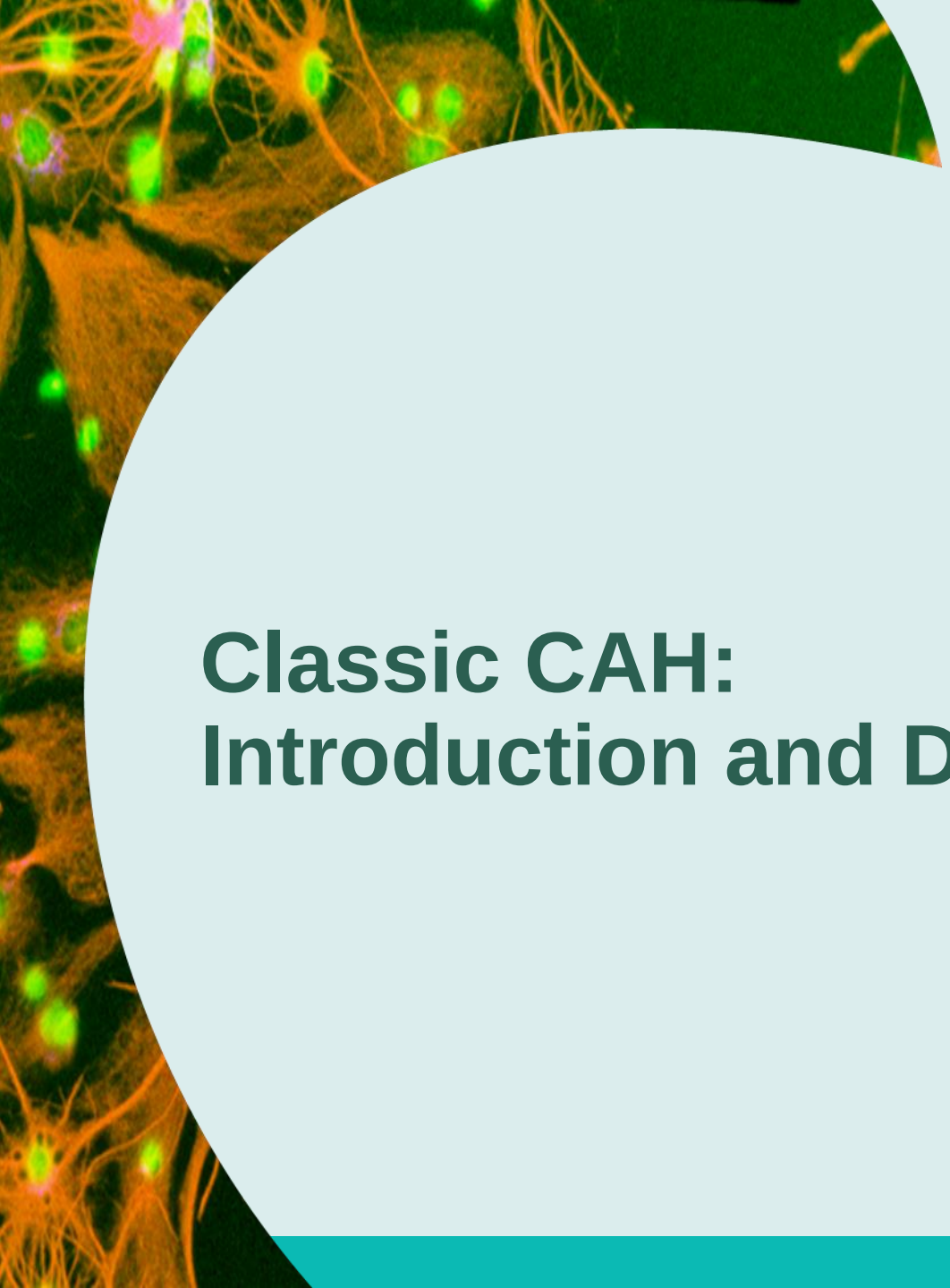
MED-MSL-CAH-US-0004 v2

Classic Congenital Adrenal Hyperplasia (CAH)

NEUROCRINE® BIOSCIENCES

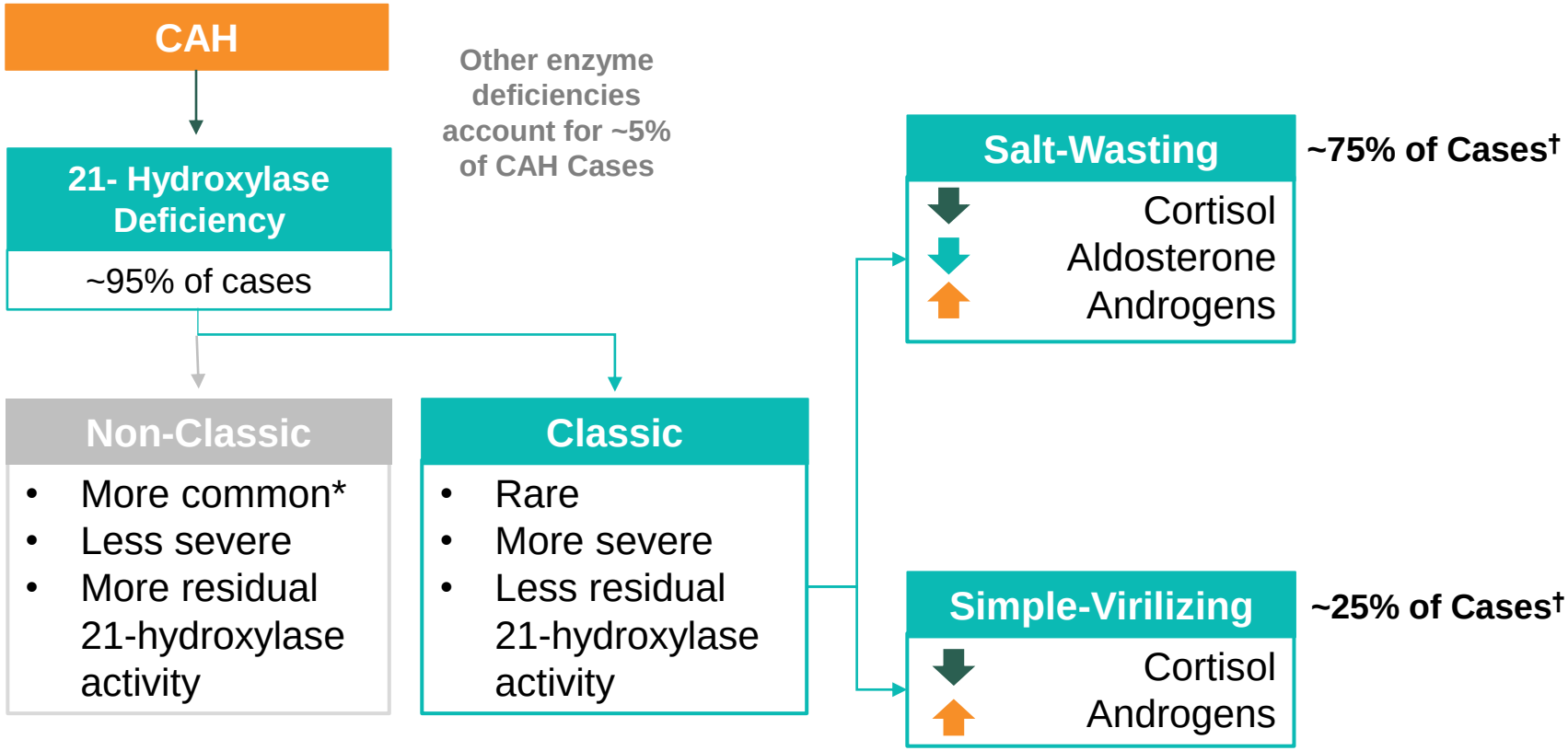
Table of Contents



Classic CAH:
Introduction and Definitions

Congenital Adrenal Hyperplasia (CAH)[1-4]

A Group of Autosomal Recessive Disorders



*Estimated prevalence of Non-Classic CAH ranges from 1 case per 200 persons to 1 case per 1000 persons[5]; †Distinctions between salt-wasting and simple-virilizing are a continuum, and not absolute.[4]

1. Speiser PW, et al. *Journal of Clinical Endocrinology & Metabolism*. 2018;103(11):4043-4088. 2. Speiser PW, et al. J *Clin Endocrinol Metab*. 2010;95(9):4133-4160. 3. White PC, et al. *Endocrine Reviews*. 2000;21(3):245-291. 4. Merke DP, et al. *New England Journal of Medicine*. 2020;383(13):1248-1261. 5. Hannah-Shmouni F, et al. *Genet Med* 2017; 19: 1276-9.

