# Congenital Adrenal Hyperplasia (CAH)

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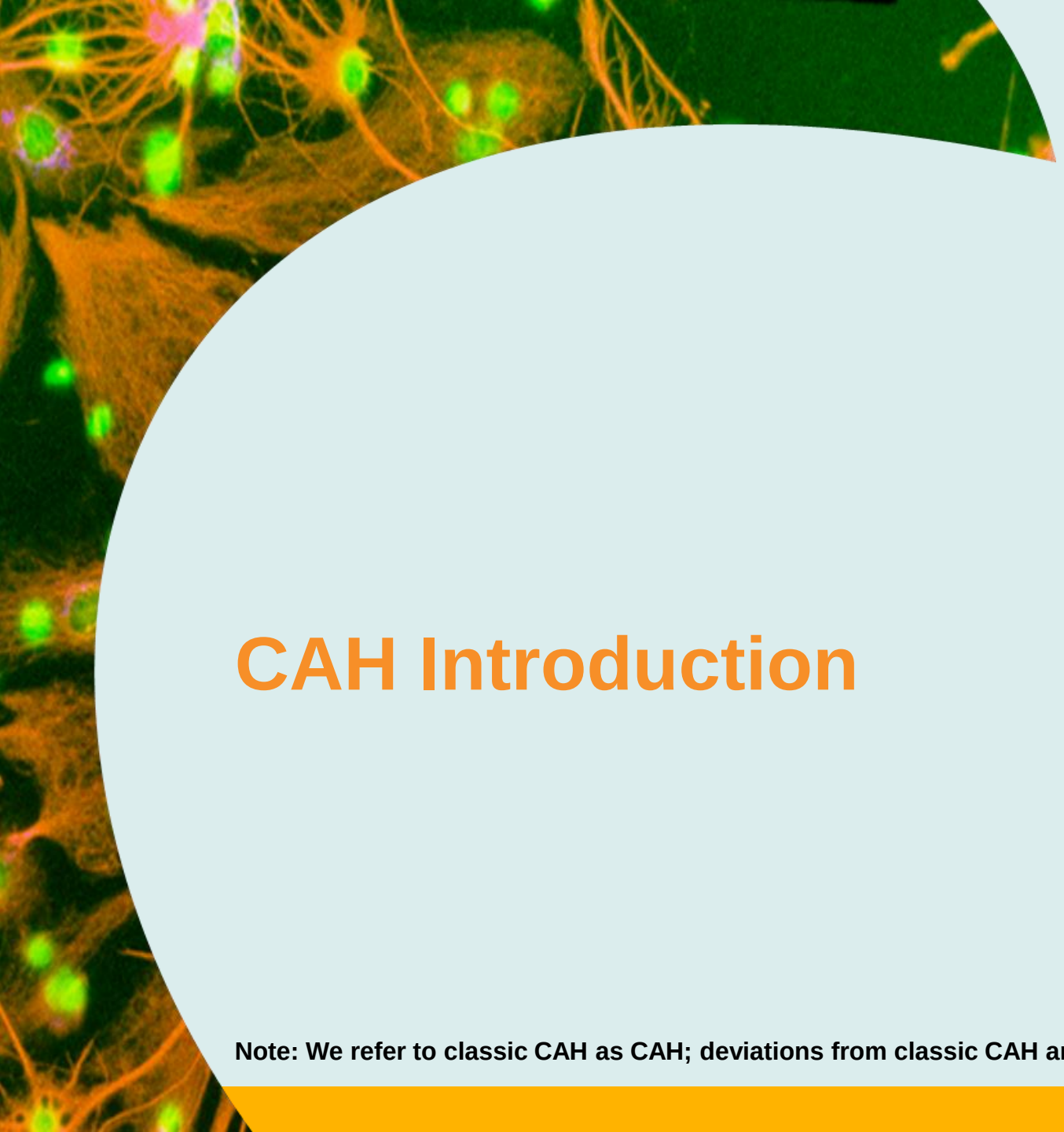
**Note: We refer to classic CAH as CAH; deviations from classic CAH are denoted by using specific terminology (e.g., non-classic CAH).**

MED-MSL-CAH-US-0004 v4

# CAH: Table of Contents



# CAH Introduction

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# Congenital Adrenal Hyperplasia

**CONGENITAL**

**Present at birth**

**ADRENAL**

**Glands synthesize and secrete multiple hormones**

**HYPERPLASIA**

**Organ enlargement, increase in cell number**

- **CAH is a rare autosomal recessive disorder that results in[1]:**
  - Deficiency in cortisol and often aldosterone, requiring corticosteroid replacement
  - Excessive production of ACTH, steroid precursors, and adrenal androgens
- **GC treatment at supraphysiologic doses are usually required for adrenal androgen reduction, which can cause complications[2]**

ACTH, adrenocorticotropic hormone; GC, glucocorticoid.

1. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088. 2. Mallappa A, et al. *Nat Rev Endocrinol*. 2022;18(6):337-352.

# Incidence of CAH

**~1:15,000 live births worldwide[1,2]**

**Alaska (Yup'ik indigenous populations): 1:288[2]**

**La Réunion: 1:4,111[2]**

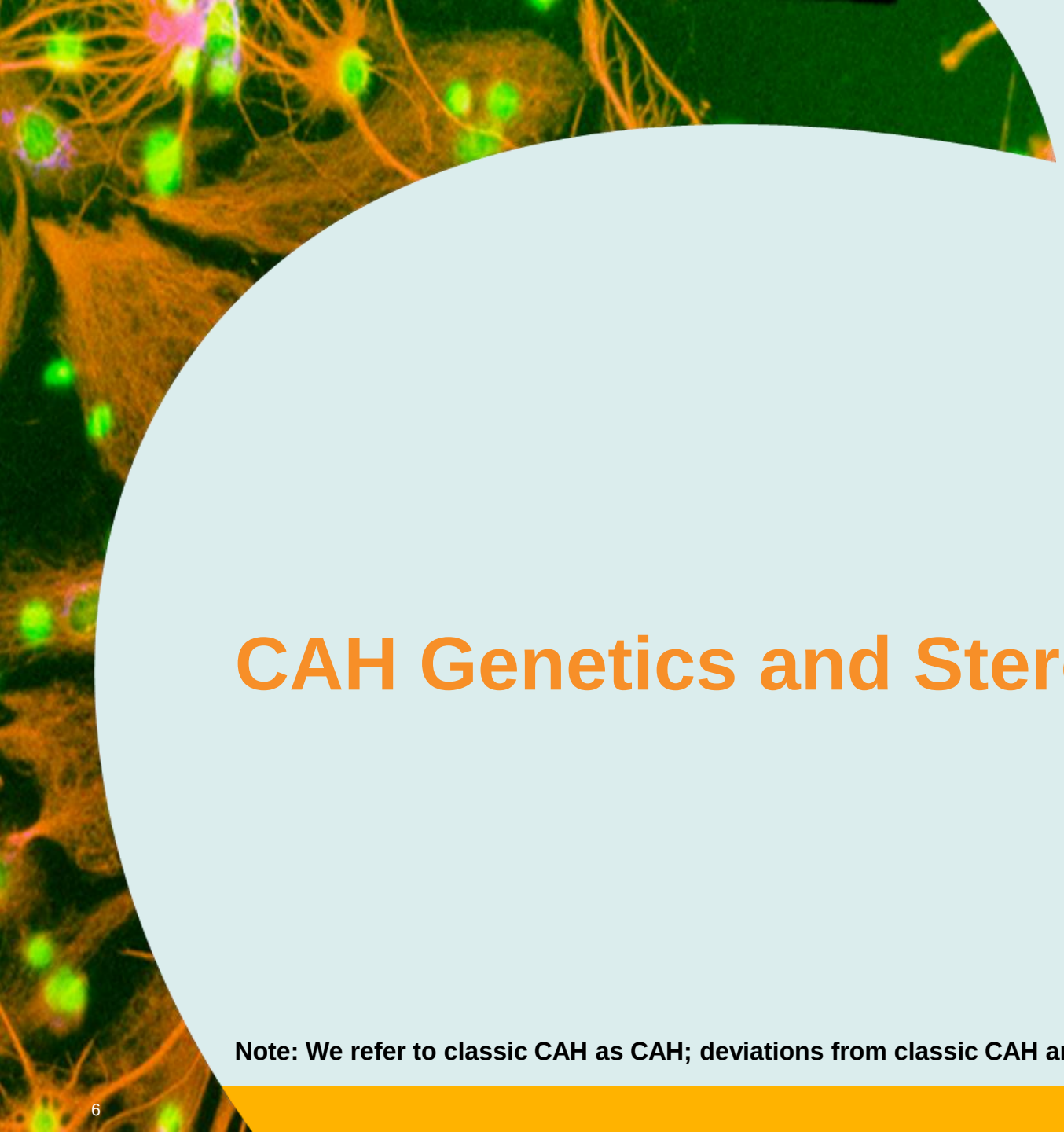
| Ethnicity or race | Incidence[3,a] |
|---|---|
| Hispanic or Latino | 1:15,109 |
| White | 1:15,731 |
| Black | 1:23,409 |
| Asian | 1:11,012 |

Click for incidence by country/region

**Globally, incidence is greater in populations that are geographically isolated, where the gene pool is smaller[1,2]**

[a]From a global systematic review and meta-analysis of studies with results from 31 countries.[1]
*CYP21A2,* steroid 21-hydroxylase or P450c21.

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. Pang S, et al. *Screening*. 1993;2(2-3):105-139. 3. Navarro-Zambrana AN, Sheets LR. *Horm Res Paediatr*. 2023;96(3):249-258.



# CAH Genetics and Steroidogenesis

**Note: We refer to classic CAH as CAH; deviations from classic CAH are denoted by using specific terminology (e.g., non-classic CAH).**

# Genetics of 21-OHD CAH[a]

**The *CYP21A2* gene provides instructions for making the enzyme, 21-hydroxylase[1,a]**

**10 common mutations** in the *CYP21A2* gene are responsible for >95% of all 21-OHD cases[1]

***CYP21A2* gene**

**Mutation in *CYP21A2***

**21-OHD CAH**

Disease severity correlates with enzyme impairment[1]

