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Guidelines

Guidelines for the Development of Comprehensive Care Centers for Congenital Adrenal Hyperplasia: Guidance from the CARES Foundation Initiative

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Patients with rare and complex diseases such as congenital adrenal hyperplasia (CAH) often receive fragmented and inadequate care unless efforts are coordinated among providers. Translating the concepts of the medical home and comprehensive health care for individuals with CAH offers many benefits for the affected individuals and their families. This manuscript represents the recommendations of a 1.5 day meeting held in September 2009 to discuss the ideal goals for comprehensive care centers for newborns, infants, children, adolescents, and adults with CAH. Participants included pediatric endocrinologists, internal medicine and reproductive endocrinologists, pediatric urologists, pediatric surgeons, psychologists, and pediatric endocrine nurse educators. One unique aspect of this meeting was the active participation of individuals personally affected by CAH as patients or parents of patients. Representatives of Health Research and Services Administration (HRSA), New York-Mid-Atlantic Consortium for Genetics and Newborn Screening Services (NYMAC), and National Newborn Screening and Genetics Resource Center (NNSGRC) also participated. Thus, this document should serve as a "roadmap" for the development phases of comprehensive care centers (CCC) for individuals and families affected by CAH.

1. Introduction

Patients with rare and complex diseases often receive fragmented and inadequate care unless efforts are coordinated among providers. For some diseases such as cancer and cystic fibrosis, the development of comprehensive care centers (CCCs) has dramatically improved outcomes and quality of life [1]. In conceptualizing CCCs for the treatment of congenital adrenal hyperplasia (CAH) the Congenital Adrenal hyperplasia Research, Education, and Support (CARES) Foundation, Inc., organized a conference attended by pediatric endocrinologists, medical endocrinologists, reproductive endocrinologists, pediatric urologists/surgeons, endocrine nurses, psychologists, and consumers (affected individuals and their family members). The goal of the conference was to discuss creation of an environment focused on health and quality of life for patients with CAH and their families [2]. The diverse backgrounds of the participants were fundamental to the planning process and influenced the idealized design of these centers.

2. Components of a Comprehensive Care Center

2.1. Setting. A CCC will be most often located in an academic-oriented tertiary-care hospital and consists of multiple healthcare providers in close geographic proximity to enable easy access for patients and their families. These healthcare providers should be united in their common interest and expertise in CAH. Research, training, and advocacy should be inherent parts of the CCC, and the CCCs will be in an ideal position to collect outcomes data to improve patient care and to support research (Table 1).

2.2. Intake/Entry to System. Community health care providers and state newborn screening programs should be able to make referrals to the CCC [3]. Establishment of effective and efficient active lines of communication with local hospitals, state newborn screening programs, and regional Primary Care Practitioners (PCPs) should facilitate referrals and longitudinal care. A single intake point through a clinical care coordinator should be established and advertised. Generally, this will be the telephone number for a designated person in the pediatric endocrine office, who can triage calls to the appropriate provider(s). Timely followup is critical for CAH because this disorder can be rapidly fatal. Infants strongly suspected of having CAH should be seen and treated within 24 hours of identification and/or notification. A hotline or pager should be established for emergencies. PCPs should be made aware of the availability of tertiary referral to CCCs for conclusive diagnostic studies and management of children with CAH due to 21-hydroxylase deficiency (21OHD) detected through newborn screening. PCPs should also be aware that newborn screening may fail to identify some infants with simple-virilizing and nonclassical forms of CAH and does not seek to identify forms of CAH other than 21OHD.

The first visit will likely involve the pediatric endocrinologist, pediatric endocrine staff, and pediatric urologist/pediatric surgeon. CCCs should make every effort to schedule patients for visits with multiple health care providers on the same day to accommodate families coming from long distances and to minimize loss of time from school or work (i.e., pediatric endocrinology and pediatric urology, medical endocrinology and gynecology, education sessions, etc.). Attempts should be made to concentrate subsequent followup visits of several CAH patients on the same day and to facilitate the peer support process for patients and their families without compromising confidentiality. Paperwork details at entry into the system should include completion of forms that may be required to share health information with parents and emergency notifications in compliance with the Health Insurance Portability and Accountability Act (HIPAA) and making sure that patients have medical alert identification, such as wallet card and/or jewelry.

2.3. Providers. The CCC should have participation or availability of an interdisciplinary team, which includes pediatric endocrinologists, internal medicine endocrinologists, reproductive endocrinologists, pediatric urologists/pediatric surgeons, gynecologists, geneticists/genetic counselors, behavioral health professionals, nutritionists, social workers, pediatric endocrine teaching nurses, and nursing staff. To provide continuity of care, each family should identify a specific physician as the primary physician for their child. The care coordinator and educator functions should be distributed among the available nursing and administrative personnel. As nurses in the CCC acquire expertise, they should assume progressively greater responsibility for education of patients and their families. Adolescents and adults should be provided with educational opportunities as they assume responsibilities for their own care. Social work and translation services should be available and centralized if possible. In addition to the previously mentioned providers, access to providers specialized in treating the various medical, surgical, cosmetic, and psychological consequences encountered during the long-term care of adult women and men with CAH should be available.

2.4. Behavioral Health Counseling. Behavioral health specialists are key members of the assessment and treatment team; behavioral health services should be viewed as a component of routine care. Access to CARES Foundation, Inc. and other support and educational resources should be provided. CCCs should facilitate local support group meetings. Both pediatric and adult behavioral health specialists should be identified for complex problems beyond basic support and problem solving. Given the shortage of such trained professionals, webcasting, or telemedicine among CCCs may be helpful to provide skilled behavioral health assessment and care plans for difficult cases.

2.5. Delivering Patient and Family Education. Patient and family education should be a central focus of the CCC. Trained nurses, physician extenders (nurse practitioners and physician assistants), and nurse educators can help educate patients about the details of CAH and their medications. They should help parents plan for school, summer camp, college, and transition to adult care providers. Parents should be informed about health promotion and disease prevention and be trained in the emergency use of injectable glucocorticoids. The educator should also help coordinate services with subspecialists and secondary healthcare providers within the team.

A nonphysician caregiver who has an ongoing relationship with a CAH patient can effectively and simultaneously act as a patient advocate and play an important role in guiding the patient through transitions from infancy to adult care. At times, nurses, nurse practitioners, fellows, and physician assistants may be more accessible to the patient than the physicians. Patients may share additional information which they feel uncomfortable telling the physician; that is, they have not been consistently taking their medications or that they have added an herbal supplement to their regimen.

When scheduling the first visit, families of a newborn with CAH should be advised that the initial encounter will likely involve an extended visit, which includes a comprehensive educational experience. This visit is often

Table 1: Measuring success.

