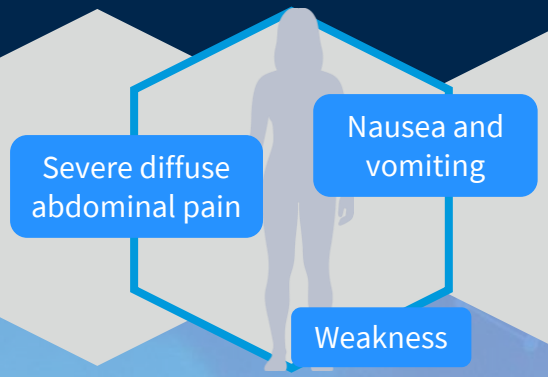
# Accurate, Prompt Diagnosis of AHP is Essential to Reduce the Risk of Serious Chronic and Acute Disease Complications[1,2]

Click on '⊕' to learn more

## Diagnostic Scenario*

**40-year-old female presents with…**




**These key clinical features should raise suspicion of AHP[2]**

Note that not all patients will appear with severe diffuse abdominal pain.[3]

- Patients with key clinical features should be considered for AHP screening, including AIP which corresponds to ~80% of AHP cases[4,5] ⊕
- AHP is a group of rare diseases with variable presentation and non-specific manifestations[1] ⊕
- Diagnosis of AHP is frequently delayed, with an average of 15 years from onset of symptoms to diagnosis[6] ⊕
- Undiagnosed AHP is associated with significant patient burden and can lead to serious long-term complications[2] ⊕

## Once suspected, appropriate testing can help diagnose AHP[2]

AGA Clinical Practice Update[4] → Symptoms suggestive of AHP → **Spot urine** for ALA, PBG, creatinine[†,‡] → Urine ALA/PBG >10 mg/g creatinine[§] → AHP confirmed → **Genetic testing** to determine AHP type

Early and accurate diagnosis of AHP starts with:

- An **accurate history**
- First-line screening **biochemical tests**
- Confirmatory **genetic testing** if first-line testing is abnormal[7]

Biochemical testing measuring ALA, PBG, and Cr in a random urine sample[4] ⊕

Urine ALA/PBG normal → AHP excluded as cause of symptoms

Genetic testing should be used to confirm the AHP type or for screening of individuals with a first-degree family member with AHP[4] ⊕

*Hypothetical case; †Urine total porphyrins are not recommended as a screening test for AHP. Testing is most informative if done while patients are symptomatic;[4] ‡During acute attacks, both ALA and PBG are elevated at least 5-fold the ULN;[4] §If only ALA is elevated, check lead levels and urine organic acids to rule out lead poisoning and hereditary tyrosinemia.[4]

⊕ Click for abbreviations and references

**Intended for US HCPs**

Scan the QR code to learn more on the RNAi Science website



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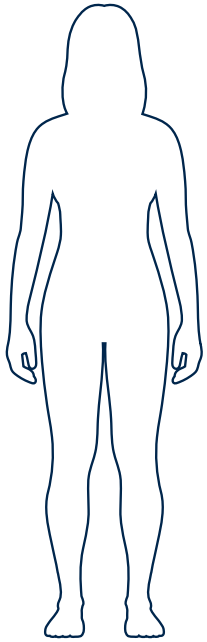
# Consider AHP in Any Patient, Especially Any Woman of Childbearing Age, Who Presents with Unexplained Recurrent, Severe Abdominal Pain[4,*]

## Patient Profile



Age of onset of clinical manifestation varies, but the majority of patients are aged 15–50 years at onset[4,8]

Women are predominantly affected[4,9]

**~1 in 1600–1700**
Mutation prevalence of the most common type of AHP, AIP[10,11]

**~1%**
Estimated phenotypic penetrance of symptomatic disease among AIP gene carriers[4]

**~10 in 1,000,000**
People diagnosed with symptomatic AIP in the US[12]

*Note that not all patients will appear with severe diffuse abdominal pain.[3]

Click for abbreviations and references

# Key Symptoms of AHP That Should Prompt Referral for Testing Include Severe Diffuse Abdominal Pain, Nausea, and Vomiting