**Enzyme activity abolished**

**Some enzyme activity remains**

**Salt-wasting CAH[1,2]**

**Simple-virilizing CAH[1,2]**

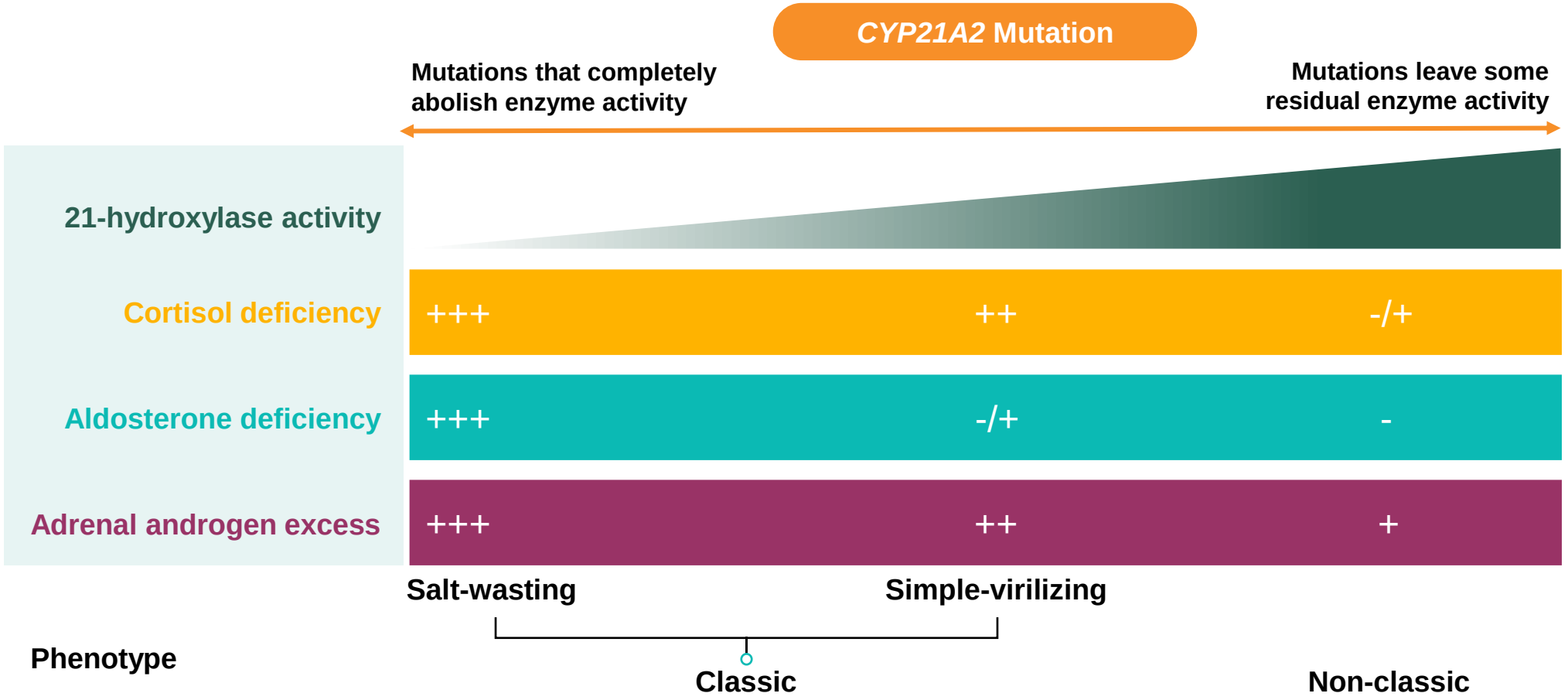
**Non-classic CAH[1,2]**

**21-OHD CAH is transmitted as an autosomal recessive disorder[3]**

[a]This schematic is a general summary and is not meant to represent all CAH patients with 21-OHD. Distinctions between CAH phenotypes are a continuum, and not absolute.
*CYP21A2*, steroid 21-hydroxylase or P450c21.

1. Nordenström A, et al. *Curr Opin Endocrinol Diabetes Obes*. 2021;28(3):318-324. 2. Speiser PW, et al. *J Clin Invest.* 1992;90(2):584-595. 3. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088.

# CAH Disease Spectrum Due to 21-OHD[1,2,a]

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21-OHD, 21-hydroxylase deficiency; *CYP21A2*, steroid 21-hydroxylase or P450c21.
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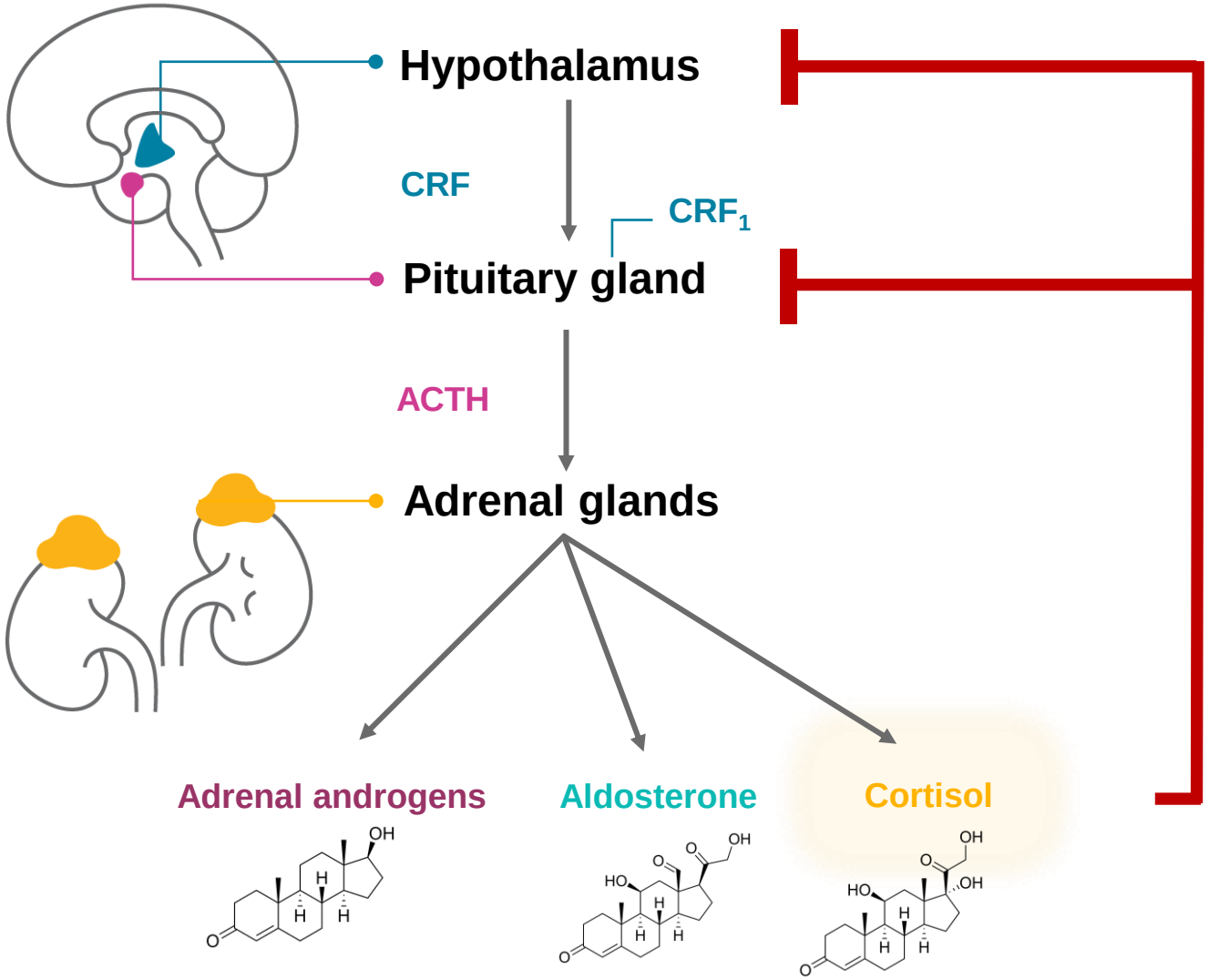
1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. Auer MK, et al. *Lancet*. 2023;401(10372):227-244.

# The Hypothalamic-Pituitary-Adrenal (HPA) Axis

- The adrenal glands normally produce several hormones (e.g., **cortisol, aldosterone, and adrenal androgens**) that are tightly regulated[1-3]
- Balance in the **HPA axis** relies on sufficient cortisol levels[1-3]:
  - Cortisol regulates hypothalamic and pituitary secretion of stimulatory hormones **CRF** and **ACTH** through **negative feedback**, decreasing their secretion when cortisol levels are sufficient
  - Conversely, cortisol deficiency leads to **increased CRF** and **ACTH** secretion

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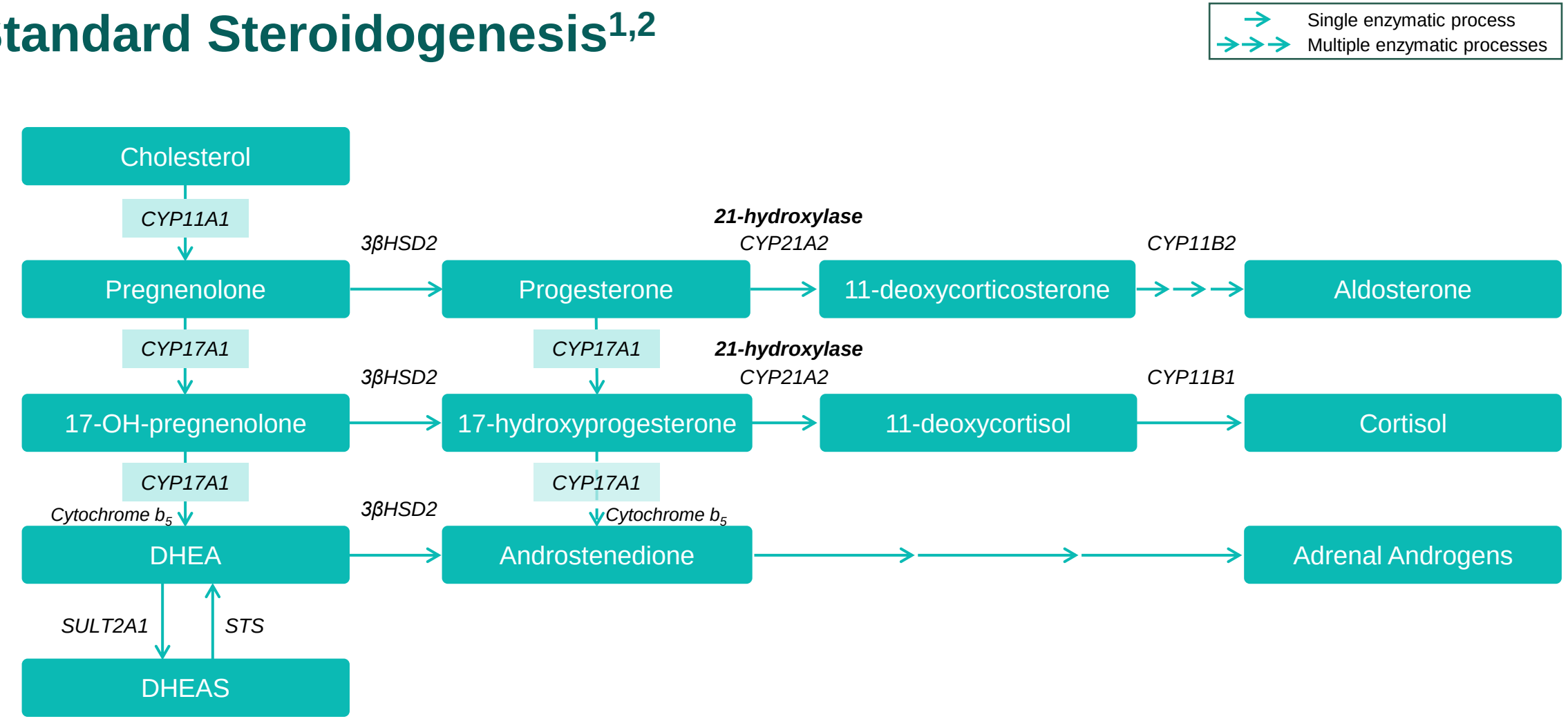
# Standard Steroidogenesis[1,2]




3βHSD2, 3β-hydroxysteroid dehydrogenase; CYP, cytochrome P450; CYP11A, cholesterol side chain cleavage enzymes; CYP17A1, steroid 17-hydroxylase/17,20-lyase; CYP21A2, steroid 21-hydroxylase or P450c21; CYP11B1, 11β-hydroxylase; CYP11B2, corticosterone 11/18β-hydroxylase; DHEA, dehydroepiandrosterone; DHEAS, dehydroepiandrosterone-sulfate; STS, steroid sulfatase; SULT, sulfotransferase.

1. Merke DP, Auchus RJ. *N Engl J Med*. 2020;383(13):1248-1261. 2. Auchus RJ, Wiebke A. *J Clin Endocrinol Metab*. 2013;98(7):2645-2655.

