to educate other health care staff in the appropriate initial management of affected newborn infants and their families. For new DSD patients, the team should develop a plan for clinical management with respect to diagnosis, gender assignment, and treatment options before making any recommendations. Ideally, discussions with the family are conducted by one professional with appropriate communication skills.[24] Transitional care should be organised with the multidisciplinary team operating in an environment comprising specialists with experience in both paediatric and adult practice. Support groups have an important role in the delivery of care to DSD patients and their families[25] (see appendix 1).

Clinical evaluation

A family and prenatal history, a general physical examination with attention to any associated dysmorphic features, and an assessment of the genital anatomy in comparison with published norms needs to be recorded (table 3). Criteria that suggest DSD include:

- overt genital ambiguity (for example, cloacal exstrophy);

Table 2 An example of a DSD classification

Sex chromosome DSD	46,XY DSD	46,XX DSD
(A) 45,X (Turner syndrome and variants)	**(A) Disorders of gonadal (testicular) development** 1. Complete gonadal dysgenesis (Swyer syndrome)	**(A) Disorders of gonadal (ovarian) development** 1. Ovotesticular DSD 2. Testicular DSD (eg, SRY+, dup SOX9)
(B) 47,XXY (Klinefelter syndrome and variants)	2. Partial gonadal dysgenesis 3. Gonadal regression 4. Ovotesticular DSD	3. Gonadal dysgenesis
(C) 45,X/46,XY (mixed gonadal dysgenesis, ovotesticular DSD)	**(B) Disorders in androgen synthesis or action** 1. Androgen biosynthesis defect (eg, 17-hydroxysteroid dehydrogenase deficiency, 5α reductase deficiency, StAR mutations	**(B) Androgen excess** 1. Fetal (eg, 21-hydroxylase deficiency, 11-hydroxylase deficiency) 2. Fetoplacental (aromatase deficiency, POR)
(D) 46,XX/46,XY (chimeric, ovotesticular DSD)	2. Defect in androgen action (eg, CAIS, PAIS) 3. LH receptor defects (eg, Leydig cell hypoplasia, aplasia) 4. Disorders of AMH and AMH receptor (persistent mullerian duct syndrome)	
	(C) Other (eg, severe hypospadias, cloacal extrophy)	**(C) Other** (eg, cloacal extrophy, vaginal atresia, MURCS, other syndromes)

While consideration of karyotype is useful for classification, unnecessary reference to karyotype should be avoided; ideally, a system based on descriptive terms (for example, androgen insensitivity syndrome) should be used wherever possible.
AMH, anti-mullerian hormone; CAIS, complete androgen insensitivity syndrome; DSD, disorders of sex development; MURCS, mullerian, renal, cervicothoracic somite abnormalities; PAIS, partial androgen insensitivity syndrome; POR, cytochrome P450 oxidoreductase.

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Table 3 Anthropometric measurements of the external genitalia

Sex	Population	Age	Stretched penile length (PL) (cm)	Penile width (cm)	Mean testicular volume (ml)	Reference
M	USA	30 wks GA	2.5			26
M	USA	Full term	3.5 (0.4)	1.1 (0.1)	0.52 (median)	26, 27
M	Japan	Term to 14 years	2.9 (0.4) to 8.3 (0.8)			28
M	Australia	24–36 weeks GA	PL = 2.27 + (0.16 GA)			29
M	China	Term	3.1 (0.3)	1.07 (0.09)		30
M	India	Term	3.6 (0.4)	1.14 (0.07)		30
M	N America	Term	3.4 (0.3)	1.13 (0.08)		30
M	Europe	10 years	6.4 (0.4)		0.95 to 1.20	27, 31
M	Europe	Adult	13.3 (1.6)		16.5 to 18.2	27, 31

Sex	Population	Age	Clitoral length (mm)	Clitoral width (mm)	Perineal length* (mm)	Reference
F	USA	Full term	4.0 (1.24)	3.32 (0.78)		32
F	USA	Adult nulliparous	15.4 (4.3)			33
F	UK	Adult	19.1 (8.7)	5.5 (1.7)	31.3 (8.5)	34

Values are mean (SD) unless specified.
*Distance from posterior fourchette to anterior anal margin.
GA, gestational age; PL, penile length.