Classic Congenital Adrenal Hyperplasia (CAH)

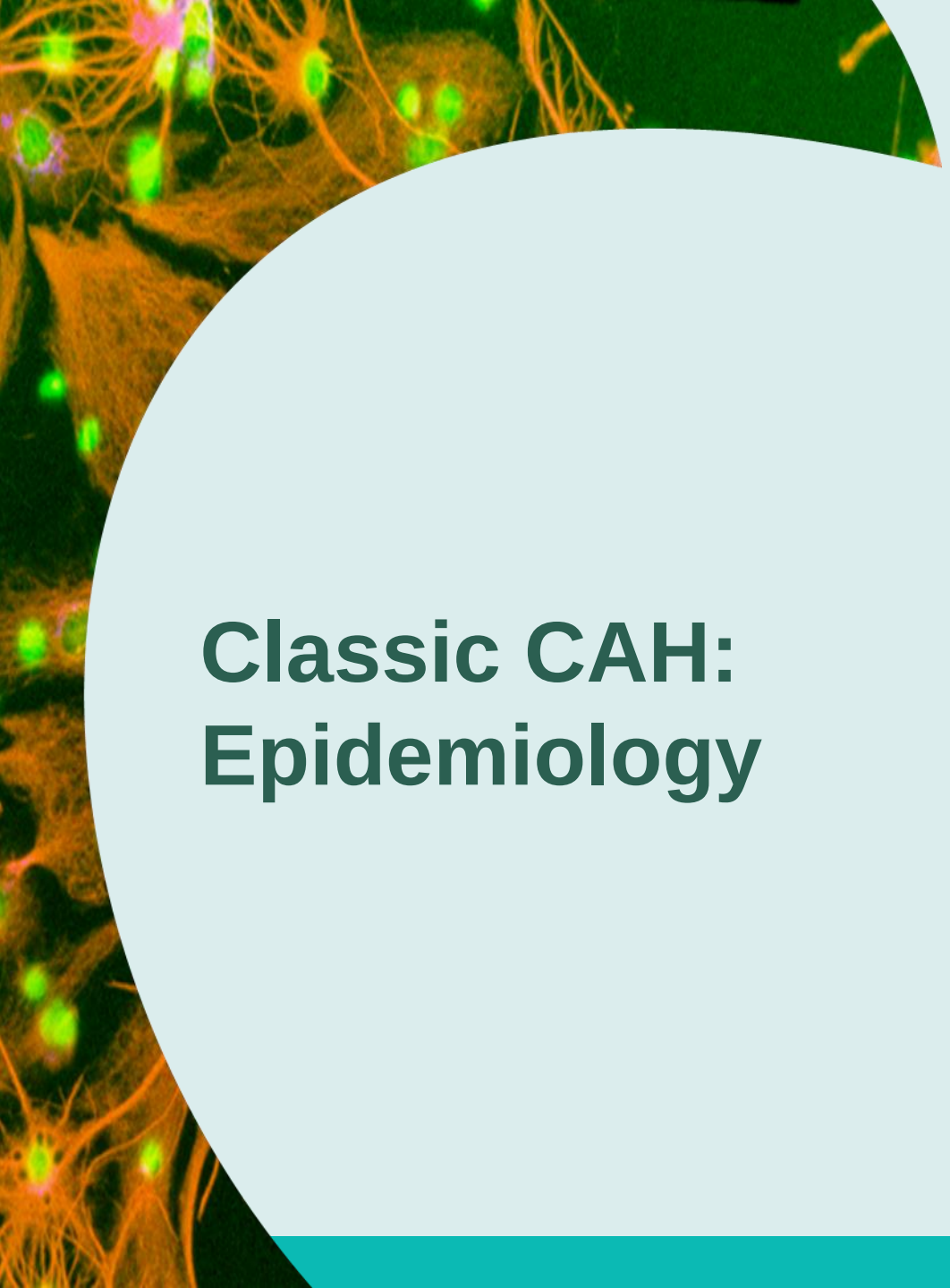
CONGENITAL — Present at Birth

ADRENAL HYPERPLASIA — May present with enlarged adrenal glands

- **Classic CAH** is a **rare autosomal recessive disorder** that results in an enzyme deficiency, altering the production of adrenal hormones[1]
- Often presents with **enlarged adrenal glands**, deficiency in cortisol (and sometimes aldosterone), & excessive androgen production[2-4]
- Patients usually require **lifelong therapy with glucocorticoids** often at **supraphysiologic doses** (with/without mineralocorticoids)[1]

Prior to the discovery of cortisol in the late 1940s and the development of synthetic glucocorticoids in the 1950s, patients with Classic CAH had a short life expectancy and died shortly after birth[3]

1. Speiser PW, et al. J Clin Endocrinol Metab. 2018;103(11):4043-4088. 2. White PC, et al. Endocr Rev. 2000;21(3):245-291. 3. Falhammar H, et al. J Clin Endocrinol Metab. 2014;99(12):E2715-E2721. 4. Merke DP, et al. Lancet. 2005;365(9477):2125-2136.



Classic CAH: Epidemiology

Classic CAH: Incidence

Alaska (Yupik Eskimos)[1]: 1:288

~1:15,000 live births worldwide[1-3]

Réunion[1]: 1:4,111

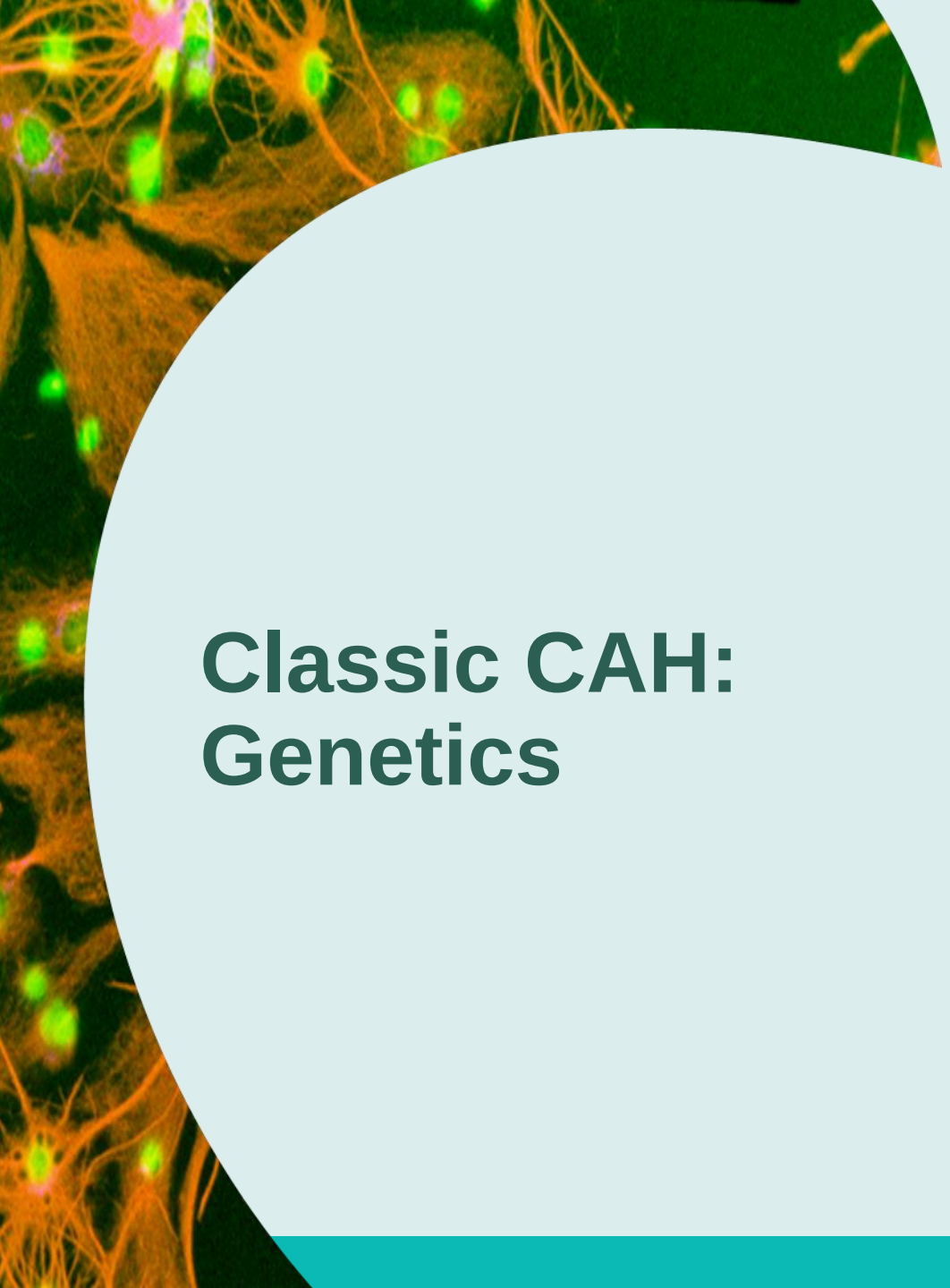
Globally, incidence is greater in populations that are geographically isolated, where the gene pool is smaller[1,4]