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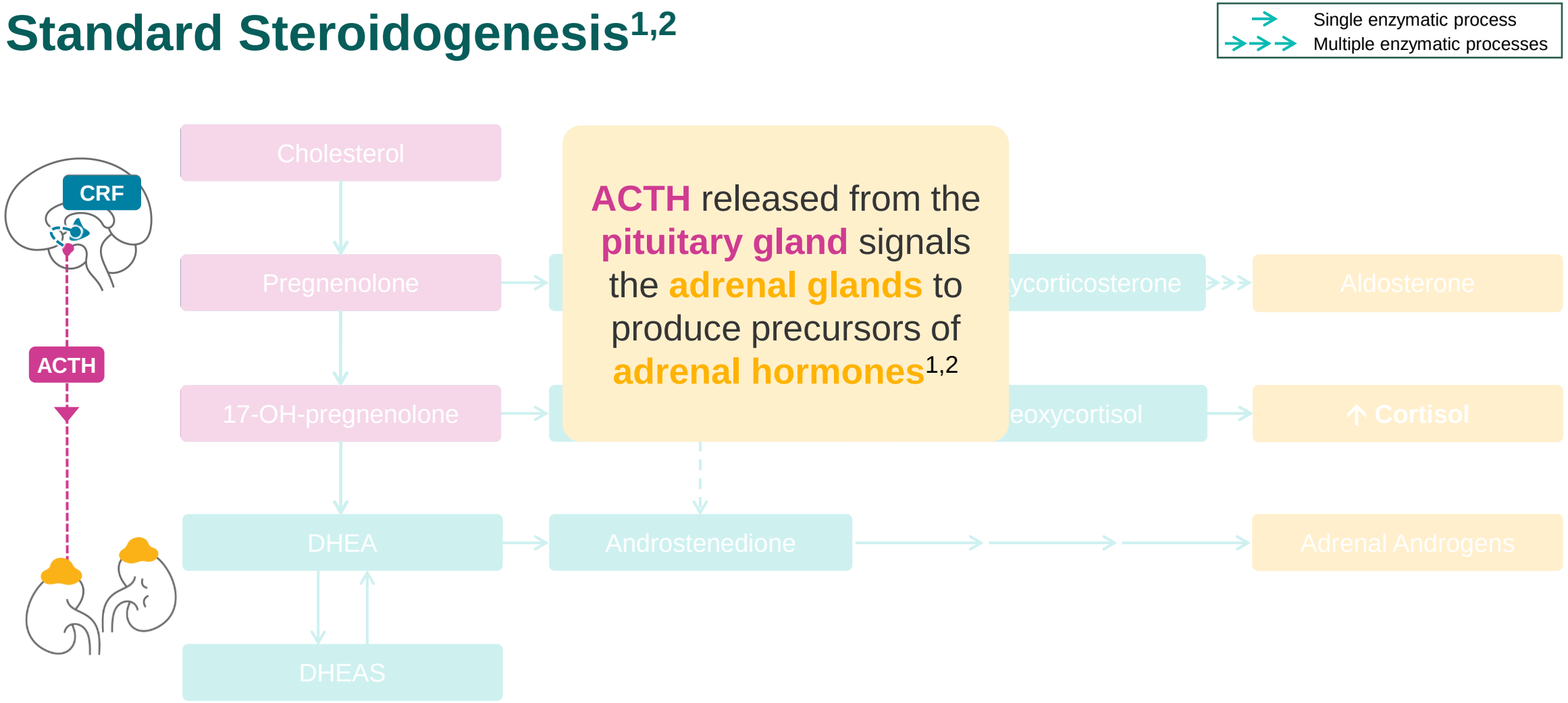


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# Standard Steroidogenesis[1,2]

→ Single enzymatic process
→→→ Multiple enzymatic processes

Cholesterol

Pregnenolone

17-OH-pregnenolone

DHEA

DHEAS

Hormone precursors undergo biosynthesis, forming intermediate products and, subsequently, adrenal hormones: **aldosterone, cortisol**, and **adrenal androgens**[1-3]

Aldosterone

↑ Cortisol

Adrenal Androgens

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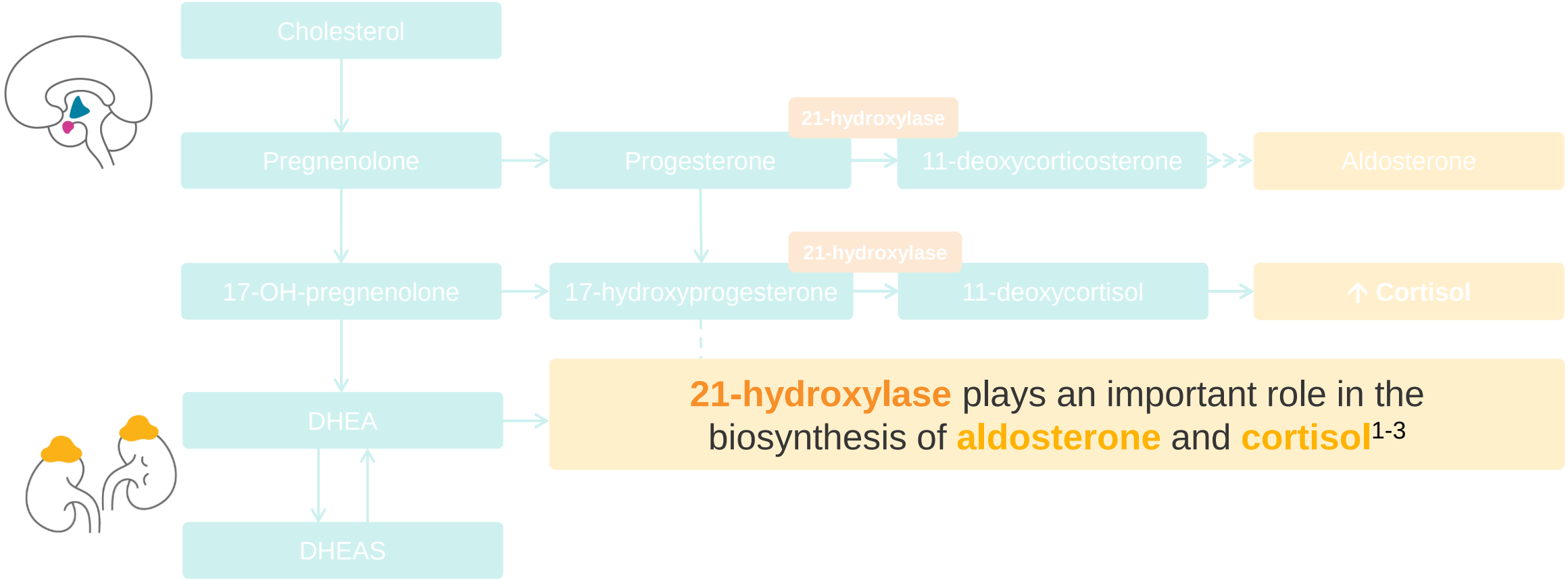


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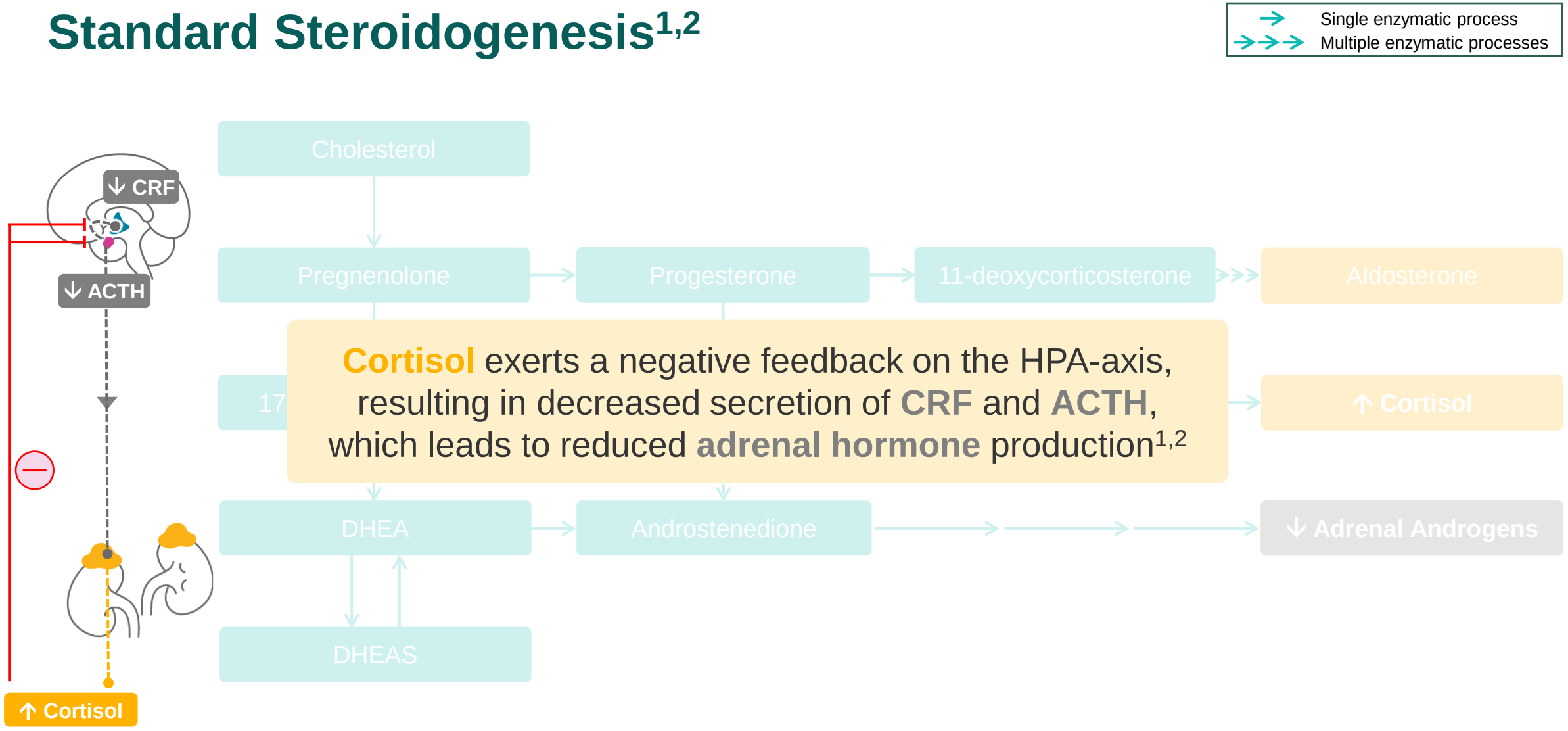


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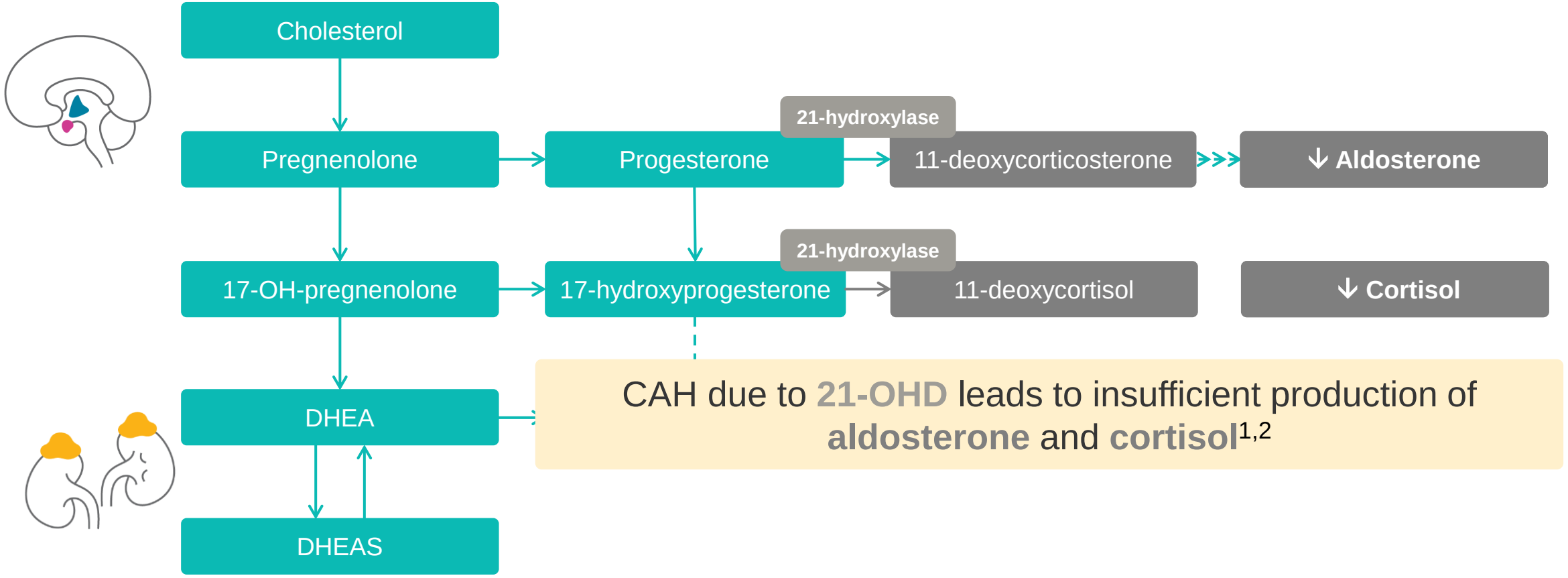