AHP is characterized by chronic symptoms, acute attacks, and long-term complications[13–16]

As a multi-system disease, AHP does not fall under the responsibility of a single medical specialty[1]

**Pick your speciality to learn more about the common presenting symptoms of AHP:**

- Hepatology
- Hematology
- Gastro-enterology
- Neurology
- Psychiatry
- Other

Click for abbreviations and references

# Key Symptoms of AHP Which Should Prompt Referral for Testing Include Severe Diffuse Abdominal Pain, Nausea, and Vomiting[1,3,13]

## Symptoms experienced by patients with AHP*,†

**Gastrointestinal symptoms**
- ✓ **Nausea**
- ❑ Constipation
- ✓ **Loss of appetite**
- ✓ **Vomiting**[A]
- ❑ Heartburn

**Mood or sleep symptoms**
- ✓ **Tiredness**
- ❑ Trouble sleeping
- ❑ Anxiety
- ❑ Trouble concentrating
- ❑ Feeling unmotivated[C]
- ❑ Hallucinations

**Pain symptoms**
- ✓ **Abdominal pain**
- ❑ Arm/leg pain
- ❑ Back pain
- ❑ Muscle pain
- ❑ Headache
- ❑ Other pain

**Other symptoms**
- ✓ **Changes in urine color**
- ❑ Weakness
- ❑ Numbness
- ❑ Fast heartbeat
- ❑ Sweating[A]
- ❑ Blisters/rashes

All symptoms can be both acute and chronic unless otherwise stated.
[A]Acute symptom only; [C]Chronic symptom only.

## Hepatologist

As a hepatologist, consider **symptoms of hepatic disorder** in **blue** in your patients that may be **suggestive of AHP**

Take a moment to consider **the other symptoms of AHP**:
- Does your patient have any other symptoms that match the AHP symptom profile?
- Does your patient fit the AHP patient profile?

If yes, consider testing for AHP as a **differential diagnosis**

*These are not all the symptoms of AHP; †Frequently reported acute symptoms (≥50%) by patients during an attack at baseline and most commonly reported chronic symptoms (proportion of patient reporting chronic symptoms at baseline n=73) in EXPLORE-A (N=112)[3]

Click for abbreviations and references

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## Hematologist

As a hematologist, consider **symptoms** in your patients that may be **suggestive of AHP**

- Does your patient fit the AHP patient profile?

If yes, consider testing for AHP as a **differential diagnosis**

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## Gastroenterologist

As a gastroenterologist, consider **GI symptoms** in **blue** in your patients that may be **suggestive of AHP**

Take a moment to consider **the other symptoms of AHP**:
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## Neurologist

As a neurologist, consider **neurological symptoms** in **blue** in your patients that may be **suggestive of AHP**

Take a moment to consider **the other symptoms of AHP**:
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If yes, consider testing for AHP as a **differential diagnosis**

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## Psychiatrist

As a psychiatrist, consider **psychological symptoms** in **blue** in your patients that may be **suggestive of AHP**

Take a moment to consider **the other symptoms of AHP**:
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- Does your patient fit the AHP patient profile?

If yes, consider testing for AHP as a **differential diagnosis**

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## Identifying Symptoms

Consider **symptoms** in your patients that may be **suggestive of AHP**

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If yes, consider testing for AHP as a **differential diagnosis**