1. Pang S, et al. *Screening.* 1993;2(2):105-139. 2. Pignatelli D, et al. Front Endocrinol (Lausanne). 2019;10:432. 3. Therrell BL. *Endocrinol Metab Clin North Am.* 2001;30(1):15-30. 4. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088. 5. Claahsen-van der Grinten HL, et al. [published online ahead of print, 2021 May 7]. Endocr Rev. 2021;bnab016. 6. Sontag MK, et al. *MMWR Morb Mortal Wkly Rep.* 2020;69(36):1265-1268. Published 2020 Sep 11.

Classic CAH: Incidence

Country or Region	Incidence	Country or Region	Incidence	Country or Region	Incidence
Alaska (Yupik Eskimos)[1]	1:288	Croatia[5]	1: 14,403	Portugal[1]	1:14,285
Argentina (Buenos Aires)[5]	1:8,937	Cuba[5]	1: 15,931	Réunion[1]	1:4,111
Australia[5]	1:18,034	Czech Republic[5]	1: 12,520	Scotland[1]	1:17,099
Australia (New South Wales)[5]	1: 15 488	France[5]	1: 15,699	Spain[1]	1:17,239
Australia (Western Australia)[5]	1: 14,869	Germany (Bavaria)[5]	1:12,457	Sweden[5]	1: 14,260
Brazil[5]	1: 14,967	India[5]	1: 6,334	Switzerland[1]	1:10,970
Brazil (Goias state)[5]	1: 10,325	Israel[5]	1: 16,910	Turkey[5]	1: 15,067
Brazil (Minas Gerais state)[5]	1: 19,927	Italy[1]	1:11,100	United Arab Emirates[5]	1: 9,030
Brazil (Rio Grande do Sul state)[5]	1: 13,551	Japan (Sapporo)[5]	1: 20,756	United Kingdom[5]	1: 18,248
Canada[1]	1:16,666	Japan (Tokyo)[5]	1: 21,264	United States[1,6]	~1:15,000
China[5]	1: 6,084	Netherlands[5]	1: 17,468	Uruguay[5]	1: 15,800
China (Beijing)[5]	1: 7,393	New Zealand[5]	1: 26,727	Worldwide[1-3]	~1:15,000

1. Pang S, et al. *Screening.* 1993;2(2):105-139. 2. Pignatelli D, et al. Front Endocrinol (Lausanne). 2019;10:432. 3. Therrell BL. *Endocrinol Metab Clin North Am.* 2001;30(1):15-30. 4. Speiser PW, et al. *J Clin Endocrinol Metab.* 2018;103(11):4043-4088. 5. Claahsen-van der Grinten HL, et al. [published online ahead of print, 2021 May 7]. Endocr Rev. 2021;bnab016. 6. Sontag MK, et al. *MMWR Morb Mortal Wkly Rep.* 2020;69(36):1265-1268. Published 2020 Sep 11.



Classic CAH: Genetics

Classic CAH: Genetics

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

CYP21A2 gene

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

Mutation in CYP21A2

21-Hydroxylase deficiency CAH

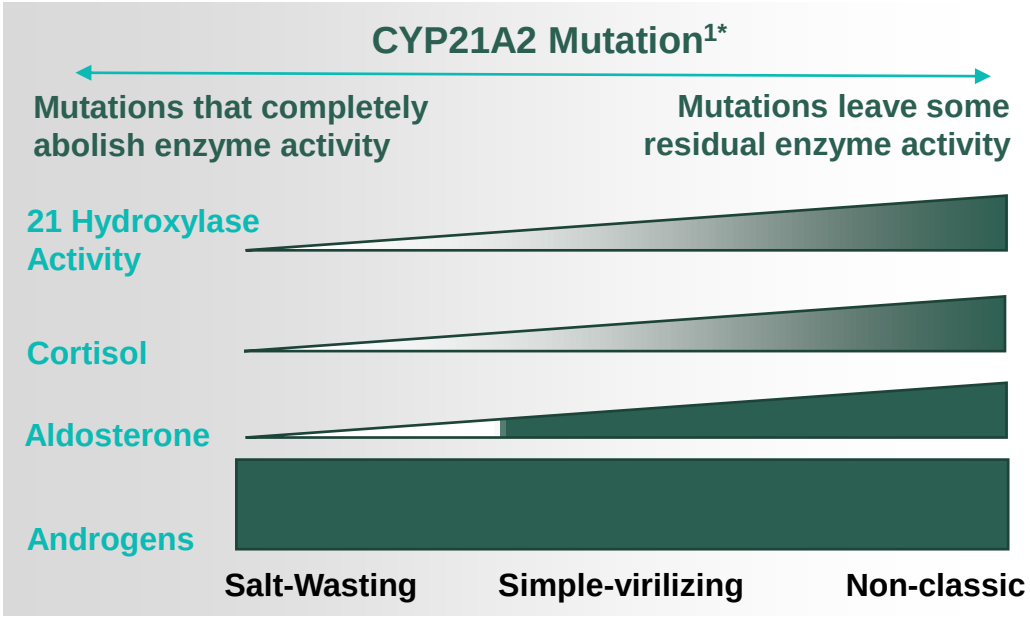
Disease severity correlates with enzyme impairment[1]

Enzyme activity abolished

Some enzyme activity remains

Classic Salt-Wasting CAH[1,3]

Classic Simple Virilizing CAH[1,3]