- apparent female genitalia with an enlarged clitoris, posterior labial fusion, or an inguinal/labial mass;
- apparent male genitalia with bilateral undescended testes, micropenis, isolated perineal hypospadias, or mild hypospadias with undescended testis;
- a family history of DSD such as CAIS;
- a discordance between genital appearance and a prenatal karyotype.

Most causes of DSD are recognised in the neonatal period; later presentations in older children and young adults include: previously unrecognised genital ambiguity; inguinal hernia in a girl; delayed or incomplete puberty; virilisation in a girl; primary amenorrhoea; breast development in a boy; and gross and occasionally cyclical haematuria in a boy.

Diagnostic evaluation

Considerable progress has been made over understanding the genetic basis of human sexual development,[35] yet a specific molecular diagnosis is identified in only about 20% of cases of DSD. The majority of virilised 46,XX infants will have CAH. In contrast, only 50% of 46,XY children with DSD will receive a definitive diagnosis.[36 37] Diagnostic algorithms do exist, but with the spectrum of findings and diagnoses, no single evaluation protocol can be recommended in all circumstances. Some tests, such as imaging by ultrasound, are operator dependent. Hormone measurements need to be interpreted in relation to the specific assay characteristics and to normal values for gestational and chronological age. In some cases serial measurements may be needed.

First line testing in newborns includes: karyotyping with X and Y specific probe detection (even when prenatal karyotype is available), imaging (abdomino-pelvic ultrasound), measurement of 17-hydroxyprogesterone, testosterone, gonadotropins, antimullerian hormone, serum electrolytes, and urinanalysis. The results of these investigations are generally available within 48 hours and will be sufficient for making a working diagnosis. Decision making algorithms are available to guide further investigation.[38] These include hCG and ACTH stimulation tests to assess testicular and adrenal steroid biosynthesis, urinary steroid analysis by GC mass spectroscopy, imaging studies, and biopsies of gonadal material. Some gene analyses are carried out in clinical service laboratories. However, current molecular diagnosis is limited by cost, accessibility, and quality control.[39] Research laboratories provide genetic testing, including functional analysis, but may face restrictions on communicating results.[40]

Gender assignment in newborn infants

Initial gender uncertainty is unsettling and stressful for families. Expediting a thorough assessment and decision is required. Factors that influence gender assignment include the diagnosis, genital appearance, surgical options, need for life long replacement therapy, the potential for fertility, views of the family, and sometimes the circumstances relating to cultural practices. More than 90% of 46,XX CAH patients[41] and all 46,XY CAIS assigned females in infancy[42] identify as females. Evidence supports the current recommendation to raise markedly virilised 46,XX infants with CAH as female.[43] Approximately 60% of 5α-reductase (5αRD2) deficient patients assigned female in infancy and virilising at puberty (and all assigned male) live as males.[5] In 5αRD2 and possibly 17β-hydroxysteroid dehydrogenase (17βHSD3) deficiencies, where the diagnosis is made in infancy, the combination of a male gender identity in the majority and the potential for fertility (documented in 5αRD2, but unknown in 17βHSD3) should be discussed when providing evidence for gender assignment.[5 44 45] Among patients with PAIS, androgen biosynthetic defects, and incomplete gonadal dysgenesis, there is dissatisfaction with the sex of rearing in about 25% of individuals, whether raised male or female.[46] Available data support male rearing in all patients with micropenis, taking into account equal satisfaction with assigned gender in those raised male or female, but no need for surgery, and the potential for fertility in patients reared male.[42] The decision on sex of rearing in ovotesticular DSD should consider the potential for fertility based on gonadal differentiation and genital development, and assuming the genitalia are, or can be made, consistent with the chosen sex. In the case of mixed gonadal dysgenesis (MGD), factors to consider include prenatal androgen exposure, testicular function at and after puberty, phallic development, and gonadal location. Individuals with cloacal exstrophy reared female show variability in gender identity outcome, but more than 65% appear to live as female.[6]