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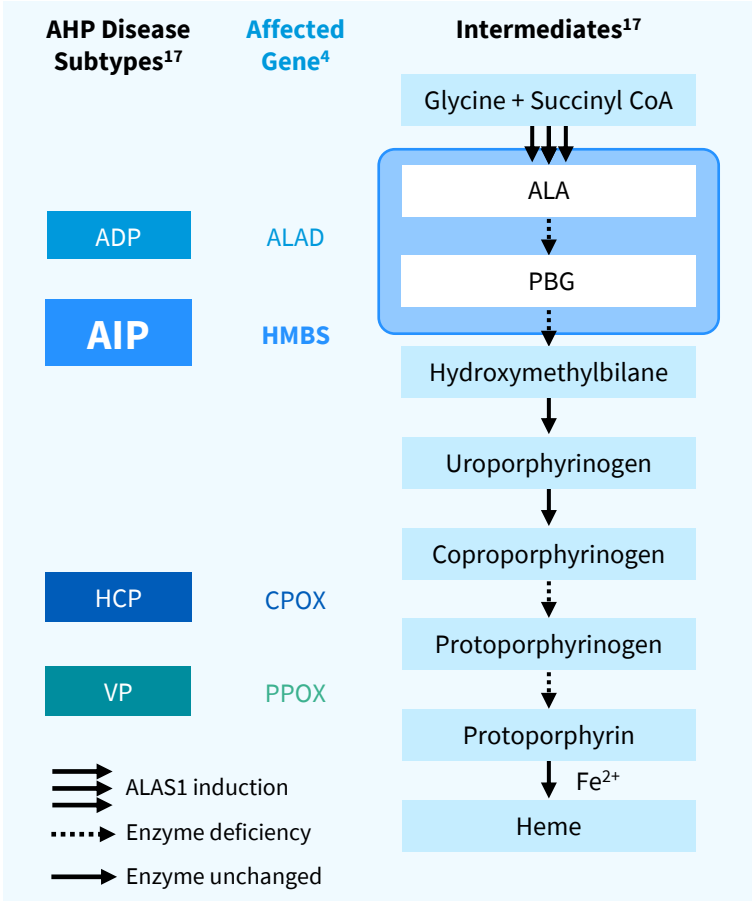
# AHP Arises from Genetic Variants that Disrupt the Heme Biosynthesis Pathway




**Neurotoxic accumulation[15,16]**

## AHP pathophysiology

- Triggers induce heme synthesis through ALAS activation[19]
- Resulting accumulation of toxic heme metabolites, leading to symptoms in several organ systems[19]

**Severe, diffuse pain in abdomen, chest, back[1,18,20]**

**Weakness, numbness, respiratory failure[1,18,20]**

**Confusion, anxiety, seizures, hallucinations[1,18,20]**

Click for abbreviations and references

# Characteristics of AHP Types

| AHP Type[21] | Sex[21] | Age of Onset | Typical Presenting Symptoms[21] | | Estimated % of AHP |
|---|---|---|---|---|---|
| | | | Acute Attacks | Cutaneous | |
| AIP | Symptomatic patients are predominantly female[21–23] | 15–50 years[4,8] | ✓ | | **Most prevalent** ~80%[5] |
| VP | | | ✓ | ✓ | Less prevalent[24] |
| HCP | | | ✓ | ✓ | Less prevalent[24] |
| ADP | All recorded symptomatic patients have been male[21] | Variable[19] | ✓ | | **Least prevalent** 12 cases ever reported worldwide[25] |

Click for abbreviations and references

# Delayed Diagnosis Can Negatively Impact Patient Morbidity and Mortality

Patients often **present to emergency departments** where less common causes of typical AHP presenting symptoms (e.g. abdominal pain) are often not considered[1]

Patients report **frequent hospitalizations and visits to multiple specialists before diagnosis**, with many being labelled as "drug seekers" because of their recurrent need for pain relief[2]

"Very few doctors understand what porphyria is or even how to treat it" *Patient with AHP*[5]

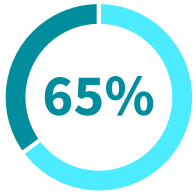
"I have to take all these stupid medications, and there's so much stigma in society about prescription pain meds" *Patient with AHP*[5]

Many patients experience delays in diagnosis or misdiagnosis, resulting in **inappropriate or harmful treatments**, including certain medications that can upregulate the heme biosynthesis pathway and **worsen AHP symptoms**[1]

Inaccurate diagnoses may also result in **ineffective surgical interventions**, for example appendectomy or hysterectomy[4]

Click for abbreviations and references

# Patients with AHP Can Experience an Array of Chronic Symptoms, Which Fluctuate in Severity, Alongside Acute Attacks Resulting in Hospitalization Which Leads to High Disease Burden[3,5]




