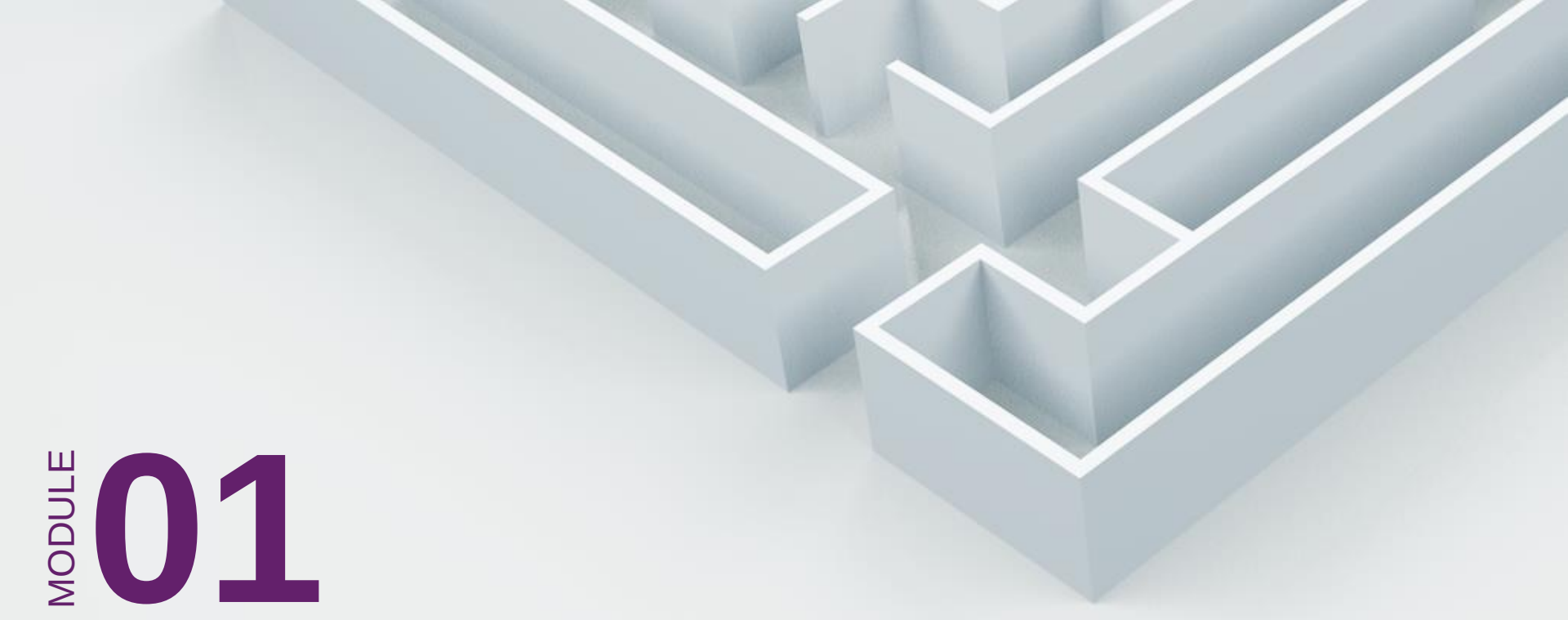


MODULE 01

Classification of Porphyria

Alnylam® PHARMACEUTICALS

Porphyria—A Rare Disease of Clinical Consequence

- Porphyria is a group of at least 8 metabolic disorders[1,2]
  - Each subtype of porphyria involves a genetic defect in a heme biosynthesis pathway enzyme[1,2]
  - The subtypes of porphyria are associated with distinct signs and symptoms in patient populations that can differ by gender and age[1,3]
- Prevalence of some subtypes of porphyria may be higher than generally assumed[3]

Estimated Prevalence of Most Common Subtypes of Porphyria[1,4]

Subtype of Porphyria	Estimated Prevalence Based on European and US Data
Porphyria cutanea tarda (PCT)	1/10,000 (EU)[1]
Acute intermittent porphyria (AIP)	0.118-1/20,000 (EU)[1,4] 5/100,000 (US)[1]
Erythropoietic protoporphyria (EPP)	1/50,000-75,000 (EU)[1]

1. Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet*. 2015;86:17.20.1-17.20.26. **2.** Puy H et al. *Lancet.* 2010;375:924-937. **3.** Bissell DM et al. *N Engl J Med.* 2017;377:862-872.
4. Elder G et al. *J Inherit Metab Dis*. 2013;36:848-857.