Potential medical outcomes:
(i) Quality-of-life using validated surveys
(ii) Biochemical control of CAH
(iii) Symptomatic control of androgen excess (hair loss, acne, hirsutism, amenorrhea, etc.)
(iv) Compliance
(v) Adult height
(vi) Frequency of adrenal crises/hospitalizations
(vii) Reproductive function
(viii) Comorbidities (obesity, hypertension, metabolic syndrome, hirsutism/polycystic ovarian syndrome [women], testicular adrenal rests [men], and myelolipomas)
Potential surgical outcomes (women):
(i) Number and types of surgeries
(ii) Complications (vaginal stenosis, urinary symptoms, urinary tract infections, etc.)
(iii) Functional and cosmetic results
(iv) Patient satisfaction
(v) Menstrual regularity, fertility
Potential behavioral health/psychosexual outcomes:
(i) Patient and family adjustment
(ii) Psychopathology (depression, anxiety, obsessive-compulsive disorder, eating disorders, substance abuse, etc.)
(iii) Sexual function
(iv) Gender identity

overwhelming because of the vast amount of information presented. The immediate survival needs, such as glucocorticoid and mineralocorticoid replacement therapy and management of adrenal crises, should be covered first. A pamphlet including links to informative websites (i.e., CARES Foundation, Inc., http://www.caresfoundation.org/, other helpful support groups, CAH message boards and other appropriate online and organizational resources; professional organizations including The Endocrine Society, http://www.endo-society.org/, Pediatric Endocrine Society (formerly Lawson Wilkins Pediatric Endocrine Society), http://www.lwpes.org/, European Society for Pediatric Endocrinology, http://www.eurospe.org/). Preprinted forms and handouts for common procedures should be provided to the family. More advanced topics and future issues should be introduced and expanded at subsequent visits. At each visit, the mechanism to access the emergency system should be reviewed with parents and patients. As the child grows and develops, the CCC should provide a resource for education and discussion of additional topics such as riding the school bus for kindergarten, school trips, sexuality, fertility, and many other concerns (see below).

2.6. Patient Confidentiality. The CCCs require a flexible environment for the sharing of pertinent information among providers. In all situations, the patient's rights and privacy are paramount. All personnel should be trained in HIPAA procedures and reminded to respect patient rights at all times. While training and research opportunities are readily available, these activities are not excuses for breaches in confidentiality of any sort. Communications should contain only information relevant to the situation at hand. Photographs should only be taken when medically necessary and should not be taken or distributed for teaching and research purposes without written informed consent and deidentification. The practice of having large numbers of individuals examine a patient's genitalia should be avoided. Exposure to sensitive aspects of the physical examination should be limited to essential providers and to members of the team of support personnel and trainees.

The Genetic Information Non-Disclosure Act of 2009 (GINA) includes penalties for breaches in confidentiality. The ARRA/HITECH Act of 2009 (the recovery act) strengthens HIPAA provisions by extending the application of HIPAA to personal health records and also by creating requirements for notification of patients about potential breaches in confidentiality. These legislative mandates strengthening confidentiality protections are particularly important given the increased use of electronic health records and information exchange. Patient preferences, patient choices, and the level of patient knowledge, including information shared with adolescent patients, should be included in electronic medical summaries as a means of promoting patient-centered care. Future data repositories should be designed with strong provisions for controlling and monitoring disclosure of personal identifiers, genetic analyses, diagnoses, and other confidential information.

2.7. Communication. Communication between the physicians and ancillary staff of the CCC with referral practices in the region is essential for continuity of patient care. CCCs are encouraged to develop pamphlets on CAH for PCPs and other medical providers, and a copy of the pamphlet on the type of CAH involved should be included in the initial

communication. Medical summaries are essential to facilitate communication between multiple providers. Centers should maintain lists of PCPs such as pediatricians, family practitioners, internists, and gynecologists who are comfortable with the care of patients with CAH and are sensitive to the particular needs and vulnerability of these individuals. Current lists of local subspecialists, such as orthopedic surgeons, otolaryngologists, ophthalmologists, and so forth, should also be maintained by the CCC. PCPs should receive a letter after each visit to the CCC, typically from the lead provider. This letter should summarize the patient's current status, management plan, the most pressing problems addressed in the interval between appointments, and any additional areas of concern. A copy of the note or an abstracted summary may be sent to the patient (or parents of minors). The patient and family need to sign a release of information form to enable the CCC providers to communicate with the PCP and other providers, particularly for emergency situations.

CCCs are also encouraged to explore the use of communication technologies to improve patient care, particularly for patients living far from the center. Infrastructure should be developed to utilize telemedicine, web-based communication systems, and portable data organizers. A CCC website should be available that includes information specific to that center (locations, events calendar, and telephone/fax numbers), links to other relevant sites, and information about ongoing research studies and support group contacts.

2.8. Financial Considerations. Information regarding financial issues, including insurance forms, prior authorizations, and statements of medical necessity should be provided to families that identify mechanisms to alleviate the financial burden of the healthcare costs associated with CAH. Financial advisors should be available through the CCC to help patients and families take advantage of available resources (such as charity care, State Children's Health Insurance Program, Medicaid, pharmaceutical company patient assistance programs, and Catastrophic Illness in Children Relief Funds), to help families negotiate the complex processes involved in applying for such services, and to help families obtain reasonably priced lodging (e.g., Ronald McDonald Houses) if overnight stays are necessary. The CCCs should advocate with private and public payers for reimbursement of necessary services, tests, and treatments, including those not typically covered, such as psychological counseling, genetic services, hair removal or hair loss treatments, consultative services by team members, and other services provided to patients outside an office visit such as counseling the patient by telephone or email. The CCC coordinator should be able to streamline testing requested by various team members to maximize cost effectiveness. CCCs should explore negotiations with laboratories for lower test costs based on economies of scale for steroid assays and genetic tests.

2.9. Infrastructure. Additional activities of the CCC should include interdisciplinary conferences to discuss specific patients, medical ethics, transition between providers, and relevant scientific studies. Paramount to coordination of care is provider access to records from visits with other providers. Centers should have defined procedures for obtaining laboratory and radiology data from reliable reference laboratories and imaging centers, either prior to or on the day of appointments. Written protocols should exist for generating requisitions, scheduling blood draws and other studies, review of results, and communication of recommendations to patients and families. Nursing staff, secretarial staff, and patients/parents should be familiar with these protocols. A single integrated electronic medical record (EMR) is ideal. In the absence of an EMR, physical, electronic, or other procedural links between systems may need to be developed. In some instances, hard copy medical records may be obtained by mail, fax, or secure electronic communication from outside physicians.

2.10. Transition. The transition of a child with CAH to an internal medicine endocrinologist's care means a fundamental shift in treatment goals, parent-patient relationships, and approach to care delivery [4, 5]. Adult patients are solely responsible for their actions, adherence, and choices; their parents will participate in these decisions less than during childhood. Loss of the longstanding relationship with the pediatric care team can be difficult for the adolescent and his/her family. One goal of the idealized CCC model is a smoother transition process by providing an integrated network during this critical phase. A well thought-out, individualized, transition plan will ensure that the patient has a positive experience and is well prepared for life as an adult with CAH.

Many adult patients will no longer be living in the same city in which they lived as children. The pediatric endocrinologist may need to assist the patient in finding an IM endocrinologist not only in a new medical center, but also in a new location. The timing of the transfer will generally occur between the ages of 16 to 21, with the pediatric endocrinologist, the patient, and the patient's family determining the exact time based on the needs and maturity of the patient. A structured program with written documents has been shown to be effective in transitioning pediatric patients to an adult health care provider with other chronic conditions [6, 7].

3. Goals and Relevant Topics Considered by Age Group

3.1. Treatment Goals. The clinical management of the patient with CAH is inherently age and gender specific [8–11]. In devising regimens for individuals with CAH, the endocrinologist should first review the treatment goals. Confirmation of the diagnosis of CAH (and also of the clinical form) may be necessary using hormonal and/or genetic testing depending on the pediatric medical information available. The CCC should develop a structured process for age-appropriate discussions to educate a patient about his or her disorder, its treatment, and how to handle emergencies away from home. Eventually, the patient should be able to describe CAH and

its potential complications, understand the need for stress glucocorticoid dosing and the need to wear medical alert identification jewelry, and know his/her own medications, dose and schedule. Therapy should be individualized based on age, gender, prior history, body composition, other illnesses, and immediate goals [12].

