



MODULE **04**

# Patient Burden of Acute Hepatic Porphyria (AHP)



## The Burden of Disease for Patients in Their Own Words

*The many dimensions of AHP adversely affecting patients' lives:*

- Debilitating symptoms<sup>1-3</sup>
- Once an exacerbation occurs, patients generally feel under constant threat of another<sup>3</sup>
- Patients' daily functioning is negatively impacted with increased disability and decreased employment<sup>2-5</sup>
  - 20% to 63% unemployment according to recent studies

“ My nausea is uncontrollable. And I—**my body just doesn't feel right anymore.**”

Simon A et al. *Patient*. 2018.

“ **It's completely unpredictable.** There's no way I could be a reliable employee to somebody because I could not guarantee that I will be there tomorrow for work.”

Simon A et al. *Patient*. 2018.

“ Some days I just feel like I hurt so bad that it's like I actually will think out loud, how is porphyria compatible with life... **You can't live like that.**”

Simon A et al. *Patient*. 2018.

“ **When I was still working,** I was a computer technician, and I had calls to make and didn't feel good. Calls would build up, customers would complain, **and that would lead straight into an attack.**”

Naik H et al. *Mol Genet Metab*. 2016.

1. Bonkovsky HL et al. *Am J Med*. 2014;127:1233-1241. 2. Naik H et al. *Mol Genet Metab*. 2016;119:278-283. 3. Simon A et al. *Patient*. 2018;11:527-537. 4. Bylesjö I et al. *Scand J Clin Lab Invest*. 2009;69:612-618. 5. Ko JJ et al. *ACG* 2018. Poster.

# Multisystem Signs and Symptoms That May Be Associated with AHP



## CENTRAL NERVOUS SYSTEM (CNS) MANIFESTATIONS<sup>1,2</sup>

### Neurologic

- Seizures
- Confusion
- Insomnia

### Psychiatric

- Mood disorders (anxiety, depression)
- Psychosis



## PERIPHERAL NERVOUS SYSTEM MANIFESTATIONS<sup>1,2</sup>

### Neurologic

- Neuropathic pain in limb
- Sensory loss
- Muscle weakness
- Fatigue

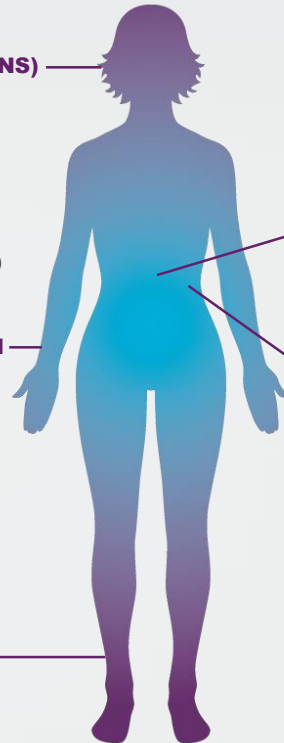
### Respiratory

- Respiratory failure



## CUTANEOUS MANIFESTATIONS (VP AND HCP ONLY)<sup>2</sup>

- Lesions on sun-exposed skin



## AUTONOMIC NERVOUS SYSTEM MANIFESTATIONS<sup>1,2</sup>

### Gastrointestinal

- Severe, diffuse abdominal pain, nausea, vomiting, constipation, diarrhea

### Cardiovascular

- Hypertension
- Tachycardia



## OTHER MANIFESTATIONS<sup>1,2</sup>

- Hyponatremia
- Reddish dark urine

HCP=hereditary coproporphyria; VP=variegate porphyria.