Classification of Porphyria

Porphyria can be classified in 2 major ways[1,2]:

1 According to major physiological sites: liver or bone marrow[1,2]

- Heme precursors originate in either the liver or bone marrow, which are the tissues most active in heme biosynthesis[1,2]

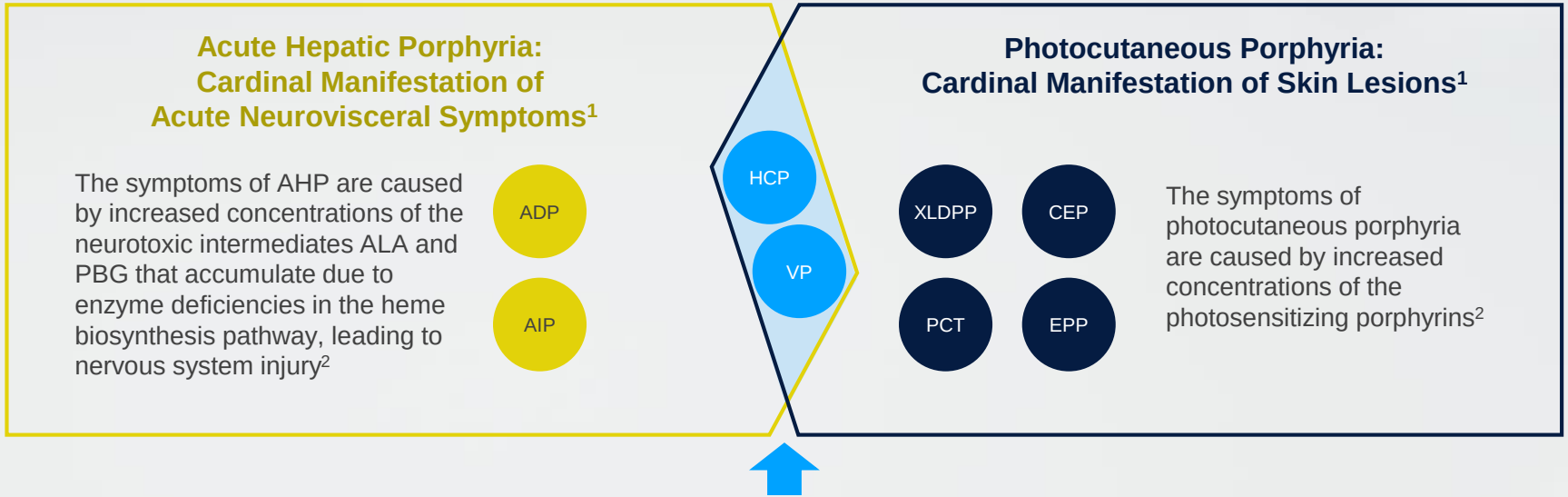
2 According to major clinical manifestations[1,2]

Acute Versus Photocutaneous Porphyria

- Major clinical manifestations are either neurovisceral symptoms (eg, severe, diffuse abdominal pain) associated with acute exacerbations or cutaneous lesions resulting from phototoxicity[1,2]
- *Acute* hepatic porphyria may be somewhat of a misnomer since the clinical features may be prolonged and chronic[3]

1. Bonkovsky HL. *Hematology Am Soc Hematol Educ Program.* 2005:24-30. **2.** Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet.* 2015;86:17.20.1-17.20.26. **3.** Anderson KE et al. *Ann Intern Med.* 2005;142:439-450.