**65% of patients with recurrent attacks experience chronic symptoms, most commonly pain, tiredness, anxiety, and nausea, with 46% of patients experiencing these symptoms daily[3,*]**

"When it's chronic, it's something I'm **constantly having to manage**… there will be pains where I feel like I'm getting **stung by a swarm of bees** or something like that. But it doesn't get to the point where I'm having to go to the emergency room and vomiting"[5]

**Click to learn more about the long-term complications of AHP that add to disease burden**

Click for abbreviations and references

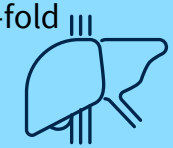
*EXPLORE-A (N=112) included patients who had 3 attacks or more or were receiving prophylactic treatment.[3]

# Delayed Diagnosis Can Lead to the Development of Serious Long-Term Complications Which Add to the Disease Burden Experienced by Patients with AHP

## Long-term complications of AHP

### Primary liver cancer

- Hepatoma should be considered if a patient develops abdominal pain after long-term remission[19]
- A Norwegian registry cohort study found the risk of **primary liver cancer** was 108-fold higher over the lifetime of patients with AHP (n=251) versus controls[26]



### Chronic sustained hypertension

- **Hypertension is more prevalent** among patients with AIP compared with the general population[19]

### Chronic kidney disease

- ALA and PBG have potential nephrotoxic effects, leading to oxidative stress and tissue injury[27]
- **Repeated AHP attacks lead to acute kidney injury[27]**

### Neuronal damage

- Both experimental and clinical data demonstrated that ALA accumulation has highly neurotoxic effects, responsible for **neuropathy and axonal degeneration** via multiple proposed mechanisms[28,29]

Click for abbreviations and references

# Practical Guidance for Measuring PBG and ALA

**Substantial elevation of urine PBG and ALA is a distinctive biochemical feature of AHP, and therefore, a key diagnostic tool[4]**

## Ordering tests

- **Porphyrin tests do not include ALA and PBG**, as they are porphyrin precursors[4]
- It is key to request the correct test to ensure informative results are obtained[1,7]

## Analyzing results

- **Substantial PBG elevation has a high degree of specificity and sensitivity for AIP, VP, or HCP** because an elevation many times above normal does not occur in any other medical condition[1]
  - ALA elevation is indicative of the ultra-rare AHP subtype ADP, in which PBG levels are normal or only slightly elevated[1]
- ALA and PBG excretion should be **normalized to creatinine** to adjust for differences in the degree of urinary concentration[4]
  - The ULN for ALA and PBG are 1.47 and 0.137 mmol/mol Cr, respectively[30]