Parents often worry about giving 3-4 doses of medication per day to their children within school and activity schedules. Many adults perceive that they cannot take divided doses of hydrocortisone due to work schedules; however, chronic therapy with longer-acting and more potent synthetic glucocorticoids may increase risks for side effects, including obesity, glucose intolerance, bone loss, skin fragility, poor sleep, and immunosuppression. The endocrinologist should emphasize that individual responses to specific medications are only somewhat predictable, and trial periods are necessary to assess the benefits and complications of each regimen. It is recommended that CCCs develop pamphlets to discuss treatment options. The CCC should be able to elicit the input of secondary providers, including dietitians, physical therapists, and personal trainers, to help the patient manage weight gain and deconditioning that might arise when therapies are intensified. Although these specialists need not be a part of the CCC, specific individuals in the region should be identified and also educated about CAH to provide better care.

3.2. Timing of Changes. Significant regimen changes should be avoided during times of major life changes, such as starting school, moving, going away to college, getting married, or starting a new job. These changes should begin several weeks prior to or started several weeks after the event transpires. For adolescents and adults, many of these events are associated with weight gain, fatigue, poor sleep, and emotional changes; consequently, these symptoms might be erroneously attributed to the new treatments if not separated in time. While laboratory monitoring is important, clinical responses are paramount, and overtreatment simply to have laboratory values in the normal range is strongly discouraged.

3.3. The Newborn. As discussed above, infants should be referred to the CCC by PCPs or by newborn screening programs. Goals include confirmation of the diagnosis of CAH, initiation of hormone replacement therapy, and family education. In addition to pediatric endocrinologists, pediatric urologists/surgeons, endocrine nurse educators, and behavioral health specialists may be involved. The initial visits should form the basis for long-term relationships between the family and the CCC.

3.4. The Child. Every clinic visit for a child or adolescent with CAH should include a comprehensive endocrine evaluation and an assessment/screening of behavioral health status. Involvement of the child in this conversation, as appropriate for his/her level of maturity, is important to educate the child about why he/she takes daily medications and may occasionally need to miss school for doctors' appointments. Medical issues addressed should include adequacy of hormone replacement therapies, adherence to treatment recommendations, evaluation of growth and pubertal status, evaluation for excessive androgen secretion, reinforcement of appropriate stress glucocorticoid coverage, and use of medical alert identification. Hormone determinations and radiographic testing should be performed as necessary to assess adequacy of hormone replacement therapy. From the time of diagnosis, sharing of information with the child with CAH should be planned with the parents through an ongoing dialogue regarding what is developmentally appropriate for the child [13]. Medical education and counseling for children is a continuous process, gradually increasing in sophistication, in which teaching occurs at a level that is commensurate with the progressing cognitive and psychological development of the child, with specific emphasis on fostering open parent-child communication [14]. Thus, open and honest communication with the patient and the family is essential. Behavioral health assessment ideally consists of a brief interview conducted separately with both patient and parents by a qualified behavioral health provider.

3.5. The Adolescent. Although the pediatric endocrinologist will continue to be the dominant care provider during adolescence, the adolescent must develop an understanding of his or her condition. The pediatric endocrinology team has the responsibility for educating the child and the parents about the child's impending independence. Discussions about puberty should be initiated at the appropriate age for each child as they develop, with discussion of privacy and appropriate boundaries. Transitioning the adolescent patient into adult care should be gradual process that begins years prior to the change in health care providers [15]. This process should include provision of medical records which include information on the type of CAH, genetic reports (if mutation(s) is/are known), age of diagnosis, current and significant past treatment regimens (including rationales for deviation from typical therapies), genital and gonadal surgeries, other medical problems and surgeries, family and social history, allergies, psychological issues (if any), and recent laboratory data. A summary paragraph capturing the patient's essential characteristics, treatment, and particular needs should conclude the transfer form or referral letter. Joint meetings between the adult and pediatric health care providers are ideal, but some centers may be structured such that the patient will see the endocrinologist in a different physical location and/or at a different hospital.

During the middle school and high school years, age-appropriate education should occur with and without the parent present, and should foster independent knowledge and eventual self-management. Patients should be encouraged to ask questions during each office visit. Independent health care behaviors should begin to develop in the pediatric setting. Parents must be educated about how to give the child increasing responsibility for his/her healthcare. Adolescents should be provided with time alone with the physician(s) without the parent(s) in the exam room. The adolescent needs to be offered the opportunity to discuss personal issues such as menstruation, contraception, fertility,

gender identity concerns, and use of tobacco, alcohol, and recreational drugs in the absence of their parents.

Subjects covered during the transition from pediatric to adult care providers should include planning for health care insurance coverage/governmental health plan for the child after age 18 years or after college. Additional topics include sexual, urological, and reproductive health including contraceptive counseling, genetic counseling, mental health issues, body weight concerns, and understanding the genetics of CAH. Pertinent discussions should include how to stay healthy in college or other after high school situations, potential alcohol/recreational drug abuse, healthy eating, and weight-gain avoidance. Discussions about how to handle illnesses and emergencies should be held. Specific plans should include telling a roommate about CAH and the potential need for glucocorticoid injections, knowing locations of college health center facilities and the local emergency department, and knowledge of insurance information. Additional topics for the college-bound adolescent include how to handle homesickness, stress, anxiety, and depression, and how to care for mental health. Emphasizing the profound cosmetic and reproductive side effects of nonadherence with medications and monitoring can often have a bigger impact for teens than merely emphasizing the health aspects of noncompliance. Young adults should be prepared with more knowledge about CAH than their new healthcare providers in college health/armed forces health services [17]. Thus, they need to learn to advocate for themselves in the healthcare setting and learn how to explain CAH and their health needs to new healthcare providers.

Adolescent girls need to understand their history, if any, regarding ambiguous genitalia at birth and the extent of surgery. Issues related to sexuality, sexual function, and genital anatomy including the use of vaginal dilators versus surgical options may warrant discussion. When appropriate, this discussion should include how to responsibly approach sexual activity, talking to a sexual partner about genital reconstruction, and preparing for the first sexual experience. Family discussions should be encouraged and some education should occur prior to gynecology referrals. Caregivers should be sensitive to cultural differences in relating information. They must educate parents about adverse long-term psychological consequences of withholding medical information if parents are resistant to such discussions. CAH nurse educators should reinforce educational content, review anatomy, teach the use of vaginal dilators, and answer questions related to and in conjunction with the first gynecologic visit. They should help the patient determine questions and goals related to such visits. Some women with CAH may have the false impression that pregnancy will not be possible. Since many women with CAH have trouble conceiving, they should be aware that pregnancy may take longer to achieve and should have this information available for family planning. They should also know that CAH is not an effective form of birth control and be informed about the types of contraception available. Counseling women about prevention of sexually transmitted infections and HPV vaccination should be included in their gynecological care.

3.6. The Adult Female. Adult females also require periodic assessments of the adequacy of glucocorticoid replacement, the possible development of myelolipomas, bone health, and reproductive function. There is also a need to address genetic counseling concerns, update health education, and assess health maintenance activities [18]. Women with nonclassical CAH (NCAH) often come to medical attention for infertility, oligoanovulation, and hirsutism; treatment should be directed to these needs [19]. The degree of androgen excess in NCAH varies, and CCC physicians should not underestimate the need for, or complexity of, treatment. The same goal-directed principles guiding therapies apply as for women with classical CAH. The care of the adult female is further complicated by additional needs for gynecological care and, in some instances, obstetrical care. Specialized behavioral health care may be required to assist the patient in discussing issues that might be unique to CAH, especially sexuality and gender identity. The adult female should be assured that although her care may be complex, the CCC has sufficient expertise in all relevant areas. Adult females should also receive routine screening and health maintenance testing (Pap smears and mammograms).