1. Pischik E, Kauppinen R. *Appl Clin Genet*. 2015;8:201-214. 2. Anderson KE et al. *Ann Intern Med*. 2005;142:439-450.

# Chronic Symptoms Can Occur in Some Patients with AHP

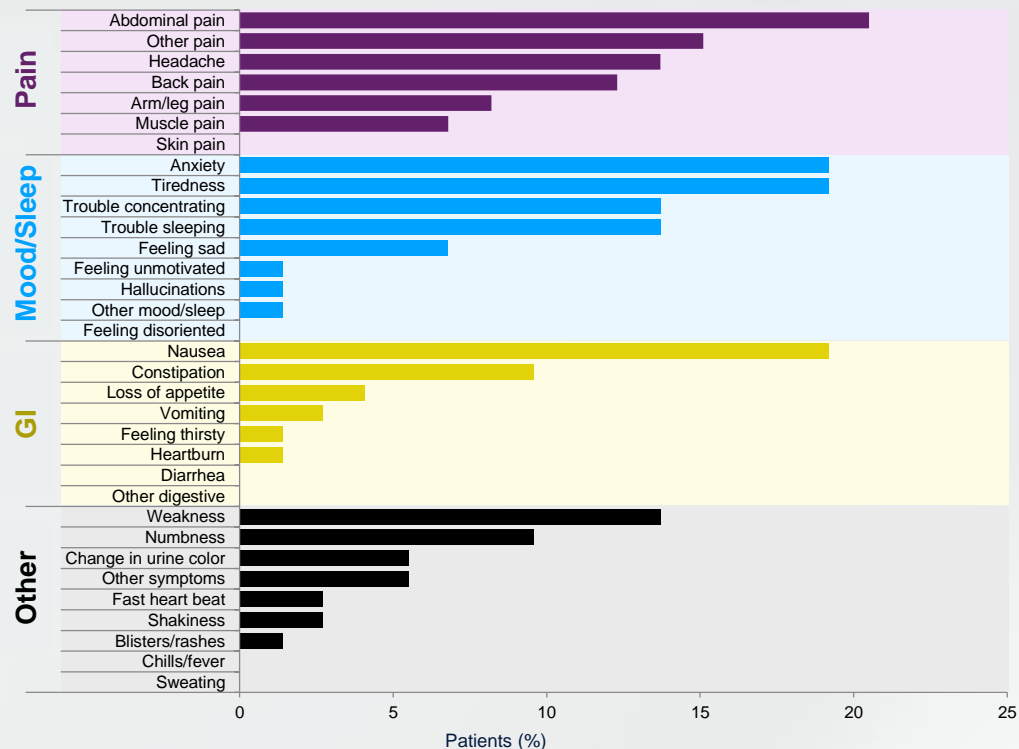
## Methods

- EXPLORE study—an observational, multinational, prospective, natural history study of 112 people living with recurrent exacerbations of AHP
- Key eligibility criteria
  - ≥3 exacerbations per year or use of prophylactic treatment

## Results

- 46% of patients reported daily symptoms
- 65% of patients reported chronic symptoms in between frequent attacks
  - Some of these patients were treated with hemin or opioid prophylaxis

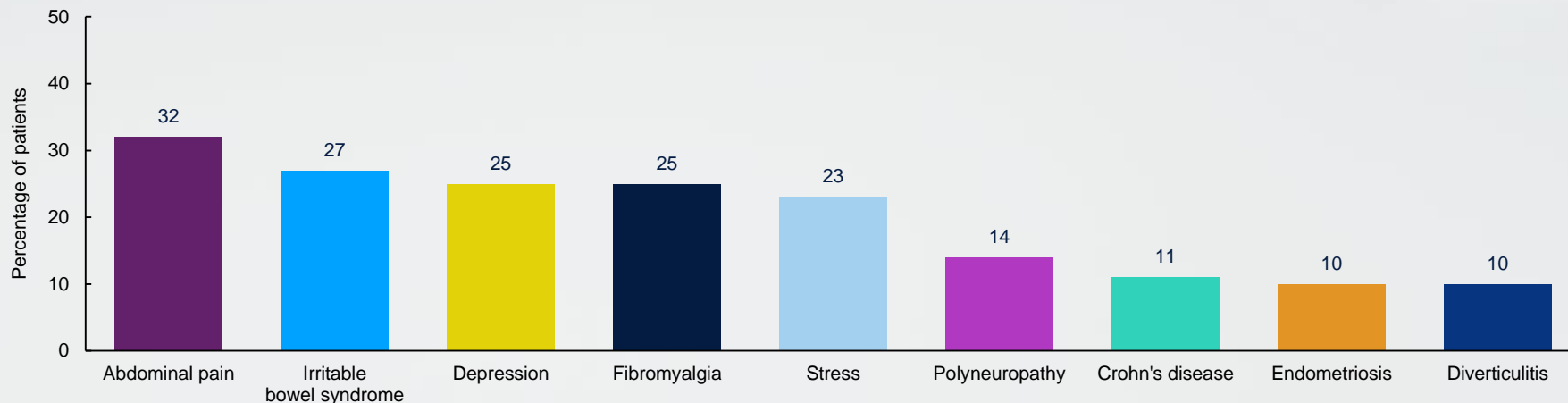
Chronic Symptoms Experienced Between AHP Exacerbations



Bonkovsky HL et al. AASLD 2018. Poster.