Surgical management

The surgeon has a responsibility to outline the surgical sequence and subsequent consequences from infancy to adulthood. Only surgeons with expertise in the care of children and specific training in the surgery of DSD should undertake these procedures. Parents now appear to be less inclined to choose

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surgery for less severe clitoromegaly.[47] Surgery should only be considered in cases of severe virilisation (Prader III, IV, and V) and should be carried out in conjunction, when appropriate, with repair of the common urogenital sinus. As orgasmic function and erectile sensation may be disturbed by clitoral surgery, the surgical procedure should be anatomically based to preserve erectile function and the innervation of the clitoris. Emphasis is on functional outcome rather than a strictly cosmetic appearance. It is generally felt that surgery that is carried out for cosmetic reasons in the first year of life relieves parental distress and improves attachment between the child and the parents.[48–51] The systematic evidence for this belief is lacking.

There is inadequate evidence currently in relation to establishment of functional anatomy, to abandon the practice of early separation of the vagina and urethra.[52] The rationale for early reconstruction is based on guidelines on the timing of genital surgery from the American Academy of Pediatrics (AAP),[53] the beneficial effects of oestrogen on tissue in early infancy, and the avoidance of potential complications from the connection between the urinary tract and peritoneum through the Fallopian tubes. It is anticipated that surgical reconstruction in infancy will need to be refined at the time of puberty.[54–56] Vaginal dilatation should not be undertaken before puberty. The surgeon must be familiar with several operative techniques in order to reconstruct the spectrum of urogenital sinus disorders. An absent or inadequate vagina (with rare exceptions) requires a vaginoplasty performed in adolescence when the patient is psychologically motivated and a full partner in the procedure. No one technique has been universally successful; self dilatation, skin substitution, and bowel vaginoplasty each have specific advantages and disadvantages.

In the case of a DSD associated with hypospadias,[57] standard techniques for surgical repair such as chordee correction, urethral reconstruction, and the judicious use of testosterone supplementation apply. The magnitude and complexity of phalloplasty in adulthood should be taken into account during the initial counselling period if successful gender assignment is dependent on this procedure.[58] At times this may affect the balance of gender assignment. Patients must not be given unrealistic expectations about penile reconstruction, including the use of tissue engineering. There is no evidence that prophylactic removal of asymptomatic discordant structures, such as a utriculus or mullerian remnants, is required although symptoms in future may indicate surgical removal. For the male who has a successful neophalloplasty in adulthood, an erectile prosthesis may be inserted but has a high morbidity.

The testes in patients with CAIS[35] and those with PAIS, raised female, should be removed to prevent malignancy in adulthood. The availability of oestrogen replacement therapy allows for the option of early removal at the time of diagnosis which also takes care of the associated hernia, psychological problems with the presence of testes, and the malignancy risk. Parental choice allows deferment until adolescence, recognising that the earliest reported malignancy in CAIS is at 14 years of age.[59] The streak gonad in a patient with MGD raised male should be removed laparoscopically (or by laparotomy) in early childhood.[35] Bilateral gonadectomy is performed in early childhood in females (bilateral streak gonads) with gonadal dysgenesis and Y chromosome material. In patients with androgen biosynthetic defects raised female, gonadectomy should be undertaken before puberty. A scrotal testis in patients with gonadal dysgenesis is at risk for malignancy. Current recommendations are testicular biopsy at puberty seeking signs of the premalignant lesion termed carcinoma in situ or undifferentiated intratubular germ cell neoplasia. If positive, the option is sperm banking before treatment with local low dose radiotherapy which is curative.[60]

Surgical management in DSD should also consider options that will facilitate the chances of fertility. In patients with a symptomatic utriculus, removal is best undertaken laparoscopically to increase the chance of preserving continuity of the vasa deferentia. Patients with bilateral ovotestes are potentially fertile from functional ovarian tissue.[35 61] Separation of ovarian and testicular tissue can be technically difficult and should be undertaken, if possible, in early life.