Each CCC should have an available gynecologist (or another caregiver trained in gynecological exams and issues) who is knowledgeable about CAH to both examine and discuss issues with CAH females. Pap smears are recommended by the American College of Obstetricians and Gynecologists by age 21 or within 3 years of sexual intercourse [20]. Having a health care provider who is comfortable discussing sexuality and has a relationship with the patient is extremely important. A comfortable patient-physician relationship will facilitate discussion of feelings about genital appearance and/or sexual and/or reproductive functioning. A solid relationship will also foster involvement of additional health providers, including psychosexual specialists and sex therapists, gynecological and/or urological specialists, and/or reproductive endocrinologists. Many females may begin seeing a gynecologist prior to or along with seeing an internal medicine endocrinologist, depending on the individual patient's needs.

For women with classical CAH, treatment regimens will vary with their reproductive needs and sensitivity to androgens and progesterone. For women who do not want to become pregnant, nonglucocorticoid therapies should be discussed and offered to minimize exposure to supraphysiological doses of glucocorticoids. These adjunctive measures include antiandrogens, oral and transdermal contraceptives, intrauterine devices, and topical or mechanical depilation methods. The CCC should provide mechanisms or forums to review and to optimize individual patient treatment plans with the endocrinologist, gynecologist, and other relevant providers in a case-review format [21]. Most importantly, the endocrinologist should emphasize that a woman is not locked into a single regimen for life, and alterations are often desirable as the needs and goals change.

3.7. Pregnancy Considerations. Women with both classical and NCAH desiring pregnancy should be offered preconception counseling prior to pregnancy. This counseling may include genetic counseling and testing the partner (when appropriate), discussing the likelihood of dose titration during pregnancy, the increased need for Caesarian section in classical patients, and the use of stress-dose glucocorticoids during labor and delivery. A reproductive endocrinologist should assess the need for fertility treatment. A team approach to pregnancy, including an endocrinologist, a reproductive endocrinologist (as needed), and an obstetrician (maternal-fetal medicine specialist when indicated), is highly recommended. Discussion regarding the risk-benefit ratio of prenatal dexamethasone therapy may be considered, but only in the context of a research setting, per current Endocrine Society guidelines [22]. The CCC team plays a key role during pregnancy, during which time close communication is important between the endocrinologist and the obstetrician. After becoming pregnant, women with CAH should be aware that their glucocorticoid and mineralocorticoid doses may change during gestation.

3.8. The Adolescent and Adult Male. Adult males with CAH require periodic evaluation to assure adequate glucocorticoid replacement, monitor for the development of testicular rests and adrenal myelolipomas, monitor bone health, and address fertility issues (if desired), and for general health maintenance. Males with CAH may have concerns about fertility if they have known adrenal rest tissue. Some may be under the false assumption that they are unable to father children and may need to be reminded that CAH is not a form of birth control. Males who have a history of precocious puberty may have concerns about the normalcy of their development. Open discussion and ongoing developmentally appropriate education is warranted throughout adolescence and adulthood [23].

For men with classical CAH, moderate doses of hydrocortisone or a longer-acting glucocorticoid, along with fludrocortisone, are generally sufficient to prevent adrenal insufficiency, maintain fluid and electrolyte balance, avoid suppression of gonadotropins, and prevent development of tumors, such as adrenal rests in the testes and myelolipomas in the adrenals. Higher doses or more potent glucocorticoids, as well as the reinforcement of good compliance may be necessary to induce regression of these tumors and promote fertility. The CCC should coordinate urological evaluation (testis size, need for sperm retrieval, etc.) and screening for complications with treatment changes and monitoring schemes instituted by the endocrinologist. Men with NCAH rarely require treatment.

The internal medicine endocrinologist should manage hormonal therapies and related endocrine issues, and the PCP should generally handle unrelated and acute problems, and routine health maintenance. Access to genetic counseling and DNA testing should be readily available for affected individuals, partners, and other interested family members. Education of the patient, who may have relied on his parents to manage his CAH, is an important goal. Patients should receive age-appropriate routine screening examinations as coordinated with their PCP (blood pressure, fasting lipids, and colon and prostate cancer screening). Attention to conditions exacerbated by chronic glucocorticoid use, for example, metabolic syndrome, obesity, and osteoporosis, should be considered.

3.9. Bone Health. Treatment of CAH demands life-long glucocorticoid replacement. However, finding the "exact" or "best" dose remains elusive. Undertreatment has been associated with adrenal insufficiency (adrenal crisis) and androgen excess (virilization and short stature), whereas overtreatment causes iatrogenic Cushing syndrome with numerous physical and metabolic consequences. Although treatment requires supraphysiological dosing compared to adrenal insufficiency of other etiologies (such as Addison's disease), excessive dosing beyond that required for good control of CAH, especially after the newborn period, may be deleterious to bone health over the lifespan. Furthermore, addition of medications to maximize a child's height potential may affect bone mineral density [24–26]. Although such treatments have positive outcomes (height, self-esteem, etc.), the risk/benefit with regard to bone health demands that the CCC be attentive to skeletal integrity and consider screening during the course of these regimens. Because the potential risk for osteoporosis remains to be quantified, the CCC should have the capacity to monitor and treat bone disease, even in young patients [27].

4. Newborn Screening, Diagnosis, and Genetics

4.1. Initial Newborn Screening. Universal newborn screening (NBS) for 21OHD identifies both male and female affected infants, decreases mortality and morbidity from severe electrolyte abnormalities, and may reduce the risk of incorrect sex assignment in severely virilized females. NBS for CAH is currently available in all 50 states and in many other countries. All screening laboratories for CAH are expected to participate in the NBS quality assurance program [2]. The state NBS program should be encouraged to recognize the CCC as the regional referral center for newborns identified by NBS. The CCC should be familiar with its state NBS protocol, sample and data collection methods, definitions for screen-negative and screen-positive test results, and detailed procedures followed for each type of test result.

Blood sampling is usually performed when newborns are older than 24 h. Most screening programs measure 17-hydroxyprogesterone (17OHP) in blood spots using time-resolved, dissociation-enhanced lanthanide fluoroimmunoassay (DELFIA, Perkin Elmer Corporation, Turku, Finland) or similar assays that are highly automated; however, this method yields many false positive results due cross-reactivity with other steroid metabolites. Moreover, increased serum concentrations of 17OHP are associated with low birth weight and illness, increasing the incidence of false positives in premature and sick infants. Adjusting the cutoff of 17OHP for gestational age instead of birth weight improves the specificity of the test if available. CAH screening

at present still has a low predictive value—approximately 1% in the United States—as a newborn screening protocol [2].

4.2. Second-Tier Newborn Screening. The issues of cross-reactivity and specificity can be alleviated by the use of liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods [28]. This methodology can detect 17OHP as well as other compounds like androstenedione, 11-deoxycortisol, 21-deoxycortisol, and cortisol. The use of precursor/product ratios such as (17OHP + 21-deoxycortisol)/cortisol eliminates most of the falsely positive screening results in infants with elevated 17OHP due to stress, illness, or prematurity. Using this approach, the positive predictive value of CAH screening improves significantly to 30%–100%. Therefore, a second-tier test by LC-MS/MS for all positive screening results should be considered in all screening laboratories that have appropriate equipment and trained personnel available [29], which may be preferably performed at a regional facility.