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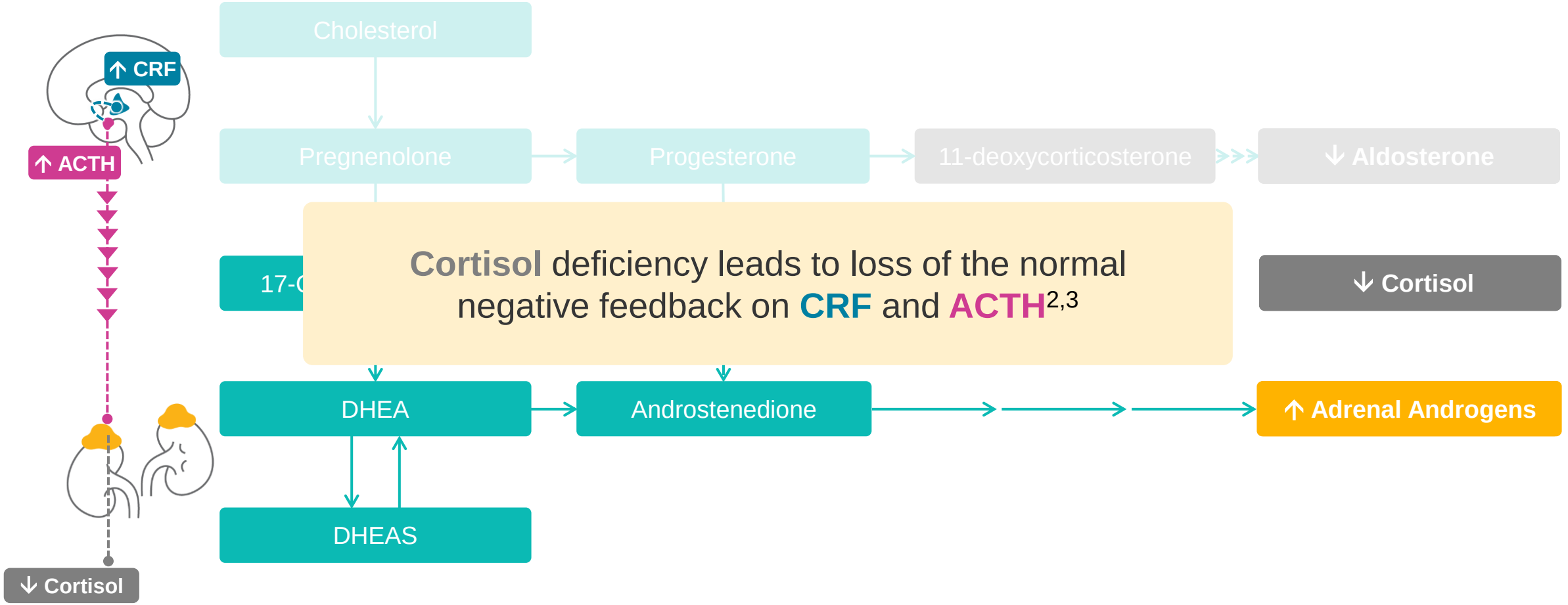


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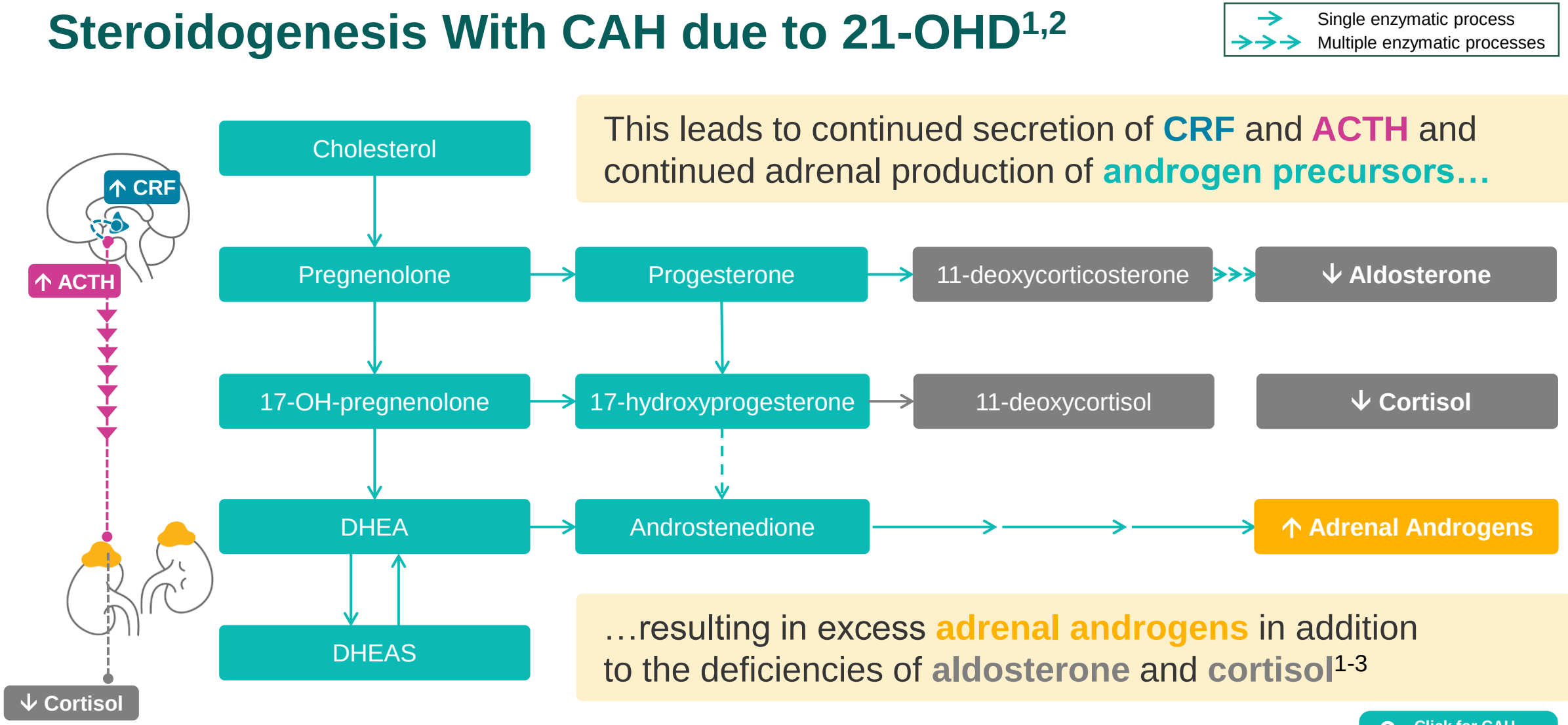


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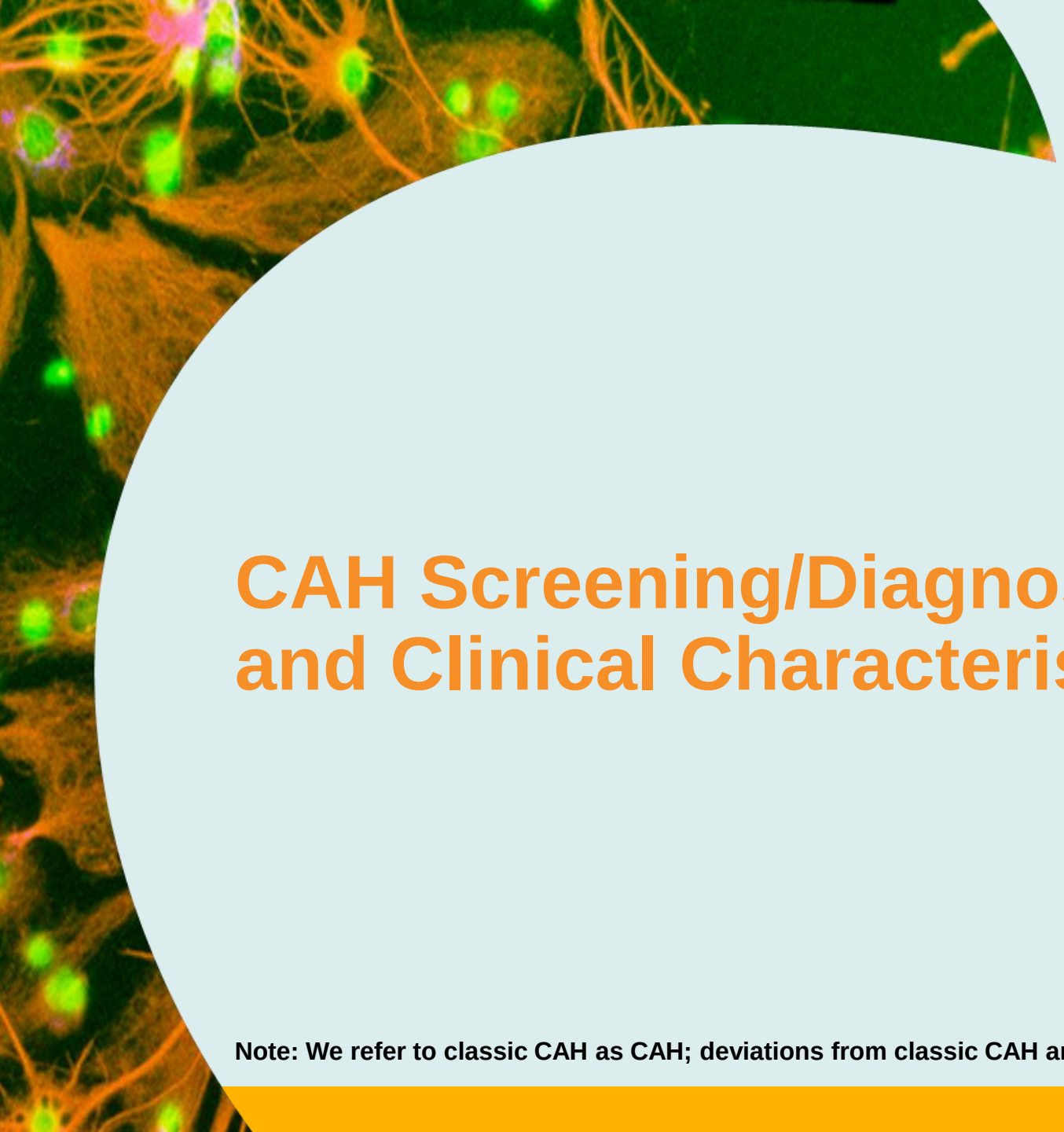


# CAH Screening/Diagnosis and Clinical Characteristics

**Note: We refer to classic CAH as CAH; deviations from classic CAH are denoted by using specific terminology (e.g., non-classic CAH).**

# CAH Screening and Diagnosis in Newborns

**2018 Endocrine Society Clinical Practice Guidelines** for CAH due to 21-OHD recommend that all newborn screening programs incorporate screening for 21-OHD CAH[1]

- Newborn screening is universal in the United States and in many other developed countries[1-3]
  - CAH was added to the United States national guideline for newborn screening in 2005[4]
- Diagnosis of CAH due to 21-OHD is based on a 17-OHP level >1,000 ng/dL[3,a]
  - Most affected infants have levels well above 5,000 ng/dL[3]
- Cosyntropin stimulation test is used to confirm diagnosis[1]
- Newborn CAH diagnosis practices vary in screening methods, equipment, 17-OHP cutoff levels, second-tier screening use, and follow-up procedures[1,4]

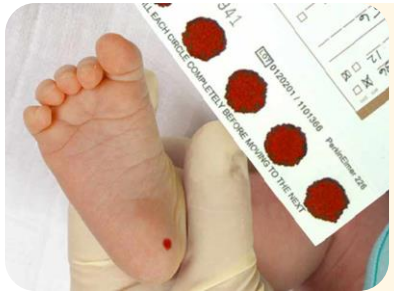
**Click for additional information on newborn screening**

[a]Reference range is <630 ng/dL (for term non-CAH infants 0-28 days after birth).[5]
17-OHP, 17-hydroxyprogesterone; 21-OHD, 21-hydroxylase deficiency.

1. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088. 2. Claahsen-van der Grinten HL, et al. *Endocr Rev*. 2022;43(1):91-159. 3. Merke DP, Auchus RJ. *N Engl J Med*. 2020;383(13):1248-1261.
4. Edelman S, et al. *Int J Neonatal Screen*. 2020;6(3):64. 5. Mayo Clinic Laboratories. 17-Hydroxyprogesterone, Serum. Mayo Foundation for Medical Education and Research. 2024. Accessed July 17, 2024. https://www.mayocliniclabs.com/test-catalog/overview/9231#Clinical-and-Interpretive.

# CAH Screening and Diagnosis in Newborns

**Endocrine Society guideline recommended newborn screening method[1]:**



## 1st Tier Screening:

Blood test from a heel prick after birth to detect elevated 17-OHP levels

## 2nd Tier Screening:

Improves the positive predictive value of 21-OHD CAH screening

In a retrospective cohort study involving 64 children with CAH, **approximately 20% of patients with CAH were missed** on newborn screenings, demonstrating the **importance of continuing to consider CAH to detect these patients** as early as possible[2]

**Prenatal diagnosis can be performed if both parents are carriers of *CYP21A2* mutations[3]**

17-OHP, 17-hydroxyprogesterone; 21-OHD, 21-hydroxylase deficiency; *CYP21A2*, steroid 21-hydroxylase or P450c21.

1. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088. 2. Saroufim R, et al. *Horm Res Paediatr*. 2023. doi: 10.1159/000535405. 3. Claahsen-van der Grinten HL, et al. *Endocr Rev*. 2022;43(1):91-159.

# Disease-related Clinical Characteristics of CAH

## Infancy

- Positive newborn screen[1]
- Atypical genitalia (females)[1]
- Salt-wasting adrenal crisis[1,a]:
  - Poor feeding
  - Weight loss
  - Dehydration
  - Low sodium
  - High potassium

## Childhood

- Increased growth velocity[1]
- Advanced bone age, premature epiphyseal fusion[2,3]
- Premature development of puberty[1,b]:
  - Presence of pubic hair before the ages of 8 years (females) and 9 years (males)
- Early-onset adult apocrine odor[1]
- Clitoromegaly (females)[1]

## Adolescence and adulthood

- Hirsutism[1]
- Acne[1]
- Short stature/height below genetic potential[1]
- Amenorrhea and oligomenorrhea
- Infertility or subfertility[1,4]
- Benign tumors
  - Testicular adrenal rest tumors (TARTs) in males[1]
  - Adrenal rest tumors in or near the ovaries (OARTs) in females[1]

**Patients with CAH are at risk for potentially life-threatening adrenal crises, throughout their lives[3]**

Click for adrenal crisis information

[a]Life-threatening clinical presentation that can occur within first 3 weeks of life if patients are not diagnosed and treated.[1]
[b]Central precocious puberty (with activation of the HPA–axis, which may be triggered by high adrenal androgen levels) can occur in some patients and exacerbate the issues with advanced skeletal maturation and premature epiphyseal fusion.[4]

1. Merke DP, Auchus RJ. *N Eng J Med*. 2020;383(13):1248-1261. 2. Reisch N. *Exp Clin Endocrinol Diabetes.* 2019;127(2-03):171-177.
3. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088. 4. Bonfig W. *Curr Opin Endocrinol Diabetes Obes*. 2017;24(1):39-42.

# CAH Treatment

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# GC Therapy Currently Has Dual Purpose in CAH

## CAH is characterized by[1]:

- Deficiency in cortisol and often aldosterone
- Excessive production of ACTH, corticosteroid precursors, and adrenal androgens

## Dual Role of GC Therapy[2]:

**GCs** are used to

**REPLACE** deficient endogenous cortisol

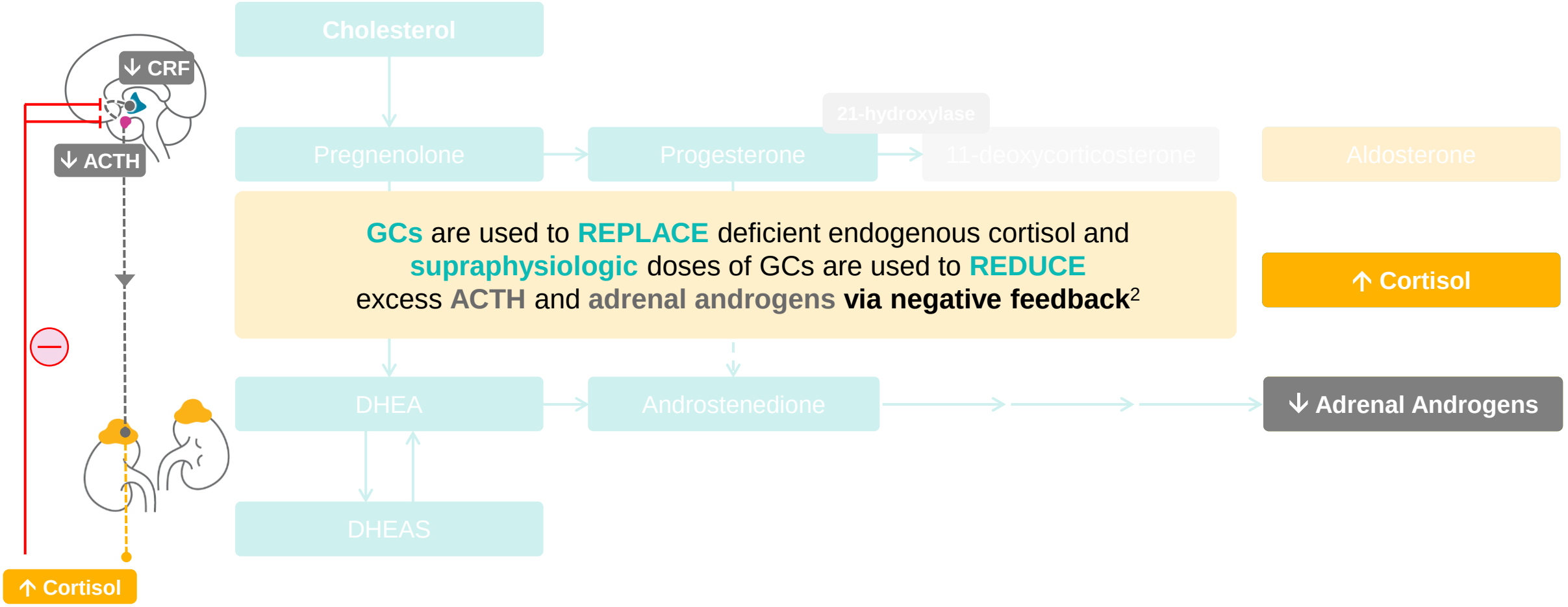
**REDUCE** excess ACTH and adrenal androgens by using **supraphysiologic** doses

**Mineralocorticoids** may also be used to help replace deficient hormones[1]

ACTH, adrenocorticotropic hormone; GC, glucocorticoid.

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. Mallappa A, Merke DP. *Nat Rev Endocrinol.* 2022;18(6):337-352.

# Supraphysiologic Doses of GCs Are Usually Needed for Adrenal Androgen Reduction in CAH

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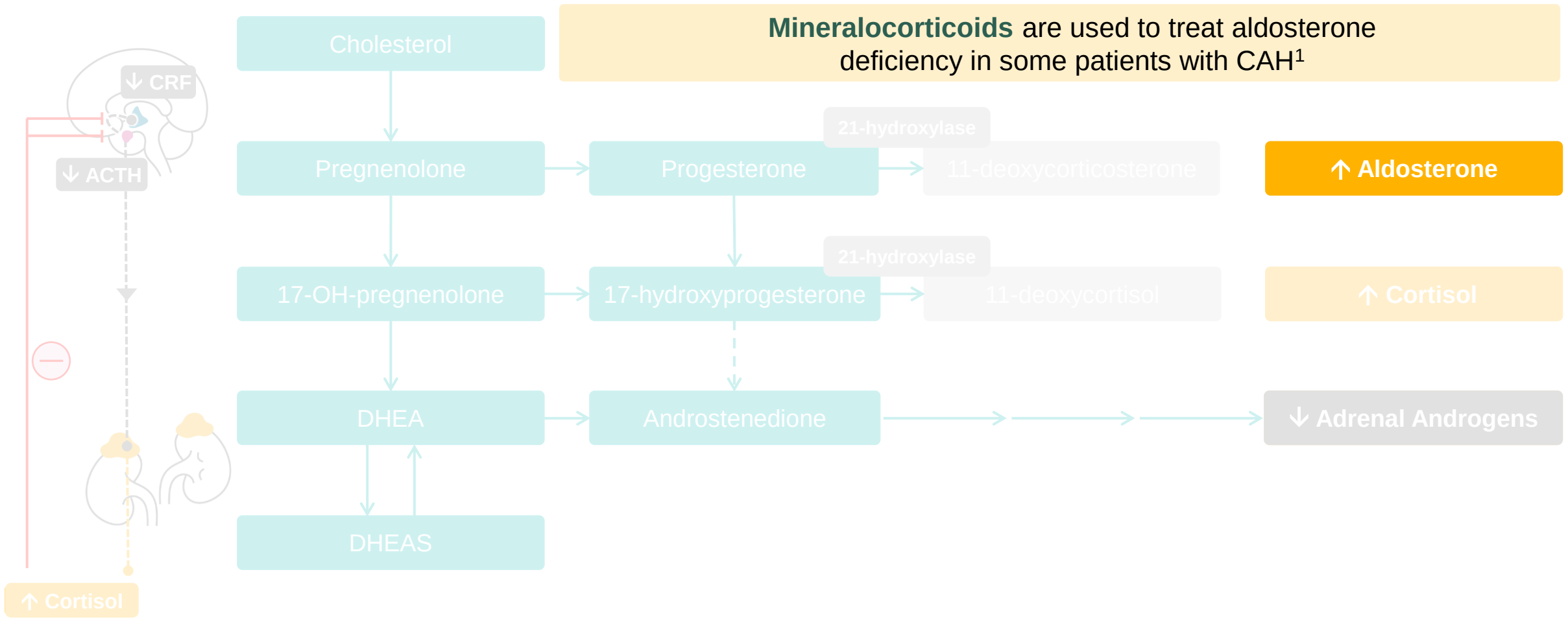
# Mineralocorticoids May Also be Used to Help Replace Deficient Hormones[1]

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# 2018 Endocrine Society Clinical Practice Guideline Treatment Recommendations for 21-OHD CAH[1]

| Growth Age | Recommended Treatment |
|---|---|
| **Newborn/early infancy** | • Hydrocortisone + fludrocortisone and sodium chloride supplements |
| **Growing individuals** | • Hydrocortisone + fludrocortisone as clinically indicated<br>  • Hydrocortisone oral suspension is generally not recommended (inconsistent formulation) & chronic use of long-acting potent GCs are generally avoided |
| **Adults** | • Hydrocortisone and/or long-acting GCs + fludrocortisone as clinically indicated |
| **All individuals** | • Monitoring for signs of GC excess, as well as for signs of inadequate adrenal androgen normalization, to optimize the adrenal steroid treatment profile<br>• Monitoring for signs of mineralocorticoid deficiency or excess |

Click for Monitoring Recommendation

21-OHD, 21-hydroxylase deficiency; GC, glucocorticoid.

1. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088.

# CAH Treatment

**CAH management varies widely and often results in the challenging balance of[1-4]:**

- Supraphysiologic GC daily doses that may not align to physiologic circadian variation
- Poorly controlled adrenal androgens

- These doses and schedules from the Endocrine Society Guidelines are meant as examples and should not be construed as a restrictive menu of choices for the individual patient[5]

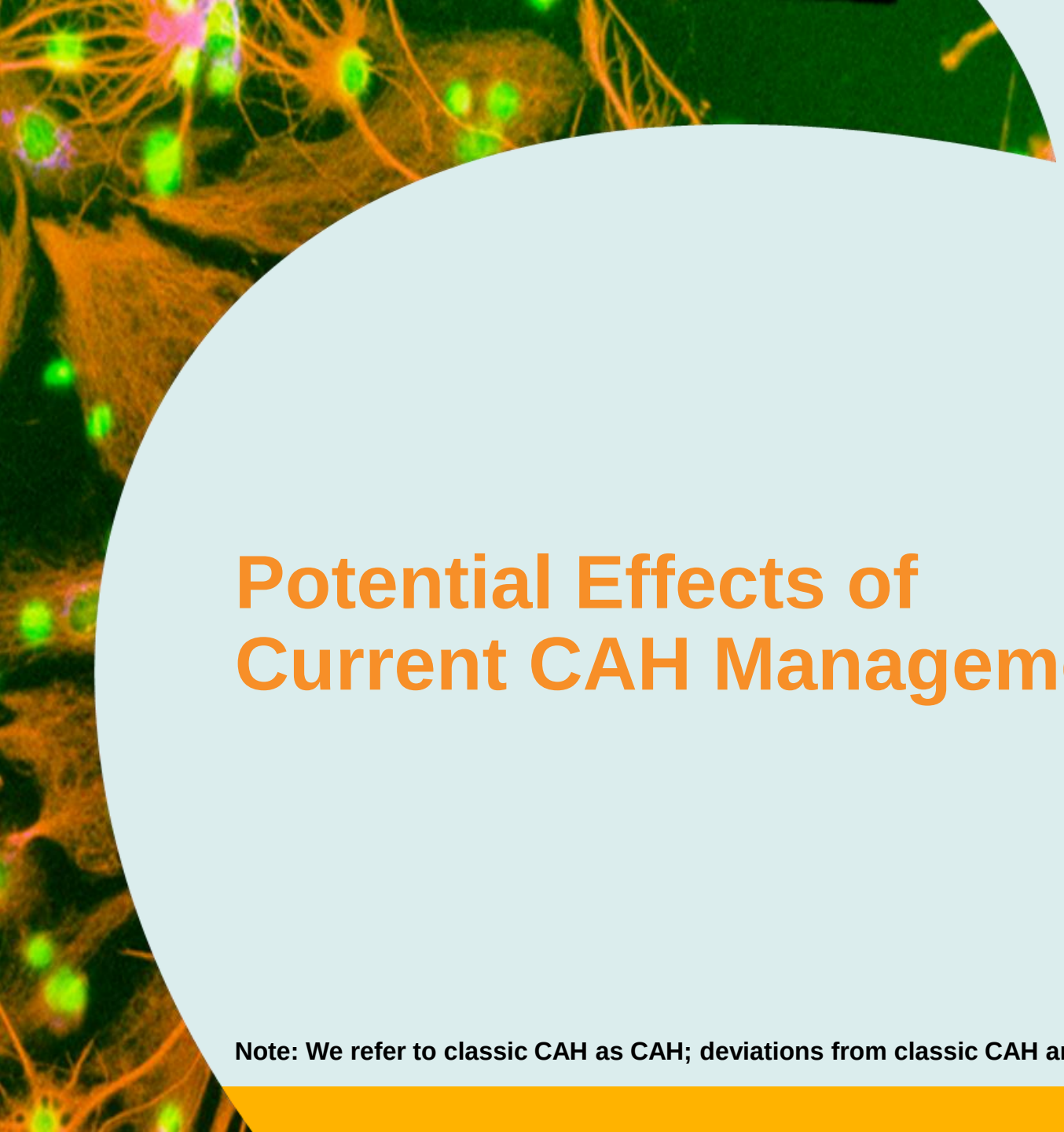
| | Growing | | Fully grown | |
|---|---|---|---|---|
| **Drugs** | **Total daily dose ranges** | **Daily dosing frequency** | **Total daily dose ranges (mg)** | **Daily dosing frequency** |
| Hydrocortisone | 10-15 mg/m$^2$ | 3 | 15-25 | 2-3 |
| Prednisone | – | – | 5-7.5 | 2 |
| Prednisolone | – | – | 4-6 | 2 |
| Methylprednisolone | – | – | 4-6 | 2 |
| Dexamethasone | – | – | 0.25-0.5 | 1 |
| Fludrocortisone | 0.05-0.2 mg | 1-2 | 0.05-0.2 | 1-2 |
| Sodium chloride supplements | 1-2 g (17-34 mEq) in infancy | Divided into several feedings | | |

Click for additional information on stress dosing

Click for Delphi study data

GC, glucocorticoid; mEq, milliequivalent.

1. Auchus RJ, et al. *Front Endocrinol (Lausanne).* 2022;13:1005963. 2. Finkielstain GP, et al. *J Clin Endocrinol Metab*. 2012;97(12):4429-4438. 3. Arlt W, et al. *J Clin Endocrinol Metab*. 2010;95(11):5110-5121.
4. Mallappa A, Merke DP. *Nat Rev Endocrinol.* 2022;18(6):337-352. 5. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088.

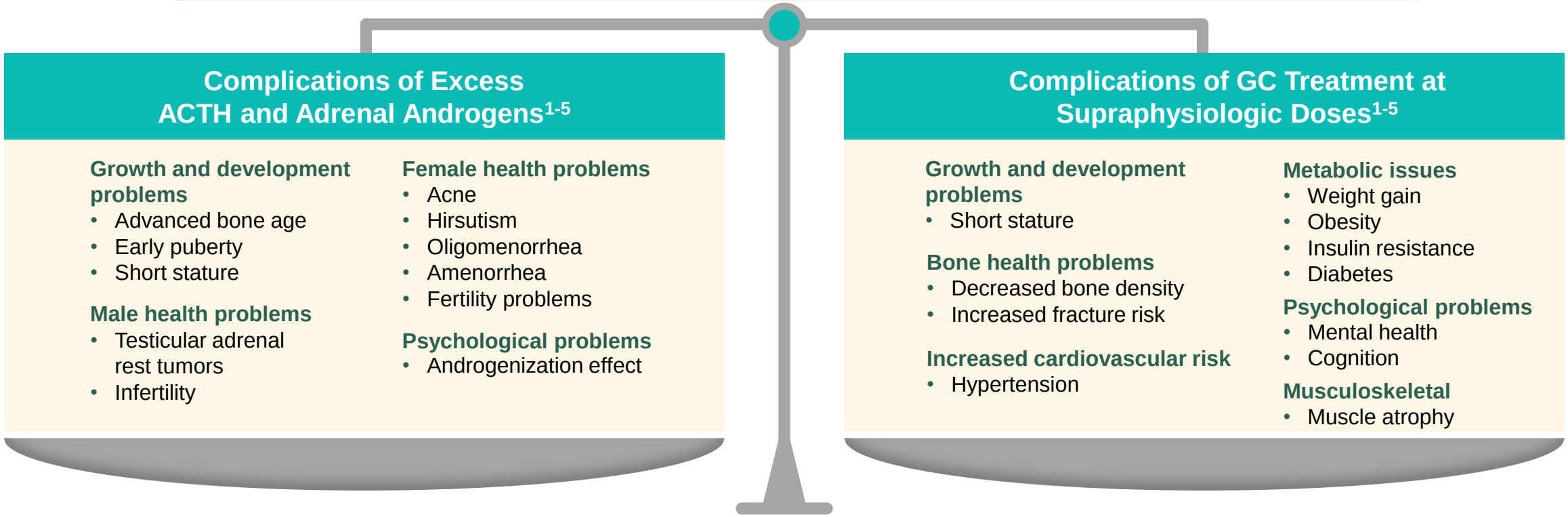


# Potential Effects of Current CAH Management

**Note: We refer to classic CAH as CAH; deviations from classic CAH are denoted by using specific terminology (e.g., non-classic CAH).**

# Current Management of CAH

**Supraphysiologic doses of GCs are usually needed for adrenal androgen reduction[1]**



## Complications of Excess ACTH and Adrenal Androgens[1-5]

**Growth and development problems**
- Advanced bone age
- Early puberty
- Short stature

**Male health problems**
- Testicular adrenal rest tumors
- Infertility

**Female health problems**
- Acne
- Hirsutism
- Oligomenorrhea
- Amenorrhea
- Fertility problems

**Psychological problems**
- Androgenization effect

## Complications of GC Treatment at Supraphysiologic Doses[1-5]

**Growth and development problems**
- Short stature

**Bone health problems**
- Decreased bone density
- Increased fracture risk

**Increased cardiovascular risk**
- Hypertension

**Metabolic issues**
- Weight gain
- Obesity
- Insulin resistance
- Diabetes

**Psychological problems**
- Mental health
- Cognition

**Musculoskeletal**
- Muscle atrophy

**Adequate adrenal androgen reduction should be balanced against the risks of chronic supraphysiologic GC exposure[2]**

ACTH, adrenocorticotropic hormone; GC, glucocorticoid.

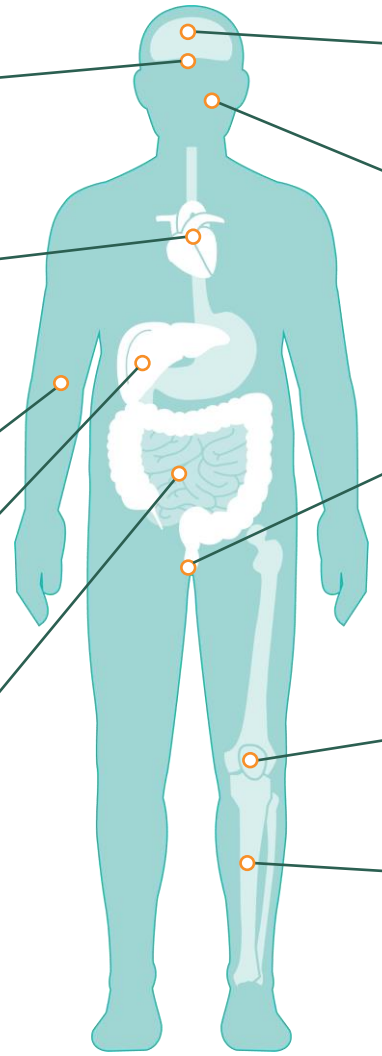
1. Mallappa A, Merke DP. *Nat Rev Endocrinol.* 2022;18(6):337-352. 2. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 3. Finkielstain GP, et al. *J Clin Endocrinol Metab*. 2012;97(12):4429-4438. 4. Arlt W, et al. *J Clin Endocrinol Metab*. 2010;95(11):5110-5121. 5. Merke DP, Auchus RJ. *N Engl J Med*. 2020;383(13):1248-1261.

# Clinical Consequences in CAH[1,2]

Disease related

GC treatment related

Combination



## Hypothalamic-pituitary

- Early puberty
- Secondary gonadal failure

## Cardiovascular risk factors

- Increased blood pressure

Click to learn more about cardiovascular risk

## Glucose metabolism

- Insulin resistance

## Adrenal

- Nodular hyperplasia and tumors
- Deficiency in cortisol and often aldosterone
- Adrenal androgen excess
- Adrenal myelolipomas

## Adipose tissue

- Increased fat mass

## Brain

- Androgenization effects
- GC effects
- Decreased quality of life
- Increased anxiety and depression

## Skin

- Hyperpigmentation
- Acne
- Hirsutism (females)
- Striae, thinning, bruising

## Reproductive

- Gonadal hypofunction
- Fertility problems
- Adrenal rest tumor formation
- **Females:** Atypical genitalia, clitoromegaly, menstrual irregularities

Click to learn more about reproductive complications

## Musculoskeletal

- Myopathy

## Bone

- Accelerated childhood growth, early epiphyseal fusion
- Decreased bone density
- Osteoporosis
- Fractures
- Adult short stature

Click to learn more about height below genetic potential

GC, glucocorticoid.