Sex steroid replacement

Hypogonadism is common in patients with dysgenetic gonads, defects in sex steroid biosynthesis, and resistance to androgens. The timing of initiation of puberty may vary but this is an occasion that provides an opportunity to discuss the condition and set a foundation for long term adherence to treatment. Hormonal induction of puberty should attempt to replicate normal pubertal maturation to induce secondary sexual characteristics, a pubertal growth spurt, and optimal bone mineral accumulation, together with psychosocial support for psychosexual maturation.[62] Intramuscular depot injections of testosterone esters are commonly used in males; other options include oral testosterone undecanoate, and transdermal preparations are also available.[63–65] Patients with PAIS may require supraphysiological doses of testosterone for optimal effect.[66] Females with hypogonadism require oestrogen supplementation to induce pubertal changes and menses. A progestin is usually added after breakthrough bleeding develops or within one to two years of continuous oestrogen. There is no evidence that the addition of cyclic progesterone is beneficial in women without a uterus.

Psychosocial management

Psychosocial care provided by mental health staff with expertise in DSD should be an integral part of management in order to promote positive adaptation. This expertise can facilitate team decisions about gender assignment/reassignment, timing of surgery, and sex hormone replacement. Psychosocial screening tools that identify families at risk for maladaptive coping with a child's medical condition are available.[67] Once the child is sufficiently developed for a psychological assessment of gender identity, such an evaluation must be included in discussions about gender reassignment. Gender identity development begins before the age of 3 years,[68] but the earliest age at which it can be reliably assessed remains unclear. The generalisation that the age of 18 months is the upper limit of imposed gender reassignment should be treated with caution and viewed conservatively. Atypical gender role behaviour is more common in children with DSD than in the general population but should not be taken as an indicator for gender reassignment. In affected children and adolescents who report significant gender dysphoria, a comprehensive psychological evaluation[69] and an opportunity to explore feelings about gender with a qualified clinician is required over a period of time. If the desire to change gender persists, the patient's wish should be supported and may require the input of a specialist skilled in the management of gender change.

The process of disclosure concerning facts about karyotype, gonadal status, and prospects for future fertility is a collaborative ongoing action which requires a flexible individual based approach. It should be planned with the parents from the time of diagnosis.[70] Studies in other chronic medical disorders and of adoptees indicate that disclosure is associated with enhanced psychosocial adaptation.[71] Medical education and counselling for children is a recurrent gradual process of increasing

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sophistication which is commensurate with changing cognitive and psychological development.[72]

Quality of life encompasses falling in love, dating, attraction, ability to develop intimate relationships, sexual functioning, and the opportunity to marry and to raise children, regardless of biological indicators of sex. The most frequent problems encountered in DSD patients are sexual aversion and lack of arousability, which are often misinterpreted as low libido.[73] Health care staff should offer adolescent patients opportunities to talk confidentially without their parents and encourage the participation in condition specific support groups which enhance the ability of the patient to discuss their concerns comfortably. Some patients avoid intimate relationships and it is important to address fears of rejection and advise on the process of building a relationship with a partner. The focus should be on interpersonal relationships and not solely on sexual function and activity. Referral for sex therapy may be needed. Repeated examination of the genitalia, including medical photography, may be experienced as deeply shaming.[74] Medical photography has its place for record keeping and education, but should be undertaken whenever possible if the patient is under anaesthesia for a procedure and with appropriate consent. Medical interventions and negative sexual experiences may have fostered symptoms of post-traumatic stress disorder and referral to a qualified mental health professional may be indicated.[75]

OUTCOME IN DSD

As a general statement, information across a range of assessments is insufficient in DSD. The following is based on those disorders where some evidence base is available. They include CAH, CAIS and PAIS, disorders of androgen biosynthesis, gonadal dysgenesis syndromes (complete and partial), and micropenis. Long term outcome in DSD should include the following: external and internal genital phenotype, physical health including fertility, sexual function, social and psychosexual adjustment, mental health, quality of life, and social participation. There are additional health problems in individuals with DSD. These include the consequences of associated problems such as other malformations, developmental delay and intellectual impairment, delayed growth and development, and unwanted effects of hormones on libido and body image.[76]