4.3. Evaluation of Newborns with Positive Screening Results. Newborns with moderately elevated 17OHP levels (see below) are usually followed up with a repeat filter paper specimen. The PCP usually evaluates infants with higher 17OHP values, using the medical history, a standardized physical examination, and serum tests for electrolytes and a serum 17OHP level. If these are abnormal, the infant should be referred for further evaluation to a specialist. The gold standard for diagnosis of CAH is a high-dose cosyntropin ($ACTH_{1-24}$) stimulation test. Existing normal values are defined based on stimulation tests employing a pharmacological dose of 0.125–0.25 mg cosyntropin. It should be kept in mind that 17OHP levels may be elevated in other enzymatic defects besides 21OHD. To fully differentiate among these other disorders affecting steroidogenesis, the clinician should ideally measure 17OHP, cortisol, deoxycorticosterone, 11-deoxycortisol, and 17-hydroxypregnenolone 30–60 minutes after cosyntropin with at least one measurement each of dehydroepiandrosterone and androstenedione. If there is a high index of suspicion for CAH (ambiguous genitalia in females, markedly elevated 17OHP on the NBS in either sex, and/or electrolyte abnormalities), treatment should be instituted immediately without waiting for the results of a cosyntropin stimulation test. Large pediatric referral hospitals with an on-call pediatric endocrinologist may be able to conduct such testing quickly; however, the risks of delaying treatment to perform the test may outweigh the benefits, particularly in sick infants with abnormal electrolytes, and markedly elevated ACTH levels. A rapid fluorescent *in situ* hybridization (FISH) of interphase nuclei with Y chromosome probes may be done when indicated in the differential diagnosis, as well as a pelvic sonogram and genitogram in virilized female infants. DNA testing for characterization of 21OHD (*CYP21A2*) alleles should be an option available at the CCC.

4.4. Diagnosis of CAH Beyond the Newborn Period. Patients suffering from classical forms of CAH due to 21-hydroxylase deficiency can be diagnosed by measuring 17OHP, preferably in the morning. Concomitant measurement of adrenal androgens (i.e., dehydroepiandrosterone and androstenedione) may identify this and other adrenal causes of virilization. Patients with NCAH secondary to 21OHD generally require a cosyntropin stimulation test to confirm the diagnosis. In general, ACTH-stimulated 17OHP values greater than 1500 ng/dL are associated with identification of mutations on both *CYP21A2* alleles [30] but vary with the laboratory used.

4.5. Standards of Hormone Diagnostics. Specific methods should be used for hormone analyses. LC-MSMS methods give highest specificity and sensitivity; enzyme immunoassays, especially those for aldosterone, have the same limitations for specificity and sensitivity as described above. Each diagnostic laboratory should establish validated cut-off levels for different age groups and pubertal stages; regional or national reference laboratories are preferred. LC-MS/MS is extremely reproducible; normative data can be transferred from one laboratory to another if the same methodology/instrumentation is used. Analysis of urinary steroid metabolites with GC-MS methodology may also allow proper diagnosis, but extensive experience is currently lacking.

4.6. Technical Precautions. Molecular testing for CAH due to 21OHD faces painstaking technical challenges, such as the presence of the highly homologous closely linked pseudogene (*CYP21A1P*), which serves as the donor for transfer of deleterious mutations to the normally active *CYP21A2* gene, a process termed gene conversion. There is also significant variation in gene copy number, and deletions of *CYP21A2* comprise ~20% of alleles. Finally, these genes lie in the HLA major histocompatibility complex, a region with unusually high rates of genetic recombination. It is critically important to ensure that *CYP21A2* is specifically amplified and not contaminated with *CYP21A1P* sequences, which otherwise represent a source of false-positives. Prenatal molecular diagnostics should be repeated after birth for confirmation.

4.7. Technical Requirements. Whenever possible, genotyping should be performed simultaneously on samples from the patient (proband) and both parents. Obtaining samples from different generations is important to "set phase" because multiple deleterious mutations can occur on one allele. The applied techniques should be capable of detecting the most common mutations, which are all gene conversions, and should reliably determine gene copy number. Full-length DNA sequencing should be available to characterize alleles with private mutations that are not generated by intergenic recombination. Additionally, if mutations on both alleles cannot be reliably identified, laboratories should have the capability of performing diagnosis by determining segregation of alleles using closely linked variable-number-of-tandem-repeat polymorphisms. Multiplex ligation-dependent probe amplification (MLPA) assays

show promise in helping to resolve ambiguous results from standard methods.

4.8. General Considerations. CAH is inherited as an autosomal recessive trait. Thus, there is a 25% probability that siblings of the index case will also have CAH, a 50% probability that they will be asymptomatic carriers, and a 25% chance of being totally unaffected. Based on a classical CAH incidence of approximately 1 : 16,000–20,000, the prevalence of carriers in the general population is 1/63–1/71. If we assume the high-end value of 1/60 potential partners being heterozygotes for CAH, a patient with classical CAH will have a 1/120 probability of having a child with classical CAH. For NCAH, about two thirds of patients are compound heterozygotes, carrying one allele that causes classical CAH and one that causes NCAH [31]. The milder mutation determines the phenotype; hence, the NCAH parent has a 1/240 risk of having a child with classical CAH. Recent studies suggest that this risk, rather than being about 0.4%, may actually be closer to 2.5% [32]. Given the relatively higher prevalence of mild CAH mutations, there is a greater risk for offspring of a parent with either classical CAH or NCAH to have NCAH, which is significant but not life threatening.

4.9. Anticipated Pregnancies. Genetic counseling is valuable for parents who have had at least one child affected with CAH and may plan for future children. Additionally, adults themselves affected with CAH may request counseling and genotyping for themselves and/or their partner before planning for children. Genetic counseling can and should be offered to parents soon after the birth of an affected child. The genotypes of the proband and parents should be obtained well before another pregnancy is contemplated. Patients of reproductive age should also be informed and encouraged to seek genetic counseling before contemplating future pregnancies.

4.10. NCAH. NCAH patients should be offered genetic testing if a pregnancy is desired. As discussed above, 2/3 of NCAH patients carry one classical CAH allele, yielding a 2.5% risk of giving birth to a child with the classical form and a 15% risk of having a child with NCAH form [32]. The carrier frequency is high in the general population, varying from 1 : 60 for those carrying mutations predicting classical form and 1 : 16 for those carrying the NCAH mutations, depending on the ethnicity. All spouses of a patient with NCAH carrying one classical CAH gene should be encouraged to have genotyping if the couple desires a pregnancy and would consider prenatal diagnosis and/or prenatal treatment.

4.11. Delivery of Counseling. Ideally, a well-informed pediatric or adult endocrinologist or endocrine nurse specialist should deliver introductory genetic counseling and explain basic concepts at an early stage in the physician-patient relationship. Verbal discussions should be reinforced with written materials and/or reference to reliable web-based information on CAH, genetic testing, prenatal diagnosis and prenatal treatment [33]. Formal counseling should subsequently be delivered by a geneticist and/or a genetic counselor experienced in this area.

4.12. Prenatal Diagnosis and Prenatal Treatment. Well-informed pediatric/adult/reproductive endocrinologists and geneticists/genetic counselors experienced and knowledgeable in this area should participate in the discussion of the available options including "pros" and "cons". More detailed information on this topic can be found in the Endocrine Society Clinical Practice Guidelines on Congenital Adrenal Hyperplasia (http://www.endo-society.org/guidelines/Current-Clinical-Practice-Guidelines.cfm) [22].

5. Specialized Surgery for Congenital Adrenal Hyperplasia

The salt-wasting and simple-virilizing forms of CAH are often accompanied by varying degrees of prenatal masculinization of the female external genitalia as a result of excessive adrenal androgen production during gestation. In the female patient with virilizing CAH, excessive androgen concentrations can cause the clitoris, labia, and vagina to develop along a more masculine tract. As 95% of children with CAH have 21OHD, the ensuing discussion, unless otherwise indicated, will refer to females with this form of CAH. Although no specific discussion addresses the needs of undermasculinized males with rarer forms of CAH, it is acknowledged that these patients have separate yet important issues.