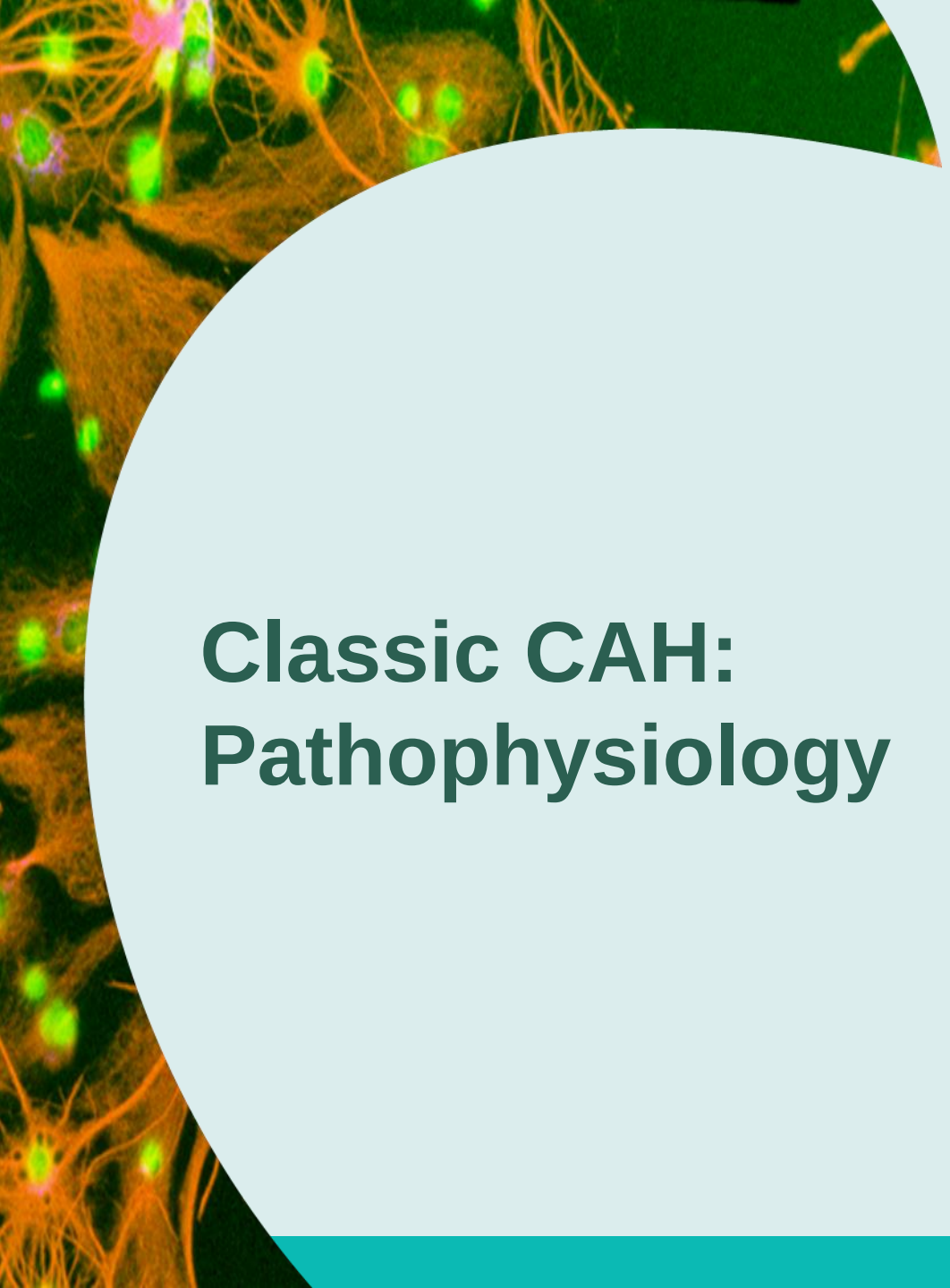


*This schematic is a general summary, and is not meant to represent all 21-OHD CAH patients

21-OHD CAH is transmitted as an Autosomal Recessive Disorder[2]

21-OHD, 21- Hydroxylase deficiency.

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



Classic CAH: Pathophysiology

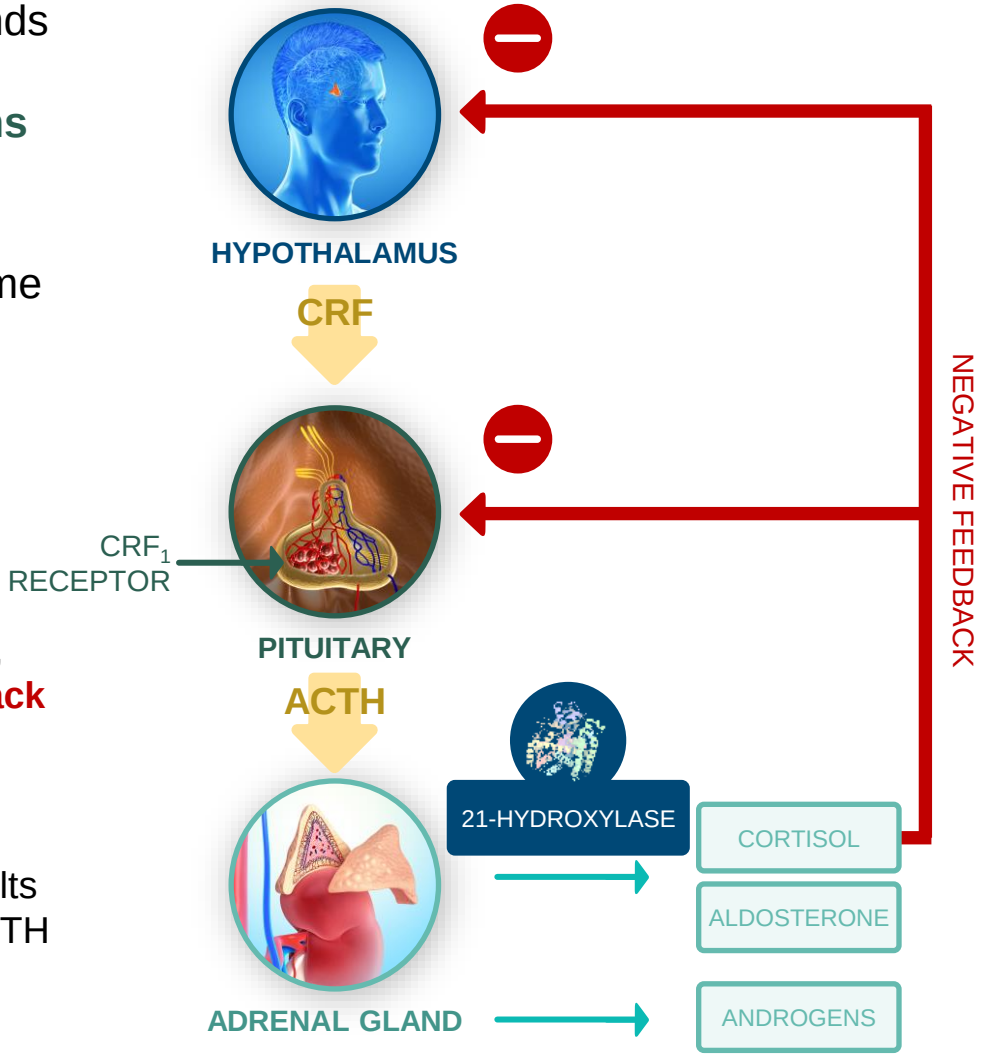
The Hypothalamic-Pituitary-Adrenal Axis

In healthy individuals, the adrenal glands produce several hormones, including **cortisol, aldosterone, and androgens** that are tightly regulated[1-3]

21-hydroxylase is an important enzyme involved in cortisol and aldosterone biosynthesis[1-3]

Balance in the **HPA axis** relies on sufficient cortisol levels[1-3]:

- Cortisol regulates hypothalamic and pituitary secretion of **CRF** and **ACTH**, respectively, by exerting **negative feedback** and decreasing secretion of these stimulatory hormones when cortisol production is sufficient
- Conversely, the deficiency of cortisol results in the increased secretion of CRF and ACTH