Surgical outcome

Some studies suggest satisfactory outcomes from early surgery.[43 46 47 77] Nevertheless, outcomes from clitoroplasty identify problems related to decreased sexual sensitivity, loss of clitoral tissue, and cosmetic issues.[78] Techniques for vaginoplasty carry the potential for scarring at the introitus, necessitating repeated modification before sexual function can be reliable. Surgery to construct a neo-vagina carries a risk of neoplasia.[79] The risks from vaginoplasty are different for high and low confluence of the urethra and vagina. Analysis of long term outcomes is complicated by a mixture of surgical techniques and diagnostic categories.[80] Few women with CAIS need surgery to lengthen the vagina.[81]

The outcome in undermasculinised males with a phallus is dependent on the degree of hypospadias and the amount of erectile tissue. Feminising as opposed to masculinising genitoplasty requires less surgery to achieve an acceptable outcome and results in fewer urological difficulties.[46] Long term data on sexual function and quality of life among those assigned female as well as male show great variability. There are no controlled clinical trials of the efficacy of early (less than 12 months of age) versus late surgery (in adolescence and adulthood), or of the efficacy of different techniques.

Risk of gonadal tumours

Interpretation of published reports is hampered by unclear terminology and by effects of normal cell maturation delay.[82–84] The highest tumour risk is found in TSPY (testis-specific protein Y encoded) positive gonadal dysgenesis and PAIS with intra-abdominal gonads, while the lowest risk (<5%) is found in ovotestis[85] and CAIS.[83 86] Table 4 provides a summary of the risk of tumour development according to diagnosis and recommendations for management.

Cultural and social factors

DSD may carry a stigma. Social and cultural factors, as well as hormonal effects, appear to influence gender role in 5α-reductase deficiency. Gender role change occurs at different rates in different societies, suggesting that social factors may also be important modifiers of gender role change.

In some societies, female infertility precludes marriage, which also affects employment prospects and creates economic dependence. Religious and philosophical views may influence how parents respond to the birth of an infant with a medical condition. Fatalism and guilt feelings in relation to congenital malformations or genetic conditions have an influence, while poverty and

Table 4 Risk of germ cell malignancy according to diagnosis

Risk group	Disorder	Malignancy risk (%)	Recommended action	Studies (n)	Patients (n)
High	GD* (+Y)† intra-abdominal	15–35	Gonadectomy‡	12	>350
	PAIS non-scrotal	50	Gonadectomy‡	2	24
	Frasier	60	Gonadectomy‡	1	15
	Denys-Drash (+Y)	40	Gonadectomy‡	1	5
Intermediate	Turner (+Y)	12	Gonadectomy‡	11	43
	17β-HSD	28	Monitor	2	7
	GD (+Y)‡ scrotal	Unknown	Biopsy§ and irradiation?	0	0
	PAIS scrotal gonad	Unknown	Biopsy§ and irradiation?	0	0
Low	CAIS	2	Biopsy§ 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	

*Gonadal dysgenesis (including not further specified, 46XY, 46X/46XY, mixed, partial, complete).
†GBY region positive, including the *TSPY* gene.
‡At time of diagnosis.
§At puberty, allowing investigation of at least 30 seminiferous tubules, with diagnosis preferably based on OCT3/4 immunohistochemistry.
CAIS, complete androgen insensitivity syndrome; DSD, disorders of sex development; HSD, hydroxysteroid dehydrogenase deficiency; PAIS, partial androgen insensitivity syndrome.