Figure adapted from Merke DP, Auchus RJ. *N Engl J Med*. 2020;383(13):1248-1261.

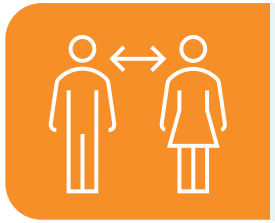
1. Merke DP, Auchus RJ. *N Engl J Med*. 2020;383(13):1248-1261. 2. Pofi R, et al. *Clin Endocrinol (Oxf)*. 2023. doi: 10.1111/cen.14967.

# Humanistic Impact of CAH

The difficulty with **balancing GC doses** to manage both cortisol insufficiency and adrenal androgen excess can lead to **decreased quality of life** for patients and their caregivers[1-3]

The risk of **life-threatening adrenal crisis** is a concern in patients with CAH through infancy, childhood, and adulthood[4]

Short stature or adult **height below genetic potential** may negatively impact patients with CAH[5,6]



Patients with CAH may experience **sex-specific issues** regarding body image, sexuality, and decreased fertility[5,7-9]

GC, glucocorticoid.

1. Gilban DLS, et al. *Health Qual Life Outcomes*. 2014;12:107. 2. Vijayan R, et al. *J Pediatr Endocrinol Metab.* 2019;32(8):871-877. 3. Yau M, et al. *Horm Res Paediatr.* 2015;84(3):165-171. 4. Falhammar H, et al. *J Clin Endocrinol Metab*. 2014;99(12):E2715-21 5. Arlt W, et al. *J Clin Endocrinol Metab*. 2010;95(11):5110-5121. 6. Backeljauw P, et al. *Growth Horm IGF Res*. 2021;57-58:101392. 7. Tschaidse L, et al. *J Clin Med*. 2022;11(15):4506. 8. Dudzińska B, et al. *Int J Endocrinol*. 2014;2014:469289. 9. Engels M, et al. *Endocr Rev*. 2019;40(4):973-987.

# CAH Summary

**Note: We refer to classic CAH as CAH; deviations from classic CAH are denoted by using specific terminology (e.g., non-classic CAH).**

# CAH Summary

**Rare genetic disorder affecting ~1:15,000 live births worldwide[1,2]**

**Dynamic disorder of adrenal insufficiency and adrenal androgen excess[1]**

**Complex symptoms affect multiple organ systems[1,3]**

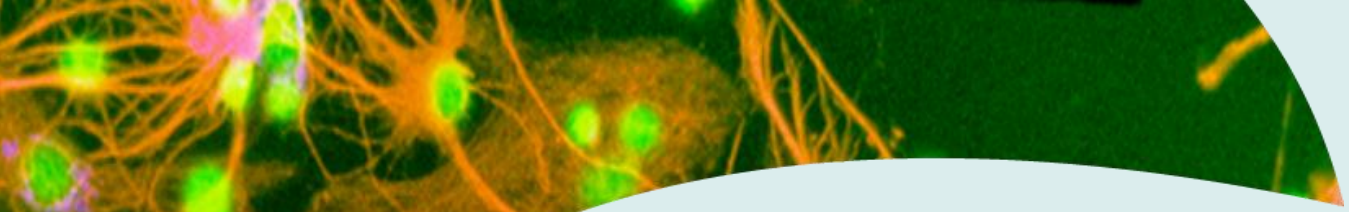
- Salt-wasting adrenal crisis, virilization in females, abnormalities in growth leading to short stature, early puberty, and infertility

**Supraphysiologic doses of GCs are usually needed for adrenal androgen reduction[4]**

**Patients may experience complications due to chronic supraphysiologic doses of GCs[5,6]**

GC, glucocorticoid.

1. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088. 2. Pang S, et al. *Screening.*1993;2(2):105-139. 3. Merke DP, Auchus RJ. *N Eng J Med*. 2020;383(13):1248-1261. 4. Mallappa A, et al. *Nat Rev Endocrinol*. 2022;18(6):337-352. 5. Finkielstain GP, et al. *J Clin Endocrinol Metab*. 2012;97(12):4429-4438. 6. Arlt W, et al. *J Clin Endocrinol Metab*. 2010;95(11):5110-5121.



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**Note: We refer to classic CAH as CAH; deviations from classic CAH are denoted by using specific terminology (e.g., non-classic CAH).**

# Appendix

**Note: We refer to classic CAH as CAH; deviations from classic CAH are denoted by using specific terminology (e.g., non-classic CAH).**

# Incidence of CAH by Country/Region From Literature

| Country or region | Incidence | Country or region | Incidence | Country or region | Incidence |
|---|---|---|---|---|---|
| Alaska (Yup'ik)[1] | 1:288 | Croatia[2] | 1:14,403 | La Réunion[1] | 1:4,111 |
| Argentina (Buenos Aires)[2] | 1:8,937 | Cuba[2] | 1:15,931 | Scotland[1] | 1:17,099 |
| Australia[2] | 1:18,034 | Czech Republic[2] | 1:11,848 | Spain[1] | 1:17,239 |
| Australia (New South Wales)[2] | 1:15,488 | France[2] | 1:15,699 | Sweden[2] | 1:14,260 |
| Australia (Western Australia)[2] | 1:14,869 | Germany (Bavaria)[2] | 1:12,457 | Switzerland[1] | 1:10,970 |
| Brazil[2] | 1:14,967 | India[2] | 1:6,334 | United Arab Emirates[2] | 1:9,030 |
| Brazil (Goiás state)[2] | 1:10,325 | Italy[1] | 1:11,100 | United Kingdom[2] | 1:18,248 |
| Brazil (Minas Gerais state)[2] | 1:19,927 | Japan[1] | 1:19,121 | United States[1] | 1:15,305 |
| Canada[1] | 1:16,666 | New Zealand[2] | 1:26,727 | Uruguay[2] | 1:15,800 |
| China[2] | 1:6,084 | Portugal[1] | 1:14,285 | Worldwide[1,2] | ~1:15,000 |

1. Pang S, et al. *Screening*.1993;2(2):105-139. 2. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088.

# Pathophysiology of CAH

- **CAH results from a deficiency in one of the enzymes involved in cortisol biosynthesis: 21-hydroxylase[1,2]**
  - Roughly 95% of all CAH cases are deficient in 21-hydroxylase
  - When 21-hydroxylase is impaired in the adrenal glands, 17-OHP is not converted to 11-deoxycortisol and ultimately cortisol is not produced
  - Aldosterone also is not produced in patients with salt-wasting CAH

- **Defective cortisol synthesis and loss of negative feedback[1,2]:**
  - ACTH levels increase
  - Adrenal androgen precursors (17-OHP) are overproduced and accumulate

- **The increase in 17-OHP causes excessive production of adrenal androgens (e.g., androstenedione and testosterone), resulting in virilization and other symptoms of adrenal androgen excess[1,2]**

17-OHP, 17-hydroxyprogesterone; ACTH, adrenocorticotropic hormone.

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. El-Maouche D, et al. *Lancet*, 2017;390(10108):2194-2210.

# Adrenal Crisis Definition

## There is no universally accepted definition of Adrenal Crisis[1]

| Source | Definition of adrenal crisis according to literature |
|---|---|
| **Allolio B. 2015 review**[2] | **(A):** Major impairment of general health **with ≥2** of the following signs/symptoms<br>• Hypotension (systolic blood pressure <100 mmHg)<br>• Nausea or vomiting<br>• Severe fatigue<br>• Fever<br>• Somnolence<br>• Hyponatremia (≤132 mmol/L) or hyperkalemia<br>• Hypoglycemia<br>**(B):** Parenteral GC (hydrocortisone) administration followed by clinical improvement |
| **Rushworth RL, et al. 2019 review**[1] | Adrenal crisis is defined as an **acute deterioration** in health status **associated with hypotension (absolute or relative)**<br>• Features that resolve within 1 to 2 hours after parenteral GC administration<br>**In infants and young children, hypotension can be more difficult to identify than in adults:**<br>• An acute hemodynamic disturbance, a marked abnormality in ≥1 electrolytes, or hypoglycemia not attributable to another illness can be used for identification |
| **Kienitz T, et al. 2023 Delphi study**[3] | Adrenal crisis must be considered if **≥1 type A criterion** and **≥2 type B criteria** can be applied:<br>**Type A criteria:**<br>• History of adrenal insufficiency or previous GC therapy for other diseases<br>• Hyponatremia ≤132 mmol/L<br>• Hyperkalemia<br>**Type B criteria:**<br>• Severe weakness or fatigue<br>• Impaired consciousness<br>• Nausea and/or vomiting<br>• Fever<br>• Hypotension with systolic blood pressure ≤100 mmHg |

GC, glucocorticoid.

1. Rushworth RL, et al. *N Engl J Med*. 2019;381(9):852-861. 2. Allolio B. *Eur J Endocrinol*. 2015;172(3):R115-R1243. 3. Kienitz T, et al. *Horm Metab Res*. 2023. doi: 10.1055/a-2130-1938.

# Adrenal Crisis: a Life-threatening Condition

**Newborns with CAH are at increased risk of developing a salt-wasting adrenal crisis,**
particularly in regions that do not require newborn screening for CAH[1,2]

- In untreated newborns with salt-wasting disease, a **salt-wasting adrenal crisis** may develop **within the first 3 weeks after birth** and can be **life-threatening** if not treated[1,2]

**Despite the reduction in infant mortality as a result of newborn screening for CAH,**
**patients of all ages are at risk of death from adrenal crises[2,3]**

In a Swedish study, **42%** of all deaths among patients with CAH were due to adrenal crisis[4]

In a retrospective German study of adults with CAH, the causes of the 257 salt-wasting adrenal crises recorded during the study included[3]:

- General infections with fever **(29%)**
- GI infections **(17%)**
- Surgical procedures **(14%)**
- Patient not taking any medication **(4%)**
- Medical noncompliance **(3%)**

**Age-related**
Respiratory infections predominate in early childhood, shifting to GI infections in older age groups[5]

Patients most at risk for compliance-related adrenal crises are[6,7]:

- **Young adults newly in charge** of their own treatment regimens
- **Adolescents transitioning care** from a pediatrician to a primary care physician

**Adhering to GC replacement therapy** is crucial to prevent adrenal crisis; patients must grasp the risks of dose omission or cessation[8]

GC, glucocorticoid; GI, gastrointestinal.

1. Merke DP, Auchus RJ. *N Engl J Med*. 2020;383(13):1248-1261. 2. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088. 3. Reisch N, et al. *Eur J Endocrinol.* 2012;167(1):35-42. 4. Falhammar H, et al. *J Clin Endocrinol Metab*. 2014;99(12):E2715-21. 5. Lousada LM, et al. *Arch Endocrinol Metab*. 2021;65(4):488-494. 6. Merke DP, Poppas DP. *Lancet Diabetes Endocrinol*. 2013;1(4):341-352. 7. Claahsen-van der Grinten HL, et al. *Horm Res Paediatr.* 2013;80(4):293-298. 8. Rushworth RL, et al. *N Engl J Med*. 2019;381(9):852-861.