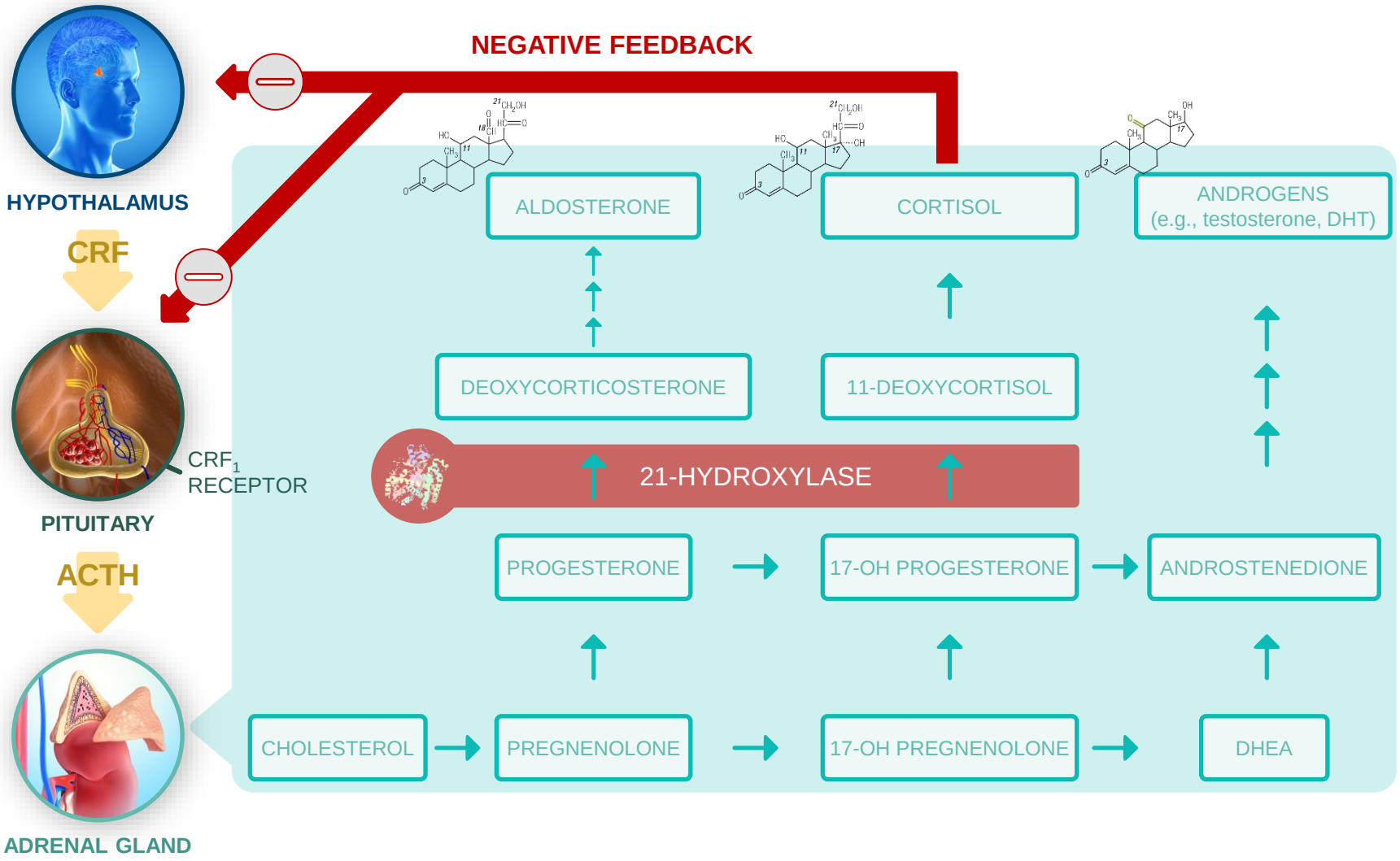


ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; HPA, hypothalamic-pituitary-adrenal.

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

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. White PC, et al. *Endocr Rev.* 2000;21(3):245-291.
3. El-Maouche D, et al. *Lancet.* 2017;390(10108):2194-2210.

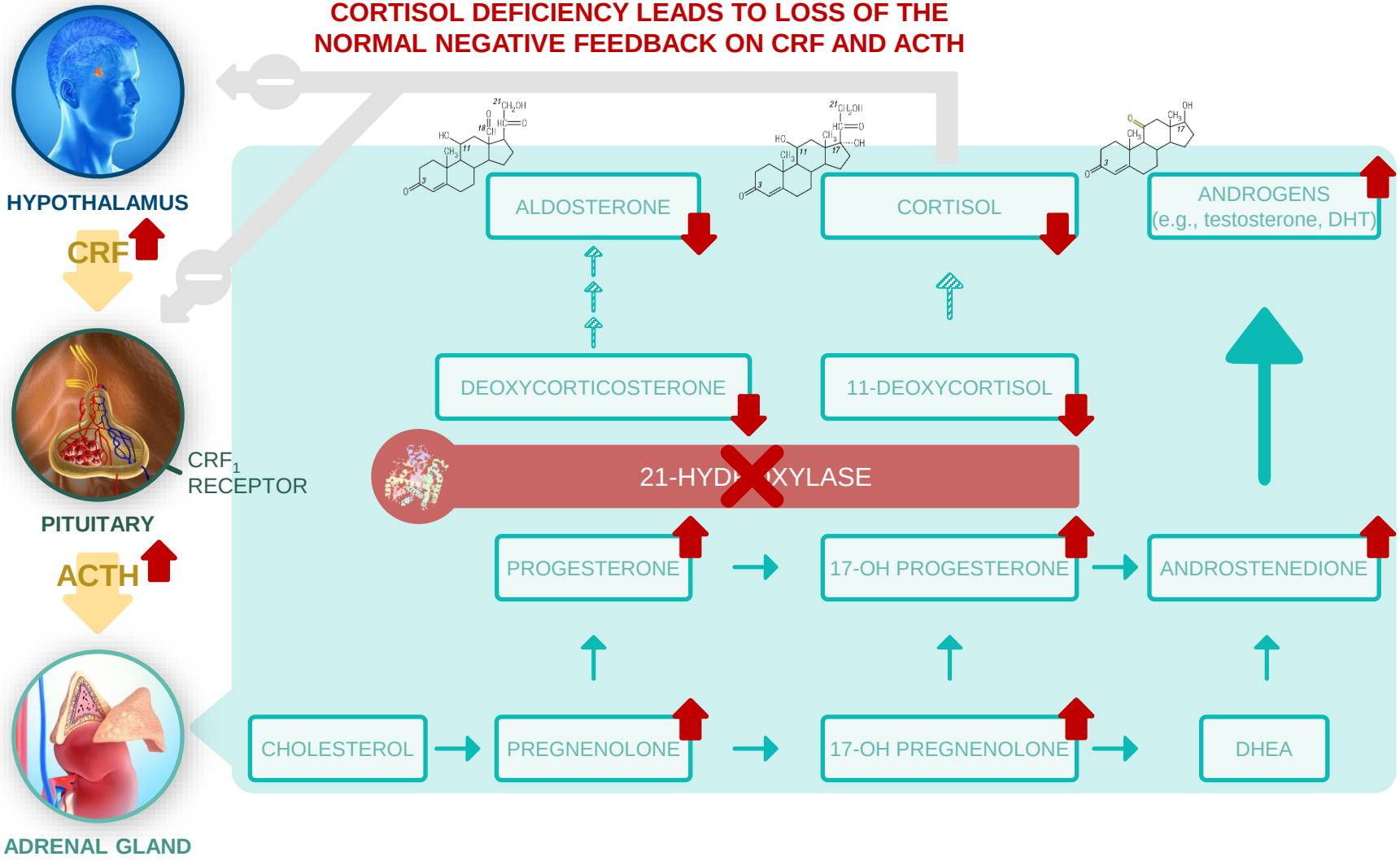
The HPA Axis & Steroidogenesis



ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; DHEA, dehydroepiandrosterone; DHT, dihydrotestosterone; HPA, hypothalamic-pituitary-adrenal axis.

Figure adapted from Merke DP, et al. *N Engl J Med*. 2020;383(13):1248-1261; Auchus RJ, et al. *J Clin Endocrinol Metab*. 2013;98(7):2645-2655; & Claahsen-van der Grinten HL, et al. [published online ahead of print, 2021 May 7]. *Endocr Rev*. 2021;bnab016.