The development of the ovaries, fallopian tubes, cervix, upper vagina, and uterus are unaffected. Thus, although girls with CAH can be born with male-appearing external genitalia, they have normal ovaries and female internal reproductive organs and retain the potential for fertility. With optimal medical treatment and, in some girls, surgery to separate the lower urinary and reproductive tracts, the potential for fertility is retained, and the issues associated with the masculinized lower genital tract can be corrected or alleviated [34].

These masculinizing changes of CAH can result in the joining of the female urinary and reproductive systems at the level of the urethra and vagina (referred to as a urogenital sinus). The higher the level of confluence of the urethra and vagina, the more likely it is that the affected individual will have difficulties with urinary, reproductive, and sexual function. These difficulties may include chronic urinary frequency, urinary incontinence, "spraying" of urine during micturition, inability to use a tampon, or inability to have penile penetrative sexual intercourse. In addition, psychological and self-image issues may also develop. In adolescent and adult patients who have clitoromegaly, painful sexual arousal may also occur. Nevertheless, despite moderate degrees of masculinization, healthy growth and development are possible for affected girls.

5.1. Surgical Considerations. In the past 20 years, understanding of the anatomy and neuroanatomy of the female genitalia has expanded greatly. Furthermore, considerable advances in surgical techniques have emerged, with the aim of improving the functional, cosmetic, and psychological results of surgical intervention, including the preservation of genital sensitivity and orgasmic potential.

5.2. Anatomic Considerations. In females with a urogenital sinus of any degree, vaginoplasty is required for penetrative penile intercourse. There are conflicting opinions regarding the optimal timing of surgery. Management of clitoromegaly is similarly controversial. For girls with significant genital virilization (Prader stage 3 or greater), there may be an indication for early genital surgery (age < 6 months), and these children should be cared for by a CCC surgeon specifically experienced with operative management of children with CAH. Nevertheless, some families may elect not to undertake early surgery for various medical, ethical, or cultural reasons. Such families should be supported in their decision.

5.3. Decision Making. The psychosocial and cultural issues relating to early versus late genital surgery have been poorly addressed, yet they play a major role in the surgical decision-making process. The factors that guide parents' decisions regarding whether to subject their infant daughter to surgical intervention of the lower urogenital tract are complex. Such factors include: (1) the likelihood that medical issues, such as urinary tract infections and urinary incontinence secondary to vaginal voiding, will ensue, (2) parental desire for early "normalization" of external genitalia, (3) parental desire to have surgery performed early to prevent the child's memory of surgery versus parental desire to have the individual partake in the decision-making process, and (4) degree of masculinization of the external genitalia.

5.4. Risks and Benefits. Although surgeons constantly strive to improve their techniques, genital surgery may not be without complications or long-term sequelae. As such, health professionals involved in the care of children with CAH recommend that masculinized girls be evaluated early in life and that parents have a thorough understanding of the options, risks, and benefits of surgical intervention, so that they can understand all of the choices available for their child. This should include the option of no surgery at all, no clitoral surgery, and the relative advantages and disadvantages of early (perinatal) versus later (postpubertal) surgical intervention. Consideration should be given to development of a standardized informed consent document describing the risks and benefits of early versus later surgery. Furthermore, considerations to comply with the 2002 Consensus Statement on 21OHD from the Pediatric Endocrine Society and the European Society for Pediatric Endocrinology [35], as well as the 2010 Endocrine Society Guidelines [22], should be included in this discussion.

5.5. Adults. The issues and needs of adult women with CAH are poorly understood, as limited long-term followup data are available. This is particularly true when comparing long-term results between early and delayed genital surgery. Residual problems with sexual and/or urinary function following surgery may be significant. Some adolescents and adult women who underwent urogenital sinus surgery may develop stenosis of the vaginal introitus. As a result, voiding may be difficult, and the use of a tampon or sexual intercourse may be painful or impossible. In these situations, nonsurgical treatments should be considered as first-line therapy. Use of estrogen creams, dilation, and focused voiding treatments may obviate the need for surgery. Furthermore, adult women who are having difficulty with sexual performance may find that sex therapy or psychological counseling is helpful.

5.6. Transition of Surgical Care from Childhood into Adulthood. One of the most challenging aspects of surgical care for patients with CAH is the transition into adult care. Neither pediatric urologists/surgeons nor adult urologists/gynecologists have significant experience with care of adult women with CAH. It is, therefore, suggested that two designations be considered for CCC surgical centers. All designated centers should be capable to care for infants, children, adolescents, and young adults to include an age range from birth to 18 years. Specialty CCC surgery centers with expertise in treating older individuals (>18 years of age) with CAH will be further certified as Adult Centers of Excellence (ACOE) (Table 2). These centers may best be established by having the pediatric and adult surgeons working together to develop combined experience to optimize outcomes. CCCs that are ACOEs should develop expertise in helping adult women with CAH using nonsurgical and, when necessary, surgical techniques to improve sexual and reproductive function. For example, postsurgical vaginal stenosis may be alleviated by vaginal dilation, which should be attempted before the more significant intervention of surgical revision of prior surgery. Also, approaches should be undertaken to demedicalize management of issues of sexual function for women with CAH, such as using small commercially available vibrators instead of medically prescribed rods for dilation. A sex therapist may be of great importance in working with postsurgical adult patients. Self-esteem and self-confidence are critical aspects of long-term overall well-being for these women.

6. Advocacy and Education

6.1. Definition. Advocacy is defined as the active support of a cause or course of action. In the context of the CAH CCC, this means every person who works in the center advocates for the well-being of people affected with CAH by both reaching out to the community outside the CCC and educating those within. In this paper, "affected people" is an inclusive term that will refer to people living with a diagnosis of CAH, as well as to other people in their lives who are also touched by CAH, including parents, siblings, partners, spouses, friends, and coworkers. Advocacy and education are fundamental to empowering all of those affected by CAH and

Table 2: Criteria for defining CCC surgical centers of excellence.

(i) Comprehensive care team including endocrinology, anesthesiology, uroradiology facilities, intensive care unit, ancillary support staff
(ii) Surgeons are fellowship-trained and board-certified (subspecialty certification) in pediatric urology or pediatric surgery
(iii) Training must have included considerable exposure to CAH surgical techniques, with a minimum of 5 CAH feminizing genitoplasty surgeries.
(iv) Surgical volume must reflect ongoing interest and competence
(v) Surgeons designated as CCC surgeons must have completed at least 10 CAH surgeries as an attending surgeon within the prior eight years from date of application.
(vi) Peer-reviewed publications related to genital surgery in CAH patients
(vii) Multidisciplinary conference at least once every 3 months
(viii) Outcome measures and submission of data to a national CAH registry
(a) Type(s) of surgical procedure(s), age at operation, complications, and initial surgical outcome 1 year postoperatively
(b) Numbers of operations and complications
(c) Pubertal evaluation for general appearance, void function, and vaginal patency for menses and tampon use
(d) Evaluation at time of desire (or potential) to begin sexual activity to assess adequacy of vaginal caliber for intercourse (self-dilation versus revision may be needed)
(e) Long-term followup at age 18 or older: the most important followup is assessed from the patient's point of view, involving detailed questionnaires (psychosocial, sexual, and functional/anatomical) and interviews by independent assessors. Evaluation for general appearance, void function, vaginal patency, and clitoral sensitivity should be performed
(f) Data on adult quality of life, sexual functioning, obstetric history, and continence should be collected and assessed to determine the quality of the surgical techniques used and quality of postsurgical psychological support services and education of patients provided.

improving their quality of life. The foremost goal of advocacy in the CCCs should be to improve the quality of life of people affected by CAH, both the individuals themselves and those with whom they share their lives.