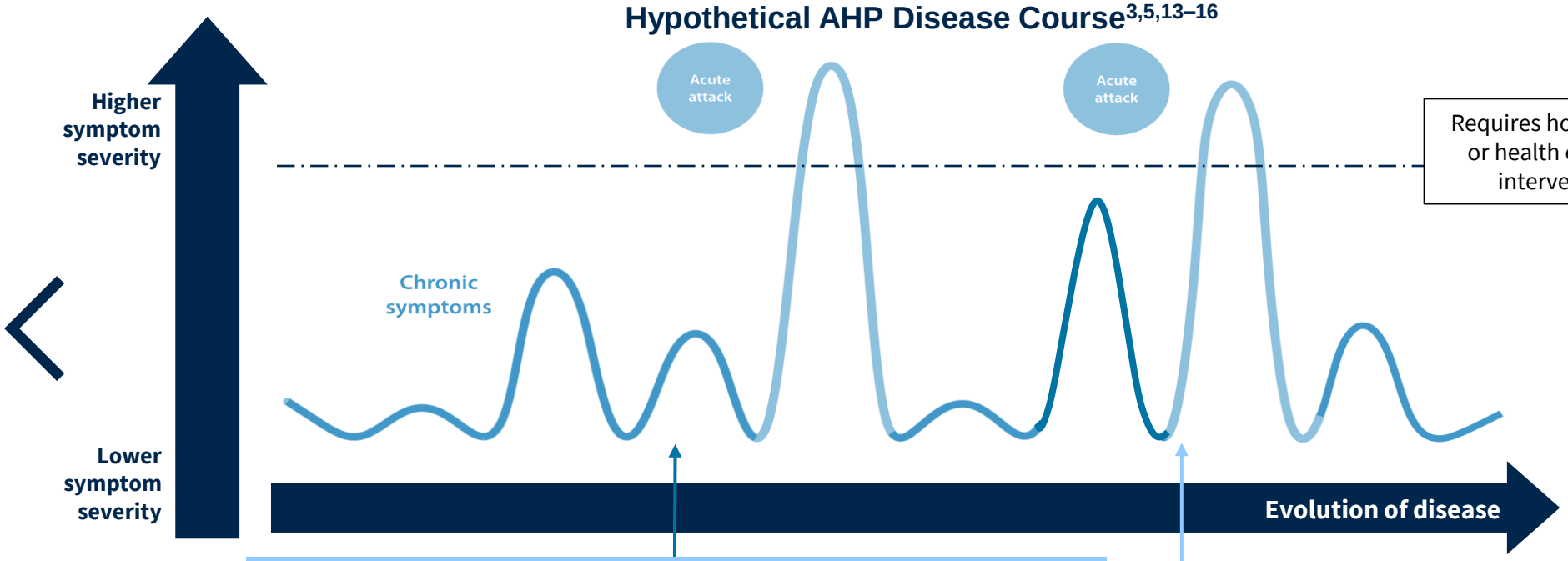
## Considerations

- Both ALA and PBG can be measured with high sensitivity and specificity, but both often require large reference laboratories and **results can take 1–2 weeks to be reported[4]**
  - Despite challenges, it is important to test for ALA and PBG as biochemical testing is required for AHP diagnosis[4]

Click for abbreviations and references

# ALA and PBG Levels Can Vary Depending on AHP Type and Timing of Measurement, Therefore Repeat Testing May be Required for a Diagnosis

## Hypothetical AHP Disease Course[3,5,13–16]




**Testing in between acute attacks[4]**

- In patients with recurrent acute attacks, urine ALA and PBG are typically elevated even at baseline between attacks
  - Studies of patients with AIP found that ALA and PBG can remain elevated in urine for months to years after an acute attack*
- If testing is performed in patients with sporadic AIP when they are asymptomatic , they can have normal urine ALA and PBG values. Confirmation testing may require repeat testing during an acute attack

**Testing during an acute attack[4]**

For most patients with AHP, testing for urine ALA, PBG, and Cr is most useful during an acute attack

*ALA and PBG levels can fall quickly after an acute attack in patients with HCP or VP.[4]

Click for abbreviations and references

# Genetic Counselling is Recommended for Patients and Carriers[4]

Genetic testing of the 4 genes *ALAD*, *HMBS*, *CPOX*, and *PPOX* leads to ADP, AIP, HCP, and VP diagnosis, respectively

Although genetic testing can confirm a diagnosis, it is **not recommended for initial screening**

- This is because the **estimated phenotypic penetrance** of symptomatic disease is **approximately 1%** of AIP gene carriers
- This increases to **>20%** in **families of symptomatic patients**

Once the familial pathogenic variant has been identified in the patient, **first-degree family members should be screened** to identify at-risk patients. Those who are mutation carriers should receive genetic counselling

Click for abbreviations and references

# Abbreviations and References

A, acute; ADP, ALA dehydratase-deficient porphyria; AHP, acute hepatic porphyria; ALAD, aminolevulinate dehydratase; ALAS1, ALA synthase 1; AIP, acute intermittent porphyria; ALA, δ-aminolevulinic acid; C, chronic; Cr, creatinine; CoA, coenzyme A; CPOX, coproporphyrinogen oxidase; CYP450, cytochrome P450, HCP, hereditary coproporphyria; HMBS, hydroxymethylbilane synthase; PBG, porphobilinogen; PPOX, protoporphyrinogen oxidase; ULN, upper limit of normal; VP, variegate porphyria.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