## Misdiagnosis of Patients with AHP Is Relatively Common

Commonly Reported Misdiagnoses of 546 Patients with AHP



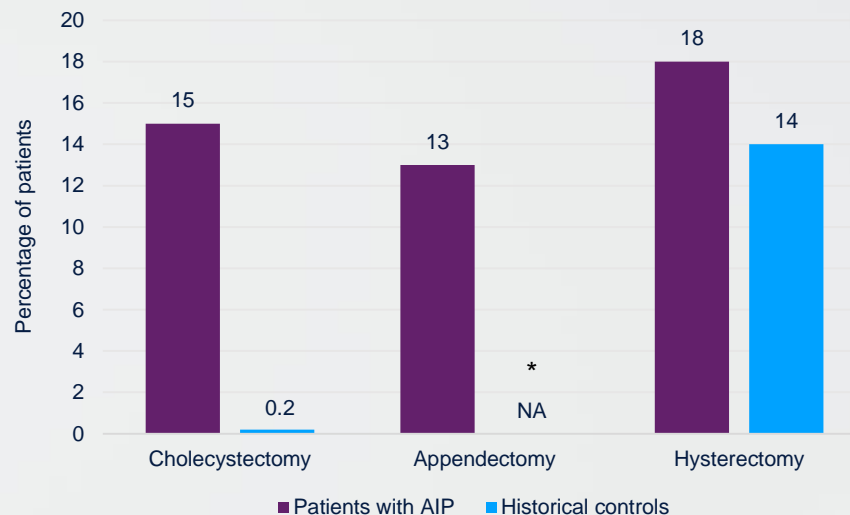
- From a retrospective review of 546 AHP patient charts submitted by 175 healthcare providers (HCPs) from the US, EU, Canada, and Japan
  - The most common HCP specialists were gastroenterologists, neurologists, and hepatologists
- 26% of patients with AHP were initially misdiagnosed while 31% were initially diagnosed correctly
  - 43% of patients had charts that did not clearly indicate whether a correct AHP diagnosis was made initially or whether it was preceded by any earlier misdiagnoses

Ko JJ et al. ACG 2018. Poster.

## Misdiagnosis or Delayed Diagnosis Can Involve Multiple Hospitalizations and Unnecessary Surgeries

- In an observational study of 108 patients with documented AHP from the US Porphyria Consortium
  - 90 patients had acute intermittent porphyria (AIP), the most common AHP
  - Diagnosis was delayed by a mean of 15 years
  - Among patients who reported a history of prior hospitalization, 55% were hospitalized 1 to 5 times in their lifetimes for exacerbations
  - Significantly more patients with AIP experienced unnecessary cholecystectomies ( $p < 0.0001$ ) compared to age and sex matched controls

Percentage of Patients with AIP Undergoing Unnecessary Surgeries vs Historical Controls

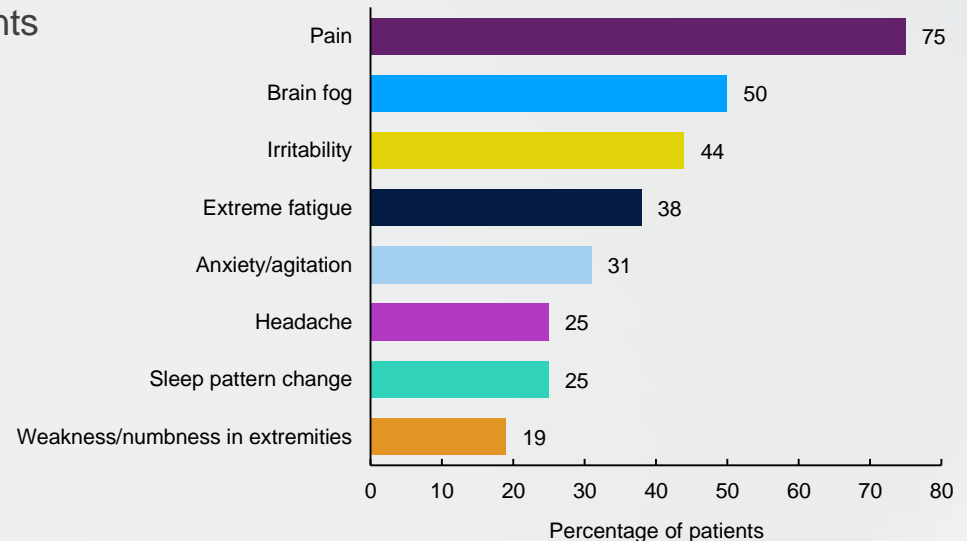


\*Data not reported.