Many families express shock and dismay regarding the lack of knowledge about CAH on the part of school employees, local emergency department personnel, and other healthcare providers. Patients and parents need to be provided with tools that enable them to be effective advocates for themselves or their children in these settings. Clear, concisely written information, provided as pamphlets or laminated placards, about CAH and response to adrenal crisis should be available to parents for dissemination to schools, EMTs, daycare centers, and other relevant settings (available through CARES Foundation).

6.2. Philosophy and Implementation. The CCC should be more than just a place where clinicians converge to see patients. Comprehensive care improves health-related quality of life for patients with other conditions, and it is likely that the same improvements will occur for CAH. While specialists from various disciplines often confer on difficult cases during the typical course of patient care, the formation of a multidisciplinary team signifies formal commitment to principles of professionalism such as communication and cooperation that underpin effective treatment of the whole patient [13]. CCCs can create models for transparent, honest, and ethical decision-making with full informed consent at its core and can help affected people understand and evaluate potential outcomes, risks, and benefits of various healthcare decisions through the presentation of information in a nondirective and nonjudgmental way while defending the patient's best interests.

6.3. Education. Advocacy and education intersect in several ways in the CCC. When team members educate their peers and colleagues through training and educational programs, and by conducting and publishing research, they are advocating for the community of people affected by CAH by raising awareness and understanding of the disorder (Table 3). When the team teaches parents and individuals diagnosed with CAH how to better communicate their needs with healthcare providers and others, they are teaching advocacy. Team members who work with support groups to provide education to affected people about living with CAH help them to better understand how to manage life with the disorder, thereby supporting individual advocacy. The healthcare providers on the CCC team empower affected people to become advocates for themselves by providing them with knowledge and strategies to improve their effectiveness. Advocacy through education improves care, creates trust in the healthcare team, and leads to better overall communication and healthcare experiences.

6.4. Education of Families and Patients Leading to Empowerment. Engaging patients/families as effective partners in care management and shared decision making is vital to assuring high quality, appropriate care [13]. Evidence from studies of patients with other chronic medical conditions confirms that openness in the sharing of information is associated with enhanced psychosocial adaptation [36, 37]. With the help and guidance of the CCC, parents should progress from being "parents only" to "parents of a child with CAH" and ultimately "parent advocates." Parents should be provided with the knowledge, the words and phrases required to educate their child and other family members, and tools to proactively deal with

Table 3: Components of advocacy and education.

(i) Designate one team member to serve as a care coordinator to provide the point of contact.

(ii) Development of uniform, standardized educational materials, and professional training modules for affected people and health care providers dealing with different periods in the life cycle. Such materials would focus on various relevant subjects, using culturally sensitive terminology and health literacy tools, and would be provided in different common languages. Examples of modules include:

(a) the newly diagnosed infant,
(b) the toddler,
(c) the school-aged child,
(d) the teenage girl,
(e) the teenage boy,
(f) the individual in transition from pediatric to adult care,
(g) the adult woman,
(h) the adult man,
(i) special needs of the patient with atypical genital development,
(j) special concerns of the patient with NCAH,
(k) emergency training for families and patients,
(l) preparing for school and child care,
(m) dealing with discrimination in school, sports, or employment situations,
(n) reproduction and fertility,
(o) identifying psychosocial adjustment issues,
(p) obesity, growth, and bone health,
(q) testicular tumors, self-examination, and fertility,
(r) genetic consequences of CAH,
(s) frequently asked questions.

(iii) Development of a timeline for the delivery of health information to affected people and provision of educational materials to affected people and their families.

(iv) Development and maintenance of a comprehensive library of materials and web-based activities which can include informational pamphlets and videos, local support group contact information, brochures from support and advocacy organizations, decision pointers, and information on informed consent, medical privacy, and patient rights.

(v) Promotion of informal contact among affected people of all ages and medical and support staff through scheduling routine appointments for adults and children with CAH on the same day, with the aim of shared learning (details provided elsewhere). CCC evaluations are performed in rooms spacious enough to accommodate those who support patients with CAH during appointments.

both medical and psychosocial issues associated with the condition.

In adults with CAH, CCC should demonstrate sensitivity to the patient's experiences with prior treatments and healthcare professionals, with an emphasis on building trust in the CCC. At all ages, affected people must be reminded that CAH is a part of their lives, but should not be defining, and that not everything about them is attributable to CAH. CCCs should proactively help affected people synthesize and interpret information from a variety of sources, including information and potential misinformation gleaned through the internet and media.

The CCCs should assist affected people in organizing or contacting local support groups, coordinating educational and social gatherings with support group members, and facilitating team involvement in support group activities. The CARES Foundation can provide helpful resources, including educational materials and training programs for group leaders. These services may provide an effective tool to assist in forming social support systems shown to buffer the negative effects that these diagnoses may engender, help new parents master relevant information in their own terms, and provide strategies and role-playing opportunities for handling various social situations.

Delivering diagnostic and medical management information is a collaborative progressive process, not a single event, with a variable tempo depending on individual circumstances. Thus, a flexible individual-based approach is preferable. During the newborn period, the number of nonessential staff who interact with the baby and family, especially virilized female babies, should be limited; however, for the purposes of training others, strategies such as technological and audio/visual approaches should be considered under certain conditions, with sensitive handling and appropriate deidentification and informed consent. Providing people affected by CAH with a lexicon of terms for describing their condition in nonstigmatizing ways may help them with social skills. Patients and families may seek help to resolve what, when, how, and with whom to share information about CAH. Cultural, ethnic, and religious sensitivities must be understood and acknowledged. Although there is no universally "correct" approach, a discussion

with the patient and family about the benefits of selective information sharing, with accompanying strategies, should offer the individuals and parents considerable psychological relief [38]. Affected individuals who wish to examine their personal medical records should be allowed full access to review their medical history and treatment from infancy to the present time.

Advocacy and education should be fundamental to empowering all of those affected by CAH and improving their quality of life. The major philosophy of comprehensive care is person/family-centered, holistic, culturally sensitive, and effective care that considers the medical, emotional, psychosocial, and financial needs of people affected by CAH. CCCs should provide patient-centered care through collaborative evaluation and management strategies, shared decision making, and promotion of medical independence. CCCs and team members should participate in advocacy outside the local setting with other centers of excellence through education, research, and outreach. CCC should provide specific strategies to educate affected people throughout the life cycle.

7. Training, Research, and Registry

7.1. Training. Improving the quality of care provided to the adult CAH patient and education of internal medicine endocrinologists and other team healthcare providers by the pediatric endocrinology team is essential. Pediatric endocrinologists have more experience with CAH for a variety of reasons, most predominantly because of the consistency and coordination of care for genetic disorders that occurs during childhood. Through the coordination of care among the pediatric, internal medicine, and subspecialty practices during transition, and regular, meaningful communication about the needs of the individual patient and how to best address those needs, the internal medicine endocrinologists and subspecialty healthcare providers will be better trained to care for those with CAH. Thus, the training of the physicians, nurses, and other healthcare providers who deliver or will deliver health care to individuals with CAH throughout the life cycle should be central to the development and implementation of CCCs [39]. Centers should also encourage research and teaching of behavioral health issues and counseling techniques to increase the number of behavioral health providers skilled in the care of patients with CAH. Care for individuals with CAH begins from the preconception period and encompasses birth, infancy, puberty and adolescence, and adulthood.