Classic CAH: Pathophysiology



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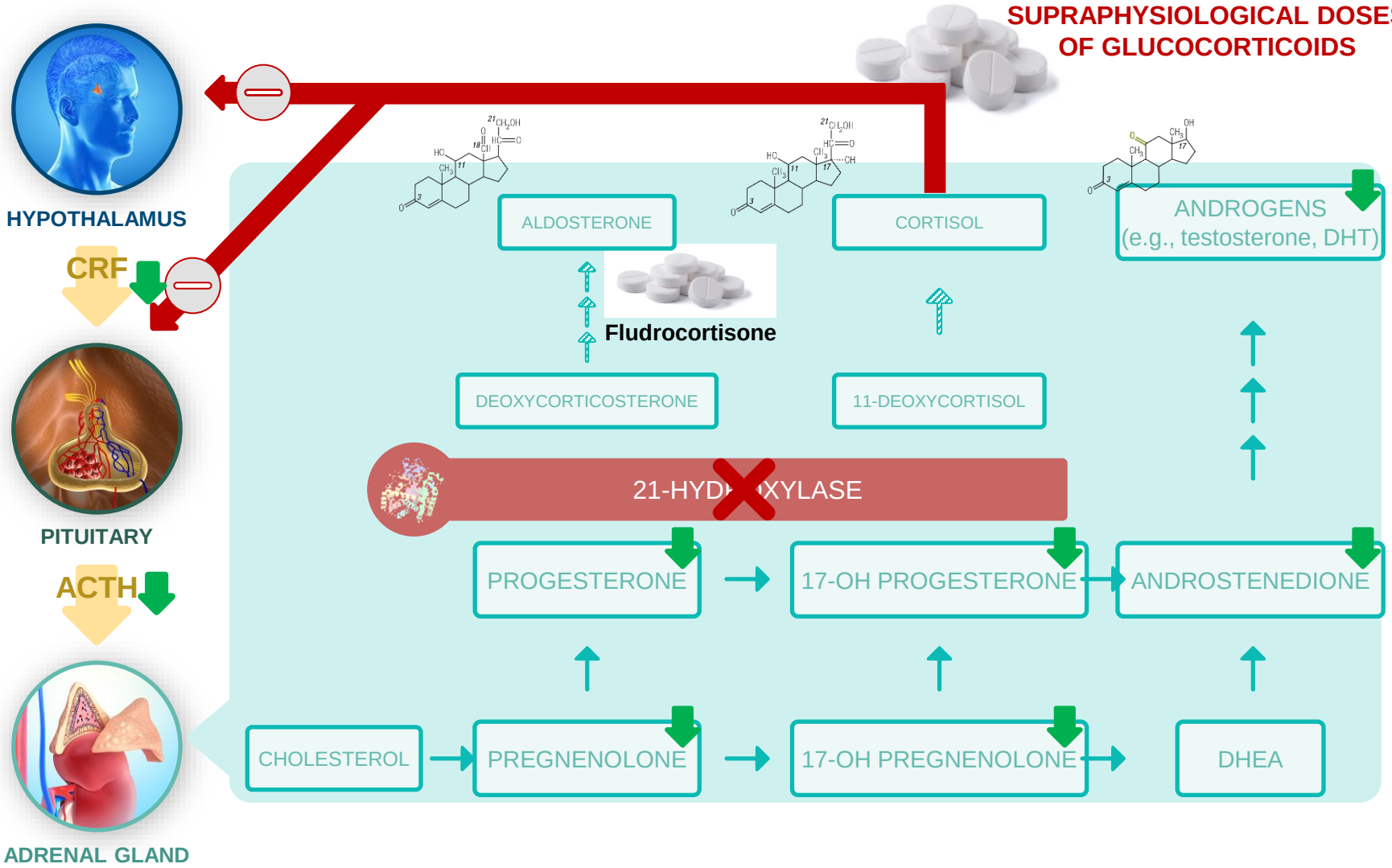
Additional Information

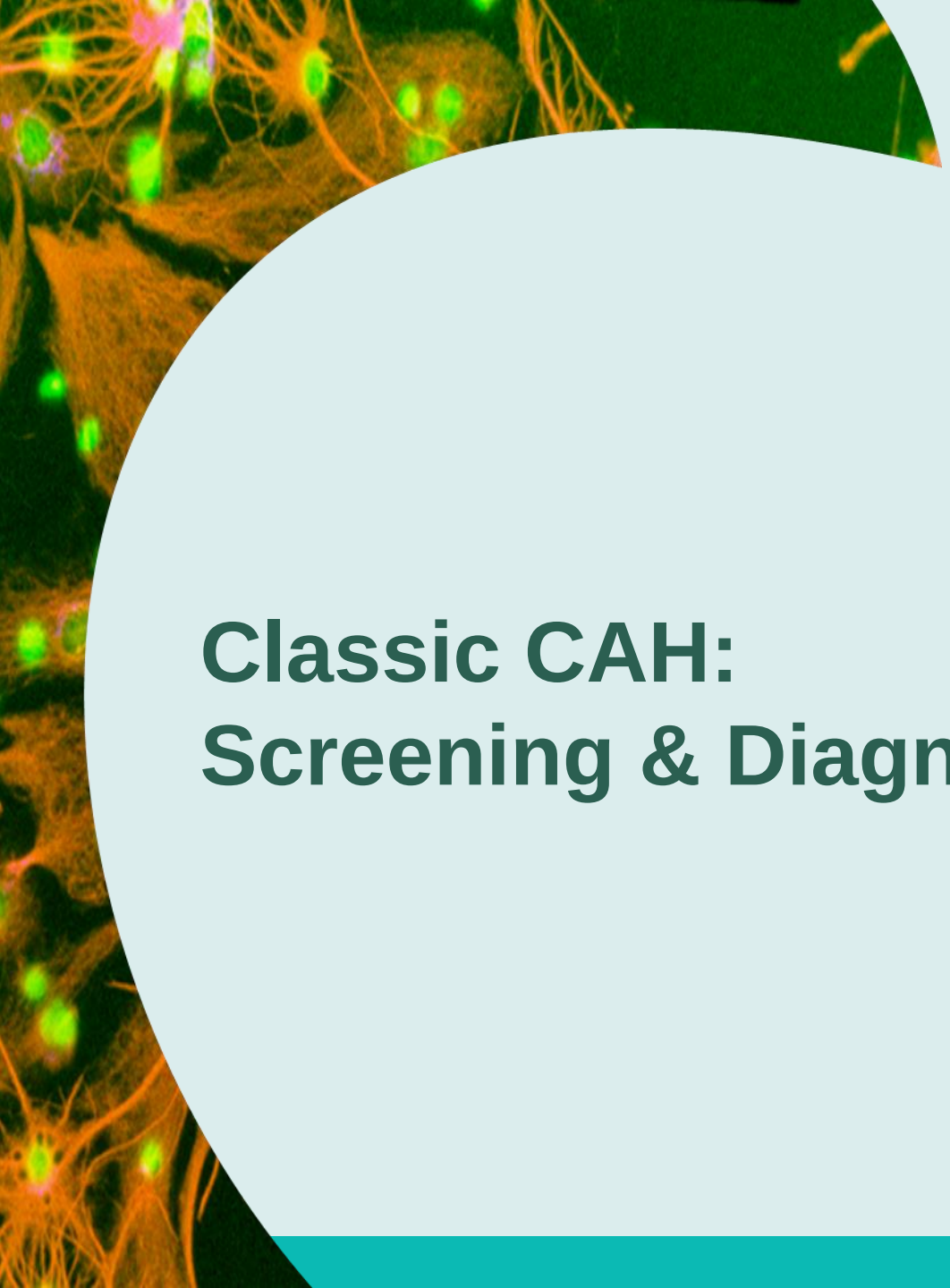
Classic CAH

Supraphysiological doses of glucocorticoids are usually required to try and control high adrenal androgens



ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; DHEA, dehydroepiandrosterone.

Figure adapted from Merke DP, et al. *N Engl J Med*. 2020;383(13):1248-1261; Auchus RJ, et al. *J Clin Endocrinol Metab*. 2013;98(7):2645-2655; Claahsen-van der Grinten HL, et al. [published online ahead of print, 2021 May 7]. *Endocr Rev*. 2021;bnab016.