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Table 5 Genes known to be involved in disorders of sex development: 46,XY

Gene	Protein	OMIM	Locus	Inheritance	Gonad	Mullerian structures	External genitalia	Associated features/variant phenotypes
46,XY DSD								
Disorders of gonadal (testicular) development: single gene disorders								
WT1	TF	607102	11p13	AD	Dysgenetic testis	+/−	Female or ambiguous	Wilms tumour, renal abnormalities, gonadal tumours (WAGR, Denys-Drash, and Frasier syndromes)
SF1 (NR5A1)	Nuclear receptor TF	184757	9q33	AD/AR	Dysgenetic testis	+/−	Female or ambiguous	More severe phenotypes include primary adrenal failure; milder phenotypes have isolated partial gonadal dysgenesis
SRY	TF	480000	Yp11.3	Y	Dysgenetic testis or ovotestis	+/−	Female or ambiguous	
SOX9	TF	608160	17q24-25	AD	Dysgenetic testis or ovotestis	+/−	Female or ambiguous	Campomelic dysplasia (17q24 rearrangements milder phenotype than point mutations)
DHH	Signalling molecule	605423	12q13.1	AR	Dysgenetic testis	+	Female	The severe phenotype of one patient included minifascicular neuropathy, other patients have isolated gonadal dysgenesis
ATRX	Helicase (?chromatin remodelling)	300032	Xq13.3	X	Dysgenetic testis	−	Female, ambiguous or male	α-Thalassaemia, mental retardation
ARX	TF	300382	Xp22.13	X	Dysgenetic testis	−	Ambiguous	X-linked lissencephaly, epilepsy, temperature instability
Disorders of gonadal (testicular) development: chromosomal changes involving key candidate genes								
DMRT1	TF	602424	9p24.3	Monosomic deletion	Dysgenetic testis	+/−	Female or ambiguous	Mental retardation
DAX1 (NR0B1)	Nuclear receptor TF	300018	Xp21.3	dupXp21	Dysgenetic testis or ovary	+/−	Female or ambiguous	
WNT4	Signalling molecule	603490	1p35	dup1p35	Dysgenetic testis	+	Ambiguous	Mental retardation
Disorders of hormone synthesis or action								
LHGCR	G protein receptor	152790	2p21	AR	Testis	−	Female, ambiguous or micropenis	Leydig cell hypoplasia
DHCR7	Enzyme	602858	11q12-13	AR	Testis	−	Variable	Smith-Lemli-Opitz syndrome: coarse facies, second-third toe syndactyly, failure to thrive, developmental delay, cardiac and visceral abnormalities
STAR	Mitochondrial membrane protein	600617	8p11.2	AR	Testis	−	Female	Congenital lipoid adrenal hyperplasia (primary adrenal failure), pubertal failure
CYP11A1	Enzyme	118485	15q23-24	AR	Testis	−	Female or Ambiguous	Congenital adrenal hyperplasia (primary adrenal failure), pubertal failure
HSD3B2	Enzyme	201810	1p13.1	AR	Testis	−	Ambiguous	CAH, primary adrenal failure, partial androgenisation due to ↑ DHEA
CYP17	Enzyme	202110	10q24.3	AR	Testis	−	Female, ambiguous or micropenis	CAH, hypertension due to ↑ corticosterone & 11-deoxycorticosterone (except in isolated 17,20-lyase deficiency)
POR (P450 oxido-reductase)	CYP enzyme electron donor	124015	7q11.2	AR	Testis	−	Male or ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency, and aromatase deficiency; sometimes associated with Antley Bixler craniosynostosis
HSD17B3	Enzyme	605573	9q22	AR	Testis	−	Female or ambiguous	Partial androgenisation at puberty, ↑ androstenedione:testosterone ratio
SRD5A2	Enzyme	607306	2p23	AR	Testis	−	Ambiguous or micropenis	Partial androgenisation at puberty, ↑ testosterone:DHT ratio,
AMH	Signalling molecule	600957	19p13.3-13.2	AR	Testis	+	Normal male	Persistent mullerian duct syndrome
AMH-Receptor	Serine-threonine kinase transmembrane receptor	600956	12q13	AR	Testis	+	Normal male	(PMDS). Male external genitalia, bilateral cryptorchidism
Androgen receptor	Nuclear receptor TF	313700	Xq11-12	X	Testis	−	Female, ambiguous, micropenis or normal male	Phenotypic spectrum from complete androgen insensitivity syndrome (female external genitalia) and partial androgen insensitivity (ambiguous) to normal male genitalia/infertility