Graduate medical education (GME) programs will benefit from having proficiency-based goals with opportunities for didactic lectures, informal discussion, and supervised clinical experiences [40]. The specific goals should be tailored to the particular needs of the trainees. Modeling on the Accreditation Council for Graduate Medical Education (ACGME), specific competencies should be developed for patient care, medical knowledge, practice-based learning, professionalism, systems-based practice, and interpersonal and communication skills. Clinical rotations in pediatric endocrinology for internal medicine endocrinologists, reproductive endocrinologists, behavioral health professionals, and other subspecialists during fellowship will increase the exposure of these trainees to children and families with CAH. Faculty mentoring, evaluations, and constructive feedback are essential. In today's world, intermittent and recurring conflicts between academic achievement (productivity) and family life are almost inevitable. Thus, training should also involve teaching trainees how to balance professional duties with commitments to partners, children, and other family members. For the trainee, having role models and mentors can guide and help them to acquire the skills for professional and personal success.

To demonstrate competency in these areas, trainees should analyze past and current clinical management, review the current scientific literature, apply knowledge of study design and statistical analysis, and appropriately utilize information technology. Trainees should demonstrate a commitment to ethical principles pertaining to clinical care. Trainees must respect the confidentiality of patient information, understand the elements of informed consent, approach to human (clinical) research, and have current knowledge regarding business/insurance practices. Improving communication and leadership skills and training in newer technology, such as the Electronic Medical Record, should facilitate interaction and advocacy for patients and their families. Respect, compassion, integrity, sensitivity to cultural diversity, and knowledge of the healthcare systems are essential. Tracking outcomes of training will be essential for quality improvement of the educational process.

In addition to the intellectual aspects of medical knowledge, proficiency in the appropriate technical skills and informed decision-making abilities are important for the adept healthcare professional. Having a child with a chronic disorder, especially one affecting genital differentiation, has the potential to generate much emotional distress and can result in misunderstanding and miscommunication among family members [41]. This uneasiness may impact negatively on intrafamilial interactions and on relationships with healthcare professionals. Healthcare professionals need to be comfortable talking with patients and families about CAH and need to be prepared to discuss concerns related to gender identity and sexual function. Skillful interaction with the parents can be important to help them adapt to the demands of having a child with a chronic disorder. Through observation and supervised interactions, healthcare trainees should become proficient in the skills to interact with people from different cultural, ethnic, and socioeconomic backgrounds. Trainees should learn how to educate the patient and family members using age-appropriate language and information. Knowledge of family-centered strategies for clinical care and communication will be beneficial.

Each CCC should maintain regularly scheduled conferences. Conferences should include case discussions involving all relevant members of the care team, topic reviews, and research updates, as well as didactic lectures for trainees and consumers (Table 4). Interdepartmental meetings that focus on the needs of the adult and transitioning patients are encouraged and should improve adult care. More frequent

Table 4: Potential curriculum and lecture topics.

(i) Newborn screening.
(ii) Sexual differentiation.
(iii) Management of the newborn.
(iv) Treatment options and surgical management of the virilized female.
(v) Management considerations for different age groups.
(vi) Information for school and sports.
(vii) Treatment of acute adrenal insufficiency including information for emergency medical services (EMS).
(viii) Reproductive issues and concerns.
(ix) Transition to internal medicine care providers.
(x) Preconception counseling and prenatal diagnosis.
(xi) Diagnosis and molecular genetics of CAH.
(xii) Pharmacology of hormone replacement (glucocorticoids and mineralocorticoid).
(xiii) Coordination of care—working as a team.
(xiv) Adrenal physiology and pathophysiology
(xv) Steroid biosynthesis

meetings or ad hoc meetings may be appropriate for some centers or be necessary to discuss specific clinical situations. The CCC is encouraged to offer education in CAH, either with the distribution of literature or delivery of lectures, such as grand rounds, at community hospitals. Conferences for patients and families are encouraged.

7.2. Research and Registry. CCCs should participate in coordinated, multicenter, and multidisciplinary studies designed to evaluate quality of life throughout the life cycle. These studies should foster better understanding of the disorder within and beyond the CCC, which should improve care and informed decision making for affected individuals and their families. A nationwide patient registry contributed to and/or maintained by CCCs will facilitate accumulation of data with adequate statistical power to discriminate among outcomes for affected individuals and their families. By publishing such research, the CCCs can educate their colleagues, affected people, the medical community at large, and the general public. Benefits of research via a registry should lead to teams of interdisciplinary experts to investigate research topics such as improved therapeutic options, optimizing transitions, and evaluation regarding comorbid conditions (obesity, insulin resistance, and osteoporosis). Outcome studies and interviews with adult patients should provide insight into the management of long-term psychosocial implications of CAH.

Disease or patient registries provide a valuable mechanism to track the health of individuals with specific rare disorders. Registries can capture, manage, and provide information to assist with the care of affected individuals by facilitating systematic research. Data contained within the registry must be secure and access to the data should be limited. The registry should have IRB approval as a longitudinal observational study. Consistency of the information contained within the registry will provide greater numbers of patients for analysis of outcome variables and other potential research areas. Registries currently exist for a number of disorders such as cystic fibrosis (http://www.cff.org/), rare autoinflammatory diseases (http://www.esid.org/), spinal muscular atrophy (http://smaregistry.iu.edu/), and cancer (http://www.cdc.gov/cancer/npcr/about.htm). This gathering of consistent and accurate information in one location is critical for patient care, research purposes, and, ultimately, for treatment. The effectiveness of patient education materials should be assessed. Research protocols should be publicized through a registry website. Health trends and pharmacological treatments should be reviewed and analyzed. Outcome data acquired through registries should be analyzed and used to improve both individual patient care and the healthcare delivery system [1].

Since state NBSs report all confirmed cases to the National Newborn Screening Information System (NNSIS), interconnectivity with this system would be beneficial. The recent expansion of NBS programs to provide long-term followup should provide an opportunity to develop registries for the life span of patients [42]. The US Secretary of Health and Human Services' Advisory Committee on Heritable Disorders in Newborns and Children has stated that long-term followup is beneficial for quality assurance, evidence-based care, care coordination through a medical home including transition to adult care services, and acquisition of new knowledge [40]. Consequently, CCCs should work with the Newborn Screening Translational Research Network (NBSTRN) to maximize information capture and analysis.

8. Implementation

In addition to the challenges discussed above, financial support for CCCs is a major hurdle to overcome. Potential mechanisms for financial support include third party reimbursement for services provided, research grants (NIH, private foundations, nonprofit organizations such as CARES, endocrine societies, and newborn screening agencies), and/or donations. Families may need to pay a fee based on their income. The goal of this 1.5 day meeting was discussion of the components necessary for the ideal CCC. The next phase will be the implementation of CCCs, which will include minimum criteria, accreditation, and review. An important first step will be developing mechanisms to finance the CCCs. These discussions will benefit from a separate conference, which includes participants knowledgeable regarding health care policy and reimbursement [43].

9. Conclusion

The essence of a CCC is patient-centered efficient coordination of care among multiple healthcare providers extending from diagnosis through all stages of growth and development. Personalized, family-centered, holistic, culturally sensitive, and effective care should create the foundation for a CCC for patients and families affected with CAH. Comprehensive care should consider the medical, emotional,

psychosocial, and financial needs of patients and their families throughout the life span. Internal medicine and pediatric physicians, nurses, behavioral/psychosocial health providers, nutritionists, genetic counselors, care coordinators, and others should collaborate as a team to create a comprehensive plan for patients with CAH. The individual, and his or her long-term health outcomes and quality of life, in addition to his or her clinical data, should be the central focus of the CAH CCC. Collaboration, cooperation, teamwork, clinical investigation, and training must be important components of a CCC.

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