Classic CAH: Screening & Diagnosis

Classic CAH: Newborn Screening & Diagnosis

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

- Newborn screening is now universal in the United States and in many other developed countries[1-3*]
- Diagnosis of CAH due to 21-OHD is based on measurement of 17-hydroxyprogesterone (17-OHP)
  - Level >1000 ng/dL
  - Most affected infants have levels well above 5000 ng/dL
- Cosyntropin stimulation test confirms the diagnosis and rules out more rare disorders of steroidogenesis[1]

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**

Prenatal diagnosis can be performed if both parents are carriers of CYP21A2 mutations[2]

*Notably, the United Kingdom[4] and some Canadian territories[5] do not include 21-OHD CAH screening in their NBS programs. Additional information on NBS can be found on CARES Foundation website; † Second-tier screen by liquid chromatography/tandem mass spectrometry (LC-MS/MS) is preferred to all other methods (e.g., genotyping)[1]; 21-OHD, 21-hydroxylase deficiency.

1. Speiser PW, et al. *Journal of Clinical Endocrinology & Metabolism*. 2018;103(11):4043-4088. 2. Claahsen-van der Grinten HL, et al. [published online ahead of print, 2021 May 7. Endocr Rev. 2021. 3. Merke DP, et al. New England Journal of Medicine. 2020;383(13):1248-1261. 4. Hird BE, et al. Arch Dis Child. 2014;99(2):158-164. 5. Canadian Organization for Rare Disorders, Newborn Screening in Canada Status Report. 2015.

Classic CAH: Clinical Characteristics – Disease Related

Classic CAH: Clinical Characteristics – Disease Related

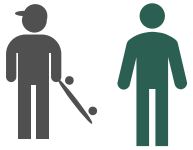
Infancy

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

Childhood

- Increased growth velocity[1]
- Advanced bone age, premature epiphyseal fusion[2]
- Premature development of puberty[1†]:
  - Presence of pubic hair before 8 years of age (girls) and 9 years of age (boys)
- Early-onset adult apocrine odor[1]

Adolescence/ Adulthood



- Hirsutism[1]
- Acne[1]
- Short stature/height below genetic potential[1]
- Amenorrhea/oligomenorrhea
- Infertility/subfertility[1,3]
- Testicular adrenal rest tumors (TARTs) in males[1]
- Adrenal rest tumors in or near the ovaries (OARTs) in females[1]
  - Likely less frequent compared to TARTs but more difficult to detect[1]
- Adrenal myelolipomas[1]

Adrenal Crisis‡

*Life-threatening clinical presentation that can occur within first 3 weeks of life if patients are not diagnosed and treated.
†Central precocious puberty due to elevation of gonadotropin levels can occur as a complication of classic CAH.[4]
‡Patients of all ages are at risk for death from adrenal crises, which are most often triggered by infectious illnesses.[1]

1. Merke DP et al. *N Eng J Med*. 2020;383(13):1248-1261. 2. Bonfig W. *Current Opinion in Endocrinology & Diabetes and Obesity.* 2017;24(1):39-42. 3. Reisch N. *Exp Clin Endocrinol Diabetes.* 2019;127:171-177. 4. Soliman AT et al. *Metabolism*. 1997;46(5):513-517.

Additional Information

Classic CAH: Treatment

Classic CAH: Treatment Recommendations

- **Proper treatment with glucocorticoids prevents adrenal crisis and virilization, allowing nearly normal growth and development during childhood[1]**
- **Supraphysiological doses of glucocorticoids are usually required to try and control high adrenal androgens[2]**

2018 Endocrine Society Clinical Practice Guidelines for Classic CAH[1]

Growth Age	Recommended Treatment
Newborn/early infancy	• Hydrocortisone + Fludrocortisone and sodium chloride supplements
Growing Individuals	• Hydrocortisone + Fludrocortisone as clinically indicated† • Hydrocortisone oral suspension‡ 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 glucocorticoid excess, as well as for signs of inadequate androgen control, to optimize the adrenal steroid treatment profile • Monitoring for signs of mineralocorticoid deficiency or excess

*Refer to Speiser 2018 guidelines for specific monitoring recommendations based on age; †The need for MCs decreases with age. Most non-hypertensive adults with classic CAH benefit from continued fludrocortisone treatment. The requirement for MC replacement should be reassessed during the transition from pediatric to adult care; ‡Hydrocortisone cypionate oral suspensions were inadequate to control classic CAH in children due to uneven distribution in liquid form. Good control can be achieved by orally administering crushed, weighed Hydrocortisone tablets mixed with a small volume of liquid, if needed, immediately before administration; §During childhood, the preferred GC is hydrocortisone because its short half-life minimizes the adverse side effects typical of longer-acting, more potent GCs (e.g., dexamethasone), especially growth suppression; GC, glucocorticoid; MC, mineralocorticoid.

1. Speiser PW, et al. Journal of Clinical Endocrinology & Metabolism. 2018;103(11):4043-4088. 2. Han TS, et al. Clinical Endocrinology. 2013;78(2):197-203.

Classic CAH: Treatment – Dose Recommendations

Maintenance Therapy Suggested in Growing Patients*		
Drugs	**Total Daily Dose**	**Divided dosing frequency (times daily)**
GCs: Hydrocortisone tablets	10–15 mg/m^2	~3
MCs: Fludrocortisone tablets	0.05–0.2 mg	1–2
Sodium chloride supplements	1–2 g (17–34 mEq/d) in infancy	Divided into several feedings

Maintenance Therapy Suggested in Fully Grown Patients*		
Corticosteroid	**Total Daily Dose (mg/d)**	**Divided dosing frequency (times daily)**
Hydrocortisone	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	1 – 2

*These doses and schedules are meant as examples and should not be construed as a restrictive menu of choices for the individual patient; †elixir may permit improved dose titration for these drugs; GC, glucocorticoid; MC, mineralocorticoid.

Speiser PW, et al. *Journal of Clinical Endocrinology & Metabolism*. 2018;103(11):4043-4088.

Classic CAH: Treatment Challenges

Two Key Problems

Two Key Problems[1,2]

1 Hormone deficiency:

Cortisol → tired, weak

Aldosterone → salt-wasting

2 Hormone excess:

Androgen (male hormone)

- Growth and development problems in children
- Irregular periods, facial hair, acne (females), testicular tumors (males)

Glucocorticoid Treatment

NORMAL dose[3]

- Treats the cortisol deficiency
- Does not control the androgen excess

HIGH dose[1,3,4]

- Treats the cortisol deficiency
- Can help control androgen excess
- May cause long-term problems

1. Merke DP et al. *N Engl J Med.* 2020;383(13):1248-1261. 2. Rushworth RL et al. *N Engl J Med*. 2019;381(9):852-861. 3. Claahsen-van der Grinten HL et al. [published online ahead of print, 2021 May 7]. *Endocr Rev*. 2021. 4. Tresoldi AS et al. *J Clin Endocrinol Metab*. 2020;105(2):418-429.

Classic CAH: Clinical Characteristics – Treatment Related

Classic CAH: Treatment Challenges

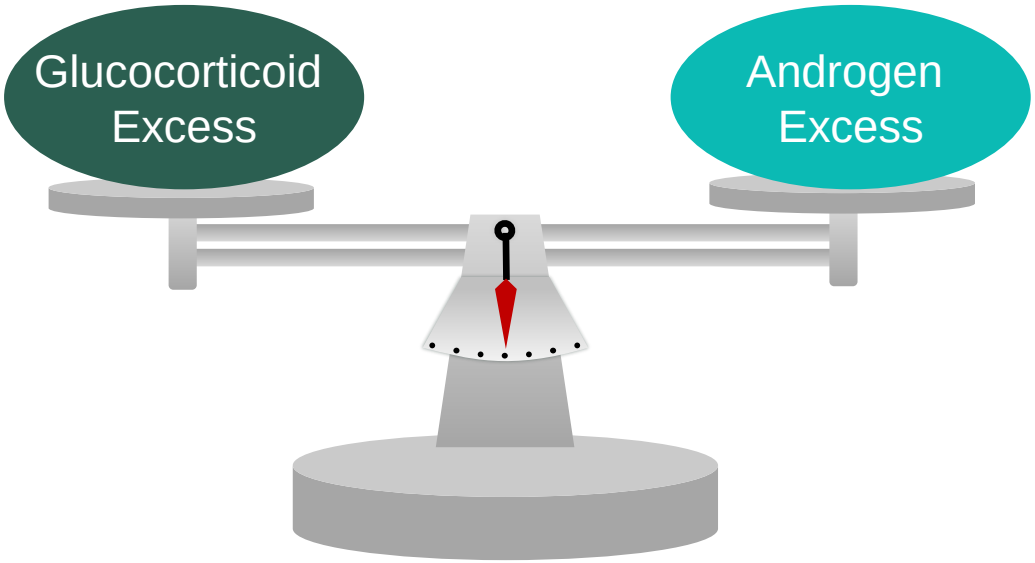
Supraphysiological doses of glucocorticoids are usually required to try and control high adrenal androgens[1]