AD, autosomal dominant; AR, autosomal recessive; CAH, congenital adrenal hyperplasia; TF, transcription factor; X, X-linked recessive; Y, Y-linked recessive.
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Table 6 Genes known to be involved in disorders of sex development: 46,XX

Gene	Protein	OMIM	Locus	Inheritance	Gonad	Mullerian structures	External genitalia	Associated features/variant phenotypes
Disorders of gonadal (ovarian) development								
SRY	TF	480000	Yp11.3	Translocation	Testis or ovotestis	–	Male or ambiguous	
SOX9	TF	608160	17q24	dup17q24	ND	–	Male or ambiguous	
Androgen excess								
HSD3B2	Enzyme	201810	1p13	AR	Ovary	+	Clitoromegaly	CAH, primary adrenal failure, partial androgenisation due to ↑DHEA
CYP21A2	Enzyme	201910	6p21-23	AR	Ovary	+	Ambiguous	CAH, phenotypic spectrum from severe salt losing forms associated with adrenal failure to simple virilising forms with compensated adrenal function, ↑17-hydroxyprogesterone
CYP11B1	Enzyme	202010	8q21-22	AR	Ovary	+	Ambiguous	CAH, hypertension due to ↑11-deoxycortisol and 11-deoxycorticosterone
POR (P450 oxido-reductase)	CYP enzyme electron donor	124015	7q11.2	AR	Ovary	+	Ambiguous	Mixed features of 21-hydroxylase deficiency, 17α-hydroxylase/17,20-lyase deficiency and aromatase deficiency; associated with Antley Bixler craniosynostosis
CYP19	Enzyme	107910	15q21	AR	Ovary	+	Ambiguous	Maternal androgenisation during pregnancy, absent breast development at puberty, except in partial cases
Glucocorticoid receptor	Nuclear receptor TF	138040	5q31	AR	Ovary	+	Ambiguous	↑ACTH, 17-hydroxyprogesterone and cortisol; failure of dexamethasone suppression (NB patient heterozygous for a mutation in CYP21)

ACTH, adrenocorticotropin; AD, autosomal dominant; AR, autosomal recessive; CAH, congenital adrenal hyperplasia; ND, not determined; TF, transcription factor; X, X chrosomal; Y, Y chromosomal.
Chromosomal rearrangements likely to include key genes are included. Modified from Achermann *et al*[88], with permission from the Endocrine Society.

illiteracy negatively affect access to health care.[87]

FUTURE STUDIES

Establishing a precise diagnosis in DSD is just as important as in other chronic medical conditions with lifelong consequences. Considerable progress has been achieved with molecular studies, as illustrated in tables 5 and 6, which summarise the genes known to be involved in DSD. Use of tissue specific animal knock out models, comparative genomic hybridisation, and microarray screens of the mouse urogenital ridge will provide benefits in identifying new genes causing DSD.[89] It is essential that the momentum for an international collaborative approach to this task is maintained.

Much remains to be clarified about the determinants of gender identity in DSD. Future studies require representative sampling to carefully conceptualise and measure gender identity, recognising that there are multiple determinants to consider and gender identity may change into adulthood. In terms of psychological management, studies are needed to evaluate the effectiveness of information management with regard to timing and content. The pattern of surgical practice in DSD is changing with respect to the timing of surgery and the techniques employed. It is essential to evaluate the effects of early versus later surgery in an holistic manner, recognising the difficulties posed by an ever evolving clinical practice.

The consensus has clearly identified a major shortfall in information about long term outcome. Future studies should use appropriate instruments that assess outcomes in a standard manner[68 69] and take cognisance of guidelines relevant to all chronic conditions (http://www.who.int/classifications/icf/en/). These should preferably be prospective in nature and designed to avoid selection bias. Several countries already have registers of DSD cases but there could be added benefit from pooling such resources to enable prospective multicentre studies to be undertaken on a larger number of cases that are clearly defined. Allied to this should be an educational programme to ensure that professionals tasked with providing care for DSD families are suitably trained to discharge their responsibilities.

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