## AHP Patients May Experience Prodromal Symptoms Before an Exacerbation

- In a National Institutes of Health (NIH)-sponsored longitudinal study of 16 patients with genetically documented AHP, 15 patients experienced recurrent AHP, defined as  $\geq 4$  exacerbations per year that required treatment
- Various prodromal symptoms were experienced by 100% of patients at least 24 hours before an exacerbation involving severe, diffuse abdominal pain

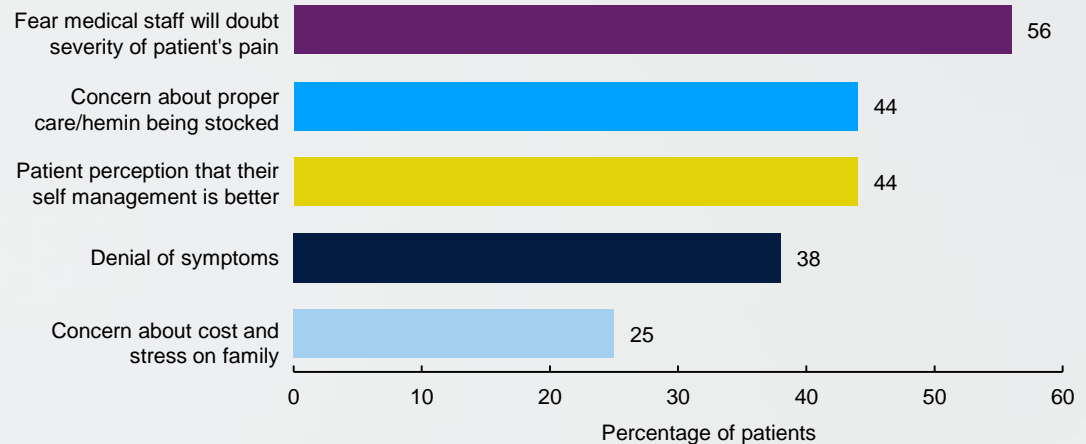
Most Frequent Prodromal Symptoms ( $\geq 19\%$ ) Experienced by Patients in NIH-Sponsored Trial (N=16)



# AHP Patients with Symptoms May Delay Going to the Hospital for Medical Care

- In the same NIH-sponsored study, AHP patients reported delaying seeking medical treatment despite prodromal symptoms
- Patients who had access to porphyria specialists and local knowledgeable physicians to manage their care had more favorable healthcare experiences

## Top Reasons for Patients' Delay in Seeking Medical Treatment Despite Experience of Prodromal Symptoms in NIH-Sponsored Trial (N=16)



Naik H et al. *Mol Genet Metab.* 2016;119:278-283.



# Symptomatic AIP Associated with Chronic Impairment

## Background

- A retrospective, population-based study of 356 latent and manifest/symptomatic AIP patients in Sweden over 4 years
  - Latent AIP patients were defined as gene carriers with no history of AIP symptoms
  - Manifest AIP patients experienced clinical symptoms during an exacerbation, with 87% reporting at least 1 or 2 symptoms in addition to abdominal pain
  - Follow-up study assessed long-term disability/sick leave due to symptomatic AIP (N=133)
  - Mean age for receiving disability was 45 years (range 21-61 years)