Using Major Clinical Manifestations for Classification of 8 Porphyria Subtypes



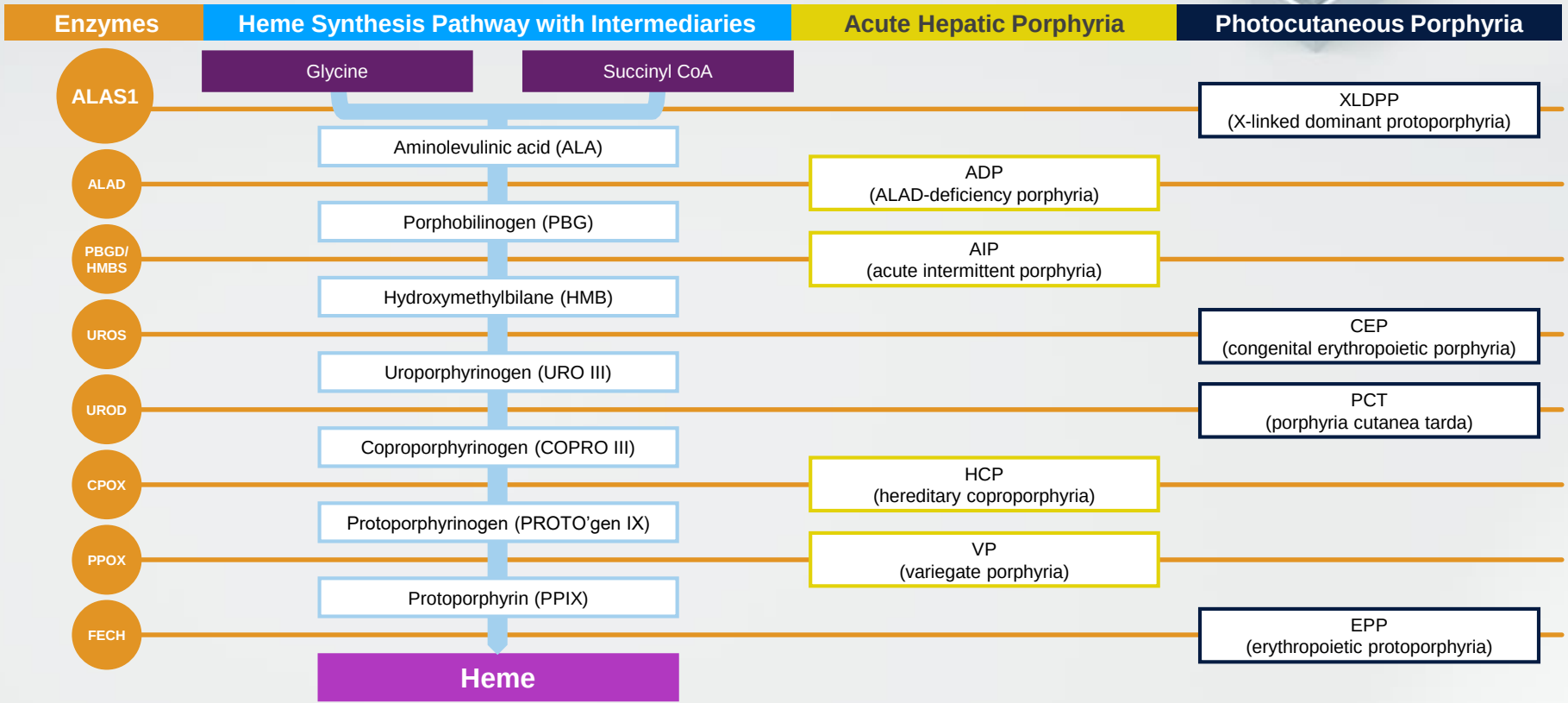
HCP and VP are associated with both acute neurovisceral symptoms and skin lesions[1]

ADP=aminolevulinic acid dehydratase-deficiency porphyria; AIP=acute intermittent porphyria; ALA=aminolevulinic acid; CEP=congenital erythropoietic porphyria; EPP=erythropoietic protoporphyria; HCP=hereditary coproporphyria; PBG=porphobilinogen; PCT=porphyria cutanea tarda; VP=variegate porphyria; XLDPP=X-linked dominant protoporphyria.