# Treatment and Monitoring Recommendations for Patients With CAH

| 2018 Endocrine Society clinical practice guidelines for CAH | |
|---|---|
| **Growth age** | **Monitoring recommendations** |
| **Newborn/ early infancy** | • For patients aged ≤18 months, close monitoring during the first 3 months of life and every 3 months thereafter is recommended<br>• After 18 months, evaluation is recommended every 4 months |
| **Growing patients** | • Regular physical examinations; assessments of growth velocity, weight, and blood pressure; and biochemical measurements recommended to assess adequacy of GC/MC therapy<br>• For pediatric patients aged <2 years, annual bone age assessments are recommended until near-adult height is attained |
| **Adults** | • Annual physical examinations, including assessments of blood pressure, BMI, and Cushingoid features, as well as biochemical measurements are recommended<br>• Closely monitor treatment via consistently timed hormone measurements<br>• Complete suppression of endogenous adrenal steroid secretion is not recommended due to the potential for adverse effects |
| **All patients** | • Monitoring for signs of GC excess, as well as for signs of inadequate adrenal androgen reduction, to optimize the adrenal steroid treatment profile<br>• Monitoring for signs of MC deficiency or excess<br>• Clinicians should adjust doses in the context of the overall clinical picture and not solely based on a single laboratory measurement<br>• Complete suppression of serum 17-OHP levels is not a treatment goal but instead indicates overtreatment<br>  • Acceptably treated patients with CAH generally have upper normal to mildly elevated 17-OHP and androstenedione levels when measured in a consistent manner<br>• Guidelines do not provide specific target levels for adrenal steroid measurement because laboratory reference ranges and sample timing varies, and clinicians must consider the overall clinical picture |

17-OHP, 17-hydroxyprogesterone; BMI, body mass index; GC, glucocorticoid.

Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088.

# Endocrine Society Treatment Considerations for CAH

Patients with severe forms of 21-OHD are unable to produce sufficient cortisol in response to stress, such as febrile illness, gastroenteritis with dehydration, surgery, or trauma and, therefore, require stress dosing with increased GC doses beyond the daily dose during such episodes

## CAH Stress Dosing Suggestion[a]

| | Suggested Stress Doses of GC for Adrenal Crisis | |
|---|---|---|
| **Patient Age** | **Initial Parenteral HC Dose** | **Successive IV HC Dose** |
| Infants | 25 mg | ¼ of the initial parenteral HC dose every 6 hours |
| Preschool children | 25 mg | |
| School-age children | 50 mg | |
| Adults | 100 mg | |

[a]These doses and schedules from the Endocrine Society Guidelines are meant as examples and should not be construed as a restrictive menu of choices for the individual patient.
21-OHD, 21-hydroxylase deficiency; GC, glucocorticoid; HC, hydrocortisone; IV, intravenous; mEq, milliequivalent.
Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088.

# Newborn Screening (NBS)

Newborns with CAH, develop progressive salt-wasting crisis evident within the first 5 days of life[1]

Prior to NBS, CAH resulted in significant morbidity and mortality[1]

## History of NBS for CAH

**1977**

Research and advocacy by the March of Dimes led to NBS for CAH[2]

**1978**

NBS for 21-OHD was first initiated in Alaska[1]

**2005**

CAH was added to the United States national guideline for NBS[3]

**2009**

NBS for CAH became mandatory in all 50 states[1]

**2018**

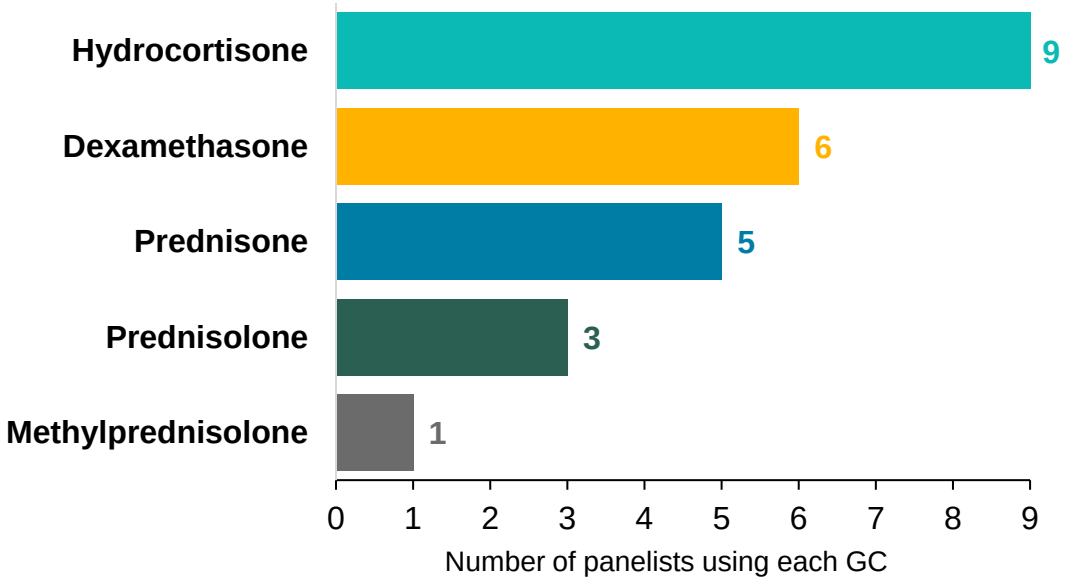
CAH screening endorsed by the Endocrine Society in clinical practice guidelines[1]

21-OHD, 21-hydroxylase deficiency; NBS, newborn screening.

1. Held P, et al. *Int J Neonatal Screen.* 2020;6(3)67. 2. McCabe E. *Newborn Screening: The Future Is Here*. https://www.aphl.org/conferences/proceedings/Documents/2014/NBS/04McCabe.pdf.
3. Edelman S, et al. *Int J Neonatal Screen*. 2020;6(3):64.

# GC Treatment Practices in CAH

- A modified Delphi consensus study that assessed GC treatment practices in adults with CAH among 9 CAH experts showed wide variations in GC treatment practices[1]:




| | Daily dose (mg/d), mean (SD) | Lower range, mean (SD) | Upper range, mean (SD) | Endocrine Society's recommended daily dose[2] (mg/d) |
|---|---|---|---|---|
| Hydrocortisone | 27.2 (3.6) | 14.2 (3.8) | 40.8 (10.2) | 15-25 |
| Dexamethasone | 0.6 (0.3) | 0.4 (0.1) | 1.5 (0.6) | 0.25-0.5 |
| Prednisone | 4.9 (1.5) | 3.8 (1.8) | 7.5 (1.8) | 5-7.5 |
| Prednisolone | 4.4 (0.9) | 3.3 (1.7) | 7.1 (2.2) | 4-6 |
| Methylprednisolone | 5.4 (1.3) | 3.8 (2.1) | 6.5 (1.9) | 4-6 |

**Among 9 clinicians with expertise in treating CAH, the average daily dose of hydrocortisone was 27.2 mg, with doses ranging from 14.2-40.8 mg[1]**

GC, glucocorticoid; SD, standard deviation.

1. Auchus RJ, et al. *Front Endocrinol (Lausanne).* 2022;13:1005963. 2. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088.

# Clinical Characteristics of CAH: Reproductive Complications

## Infertility: The result of multiple factors[1,2]

### Females:

- Anovulation due to adrenal androgen overproduction
- Effects of genital surgery
- Progesterone hypersecretion

### Males:

- TARTs due in part to excessive ACTH stimulation
- Primary hypogonadism: testicular failure resulting from TART formation
- Secondary hypogonadism: gonadotrophin suppression due to adrenal androgen excess
- There are currently no clear guidelines for initiating screening and monitoring for the development of TARTS[3]

## Complications of chronic ACTH stimulation: Ectopic adrenal cells[2]

### TARTs in males

- TARTs are benign tumors that develop in the testes of 30% to 50% of males with CAH and may lead to obstruction of seminiferous tubules, gonadal dysfunction, and infertility[2,3]
- Patients with poorly controlled disease have increased prevalence of TARTs[4]
- While elevated ACTH concentrations may play an important role in the development of TARTs, the etiology is not fully understood[5,6]
- It is hypothesized that TARTs originate from pluripotent progenitor cells, possibly from the adrenogonadal primordium or urogenital ridge, that proliferate with ACTH exposure[5,6]

### OARTs in females[3,4,7,8]

- Likely less frequent than TARTs but more difficult to detect

ACTH, adrenocorticotropic hormone; OART, adrenal rest tumors in or near the ovary; TART, testicular adrenal rest tumor.

1. Reisch N. *Exp Clin Endocrinol Diabetes.* 2019;127(2-03):171-177. 2. Turcu AF, Auchus RJ. *Endocrinol Metab Clin North Am*. 2015;44(2):275-96. 3. Merke DP, Auchus RJ. *N Engl J Med.* 2020;383(13):1248-1261. 4. Auchus RJ, Wiebke A. *J Clin Endocrinol Metab.* 2013;98(7):2645-2655. 5. Kolli V, et al. *Front Endocrinol (Lausanne).* 2021;12:730947. 6. Engels M, et al. *Endocr Rev*. 2019;40(4):973-987. 7. Tiosano D, et al. *Horm Res Paediatr.* 2010;74(3):223-228. 8. Koren R, et al. *Arch Endocrinol Metab*. 2021;65(6):841-845.

# Clinical Consequences of CAH Treatment:
## *Treatment-related Cardiovascular Risk*

**Early exposure to GCs and early development of metabolic issues are associated with cardiovascular risk in children with CAH due to 21-OHD[1,a]**

- A cross-sectional study of pediatric patients (8-16 years) with CAH due to 21-OHD found **unfavorable cardiovascular risk profiles** including[1]:
  - Increased BMI
  - Increased fat mass
  - Elevated blood pressure
  - Nondipping blood pressure profile
  - Insulin resistance

**Higher cumulative GC exposure at an early age may increase cardiovascular morbidity/mortality risk in early adulthood[2,a]**

- A case-controlled study of patients with CAH due to 21-OHD found that CAH patients had[2]:
  - Diastolic hypertension
  - Hypertrophied left ventricle with systolic and diastolic dysfunction
  - Right ventricle diastolic dysfunction

Cumulative GC dose correlated with different cardiac parameters

Meta-analysis showed small but significant **increases in systolic and diastolic blood pressure, insulin resistance, and carotid intima thickness** in patients with CAH taking GCs[3]

A Swedish population–based study found a **younger age of death in patients with CAH**[4]

The second most-common **cause of death** after adrenal insufficiency was **cardiovascular events**[4]

[a]Studies included CAH and non-classic CAH.
21-OHD, 21-hydroxylase deficiency; BMI, body mass index; GC, glucocorticoid.
1. Mooij CF, et al. *J Pediatr Endocrinol Metab.* 2017;30(9):957-966. 2. Amr NH, et al. *Clin Endocrinol (Oxf).* 2021;94(2):210-218. 3. Tamhane S, et al. *J Clin Endocrinol Metab*. 2018;103(11):4097-4103.
4. Falhammar H, et al. *J Clin Endocrinol Metab*. 2014;99(12):E2715-21.

# Clinical Consequences of CAH:
## *Growth and Development Problems*

### Disease related:

- Children with CAH tend to **grow too fast in childhood** and not enough during puberty[1]
  - Excess adrenal androgen production results in accelerated skeletal maturation during childhood and premature fusion of the epiphyseal plates, which can lead to **stunted growth**[2]
- Studies have estimated an average height deficit of ~**1 SD score** in adult height versus the normal reference population in the United States[3]

### Treatment related:

- Final height in patients with CAH treated with GCs is **lower than the population norm** and at the lower end of genetic potential[2]
- Growth impairment during high-dose, long-term GC therapy is multifactorial[4]
  - GCs have indirect **antianabolic and catabolic influences** that include bone, cartilage, and muscle proteins
  - Long-term, high-dose GC therapy can result in a **reduction of growth hormone secretion** and its actions
  - Excess GCs can have negative effects on **growth plate cartilage** and **bone density**

GC, glucocorticoid; SD, standard deviation.

1. Bomberg EM, et al. *J Pediatr.* 2015;166(3):743-750. 2. Bonfig W. *Curr Opin in Endocrinol Diabetes Obes.* 2017;24(1):39-42. 3. Muthusamy K, et al. *J Clin Endocrinol Metab* 2010;95(9):4161-4172.
4. Hochberg Z. *Horm Res.* 2002;58(suppl 1):33-38.