Glucocorticoid Excess[1-4]

- Cushingoid features
- Weight gain, central obesity
- Metabolic syndrome
- Decreased bone density, risk of fractures
- Increased infections
- Negative psychological impact
- Short stature/height below genetic potential

Androgen (and ACTH) Excess[3,4]

- Virilization, hirsutism
- Advanced bone age, premature epiphyseal fusion
- Risk for early or central precocious puberty
- Testicular/ovarian adrenal rest tumors, adrenal myelolipomas
- Negative psychological impact
- Amenorrhea, infertility
- Short stature/height below genetic potential



ACTH, adrenocorticotropic hormone.

1. Han TS, et al. *Nat Rev Endocrinol*. 2014;10(2):115-124. 2. Tresoldi AS, et al. *J Clin Endocrinol Metab*. 2020;105(2):418-429.
3. Merke DP, et al. *N Engl J Med*. 2020;383(13):1248-1261. 4. Choi JH, et al. *Korean J Pediatr.* 2017;60(2):31-37.

Additional Information

Classic CAH: Treatment Goals

The goal of classic CAH treatment is to balance therapy, in order to prevent adrenal crisis and provide optimal control of androgens, while limiting the use of glucocorticoid doses above replacement levels[1]

Glucocorticoid Excess[1-4]

- Cushingoid features
- Weight gain, central obesity
- Metabolic syndrome
- Decreased bone density, risk of fractures
- Increased infections
- Negative psychological impact
- Short stature/height below genetic potential

Androgen (and ACTH) Excess[3,4]

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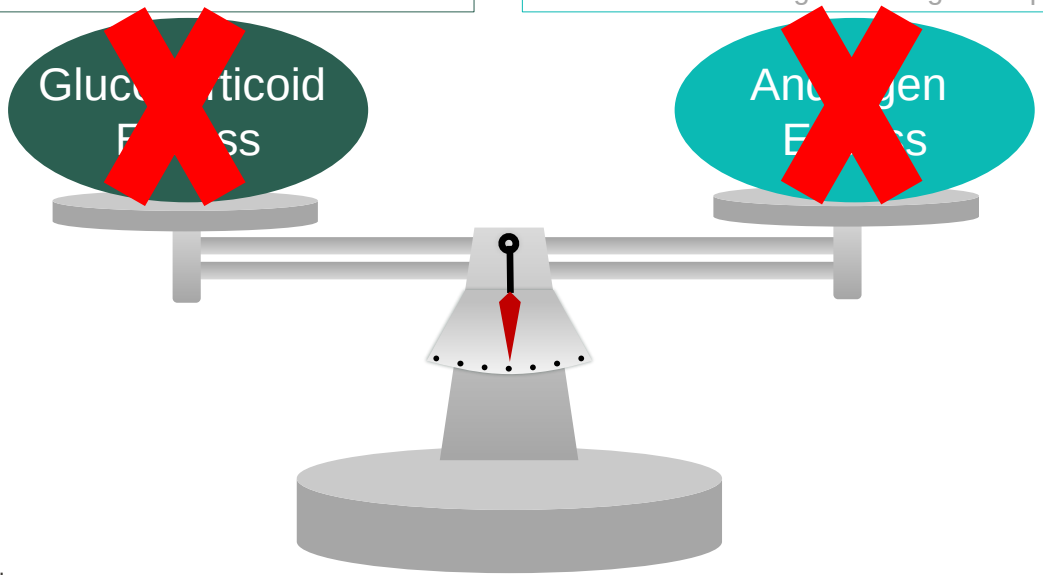


ACTH, adrenocorticotropic hormone.

1. Han TS, et al. *Nat Rev Endocrinol*. 2014;10(2):115-124. 2. Tresoldi AS, et al. *J Clin Endocrinol Metab*. 2020;105(2):418-429.
3. Merke DP, et al. *N Engl J Med*. 2020;383(13):1248-1261. 4. Choi JH, et al. *Korean J Pediatr.* 2017;60(2):31-37.

Classic CAH: Burden

Classic CAH: Burden

Health-related Quality of Life (HRQoL) is adversely affected in patients with CAH[1-4*]:

- Spectrum of clinical symptoms, including some that can be life-threatening
- Involve key aspects of sex and gender identity and fertility

CAH leads to significantly increased healthcare costs compared to those without the disease[5,6*]

- A US based claims analysis with CAH patients vs. matched controls showed[5]:
  - CAH patients cost 80% more than controls

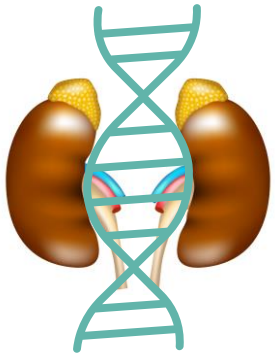
*Studies are not specific to patients with classic CAH

1. Falhammar H et al. *Endocrine*. 2014;47(1):299-307. 2. Arlt W et al. *J Clin Endocrinol Metab*. 2010;95(11):5110-5121. 3. Aulinas A et al. *Expert Rev Pharmacoecon Outcomes Res*. 2014;14(6):873-888. 4. Daae E et al. *Endocrine*. 2018;62(1):3-13. 5. Gunnarsson C et al. *J Endocr Soc*. 2017;1(5):512-523. 6. Jenkins-Jones S et al. *Eur J Endocrinol*. 2018;178(4):309-320.

Classic CAH: Summary

- **Rare genetic disorder that results in an enzyme deficiency, altering the production of adrenal hormones[1]**

Deficiency in cortisol (and sometimes aldosterone) + Excessive androgen production



Symptoms range in severity and can include:

- **Adrenal crisis, virilization in females, rapid early growth, early puberty, loss of growth potential, hirsutism, and infertility[2]**

The incidence of classic CAH in the United States is **~1:15,000 live births[3,4]**

High-dose (supraphysiologic) glucocorticoid therapy is often required to manage excessive adrenal androgen production[5]

Patients may experience complications due to chronic supraphysiologic doses of glucocorticoids[6-11]

- Decreased bone density
- Increased fracture risk
- Increased infections
- Central obesity
- Insulin resistance
- Cushingoid features
- Hypertension
- Myopathy
- Increased cardiovascular risk

1. Speiser PW, et al. *J Clin Endocrinol Metab*. 2018;103(11):4043-4088. 2. Merke DP, et al. *Lancet*. 2005;365(9477):2125-2136. 3. Sontag MK, et al. *MMWR Morb Mortal Wkly Rep*. 2020;69(36):1265-1268. Published 2020 Sep 11. 4. Pang S, et al. *Screening*. 1993;2(2):105-139. 5. Claahsen-van der Grinten HL, et al. *Pharmacol Ther*. 2011;132(1):1-14. 6. Han TS, et al. *Nat Rev Endocrinol*. 2014;10(2): 115-124. 7. Tresoldi AS, et al. *J Clin Endocrinol Metab*. 2020;105(2):418-429. 8. Merke DP, et al. *N Engl J Med*. 2020;383(13):1248-1261. 9. Choi JH, et al. *Korean J Pediatr*. 2017;60(2):31-37. 10. Falhammar H, et al. *J Clin Endocrinol Metab*. 2007;92(12):4643-4649. 11. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540.