1. Bissell DM, Wang B. *J Clin Transl Hepatol.* 2015;3:17-26. **2.** Bissell DM et al. *N Engl J Med.* 2017;377:862-872.

Heme Biosynthesis Pathway, Defective Enzymes, and Related Porphyria[1]

The Rate-Limiting Step for the Pathway is the Formation of ALA, Catalyzed by ALAS1[2]



1. Bissell DM et al. *N Engl J Med.* 2017;377:862-872. **2.** Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26.

The Prevalence of the Four Different Subtypes of AHP

Subtype of AHP[1]	Prevalence
AIP (Acute Intermittent Porphyria)	0.118-1/20,000 (EU*)[2,3] 5/100,000 (US*)[3]
HCP (Hereditary Coproporphyria)	2/1,000,000 (Denmark*)[3]
VP (Variegate Porphyria)	3.2/1,000,000 (EU*)[2]
ADP (Aminolevulinic Acid Dehydratase-Deficiency Porphyria)	6 cases of ADP reported worldwide at time of publication[3]

- AIP accounts for about 80% of AHP cases[4]
- The prevalence of AIP may be underreported due to estimates based on patients with symptomatic disease only rather than an enzyme mutation[5]
  - There is even less information about the other subtypes of AHP

*Prevalence data from these particular countries were cited due to ongoing research and relatively high prevalence.

1. Anderson KE et al. *Ann Intern Med.* 2005;142:439-450. **2.** Elder G et al. *J Inherit Metab Dis*. 2013;36:848-857. **3.** Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet.* 2015;86:17.20.1-17.20.26. **4.** Simon A et al. *Patient*. 2018;11(5):527-537. **5.** Bissell DM, Wang B. *J Clin Transl Hepatol.* 2015;3:17-26.

AHP is a Genetic Disease with a Combination of Hormonal and Environmental Precipitating Factors

- Acute exacerbations in genetically predisposed patients are frequently preceded by environmental or hormonal precipitating factors[1-4]
  - When manifested, the disease can be debilitating and even life threatening[5]
- Signs and symptoms are predominant in women of reproductive age but can occur in men as well[3]
  - It is rare to experience AHP symptoms before puberty[6]
  - Exacerbations are less likely after menopause[2]
- There is higher prevalence in Caucasians, especially northern Europeans, but AHP can occur in all races and ethnic groups[4,7]

- Hormonal and environmental precipitating factors of AHP exacerbations[1,2,4]:
  - Woman's menstrual cycle
  - Many drugs metabolized by CYP450 enzymes (eg, barbiturates, synthetic progestins, sulfonamide antibiotics)
  - Crash dieting
  - Cigarette smoking
  - Excessive alcohol use
  - Infections and surgery
  - Psychological stress

1. Anderson KE et al. *Ann Intern Med.* 2005;142:439-450. **2.** Bissell DM et al. *N Engl J Med.* 2017;377:862-872. **3.** Bissell DM, Wang B. *J Clin Transl Hepatol.* 2015;3:17-26. **4.** Bylesjö I et al. *Scand J Clin Lab Invest.* 2009;69:612-618. **5.** Ventura P et al. *Eur J Intern Med.* 2014;25:497-505. **6.** Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet.* 2015;86:17.20.1-17.20.26. **7.** Besur S et al. *Metabolites*. 2014;4:977-1006.

Summary

Definition and classification of porphyria

- Porphyria is a group of at least 8 metabolic disorders caused by alterations in enzymes involved in the heme biosynthesis pathway[1]
- Categorized as AHP or photocutaneous porphyria based on clinical manifestations[2]
  - The signs and symptoms of AHP are due to increased levels of the neurotoxic intermediates ALA and PBG, leading to nervous system injury[2]
  - The signs and symptoms of photocutaneous porphyria are caused by increased levels of photosensitizing porphyrins[2]

AHP associated with debilitating and life-threatening signs and symptoms

- The cardinal presentation of AHP is severe, diffuse abdominal pain and other signs and symptoms (eg, nausea/vomiting, limb pain/weakness) that can progress to neurologic damage and even death[3]
- The term *acute* hepatic porphyria does not capture the frequent prolonged and chronic clinical features of this disease[3]

Is the prevalence of AHP higher than thought?

- The combined prevalence of AHP subtypes has been estimated to be approximately 5 cases/100,000[3]
- However, the prevalence of AHP may be higher than current estimates because these estimates are usually limited to those with symptomatic disease[4]
- AHP is also associated with delayed diagnosis and misdiagnosis[3]

1. Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet.* 2015;86:17.20.1-17.20.26. **2.** Bissell DM et al. *N Engl J Med.* 2017;377:862-872. **3.** Anderson KE et al. *Ann Intern Med.* 2005;142:439-450. **4.** Bissell DM, Wang B. *J Clin Transl Hepatol.* 2015;3:17-26.