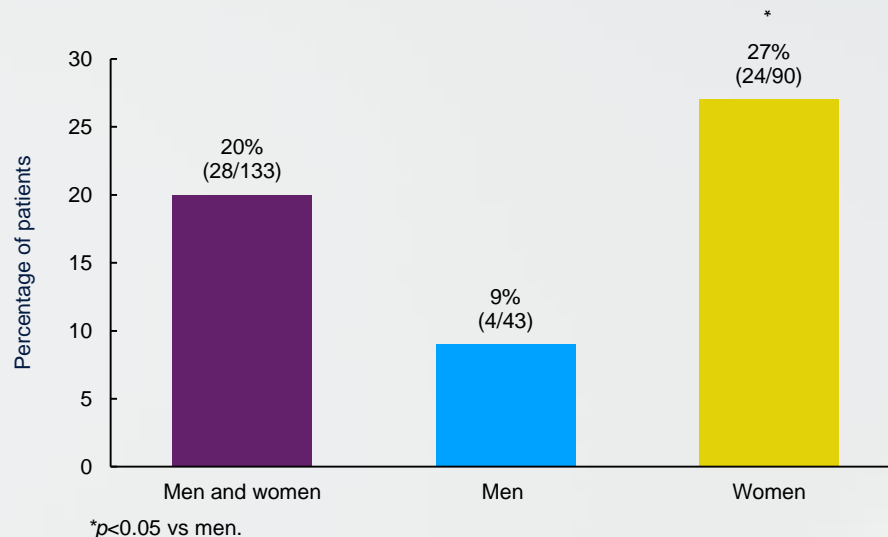
## Results

- 54% of patients with long-term disability/sick leave reported >10 exacerbations
- 46% reported chronic impairment
- Levels of urinary PBG and ALA remained above upper reference limit of normal in 79% and 42% of patients, respectively

ALA=aminolevulinic acid; PBG=porphobilinogen.

Bylesjö I et al. *Scand J Clin Lab Invest.* 2009;69:612-618.

## Percentage of Symptomatic Patients According to Gender Claiming Long-Term Sick Leave or Disability Pension Due to AIP (N=133)



# EXPLORE Natural History Study: Patients with AHP Have Diminished Quality of Life— Even Between Exacerbations

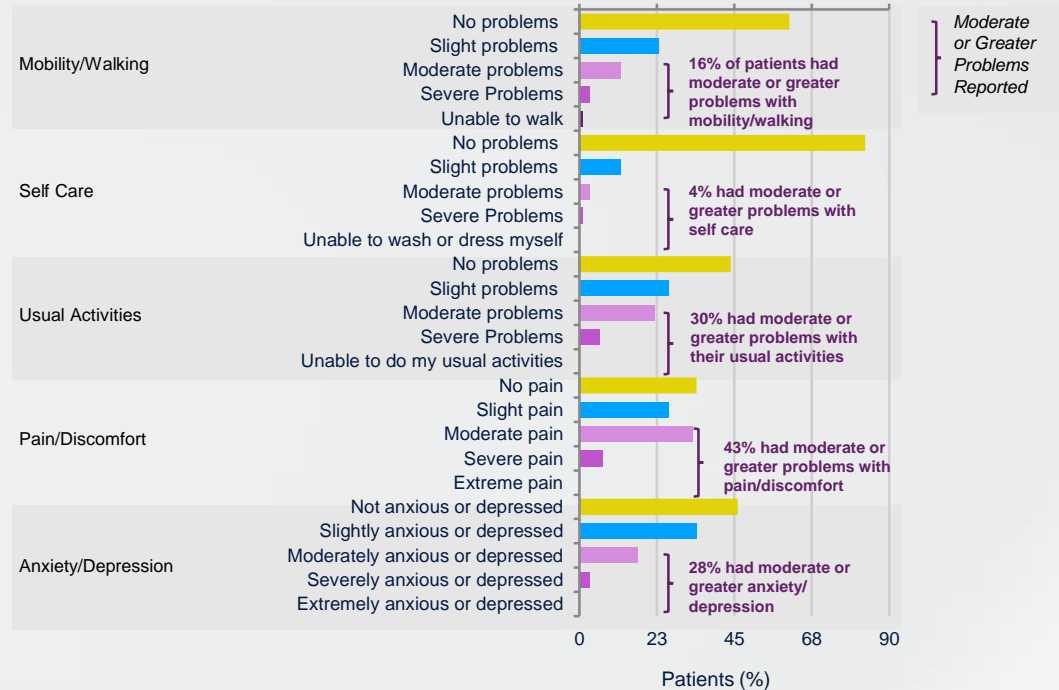
## Background

- Patient-reported outcomes substudy of 74 recurrent exacerbation patients who were surveyed using the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) assessment tool<sup>1</sup>
  - Key eligibility criteria: ≥3 exacerbations per year or use of prophylactic treatment

## Results

- The 0.80 EQ-5D-5L mean summary score was similar to diminished quality of life seen with common chronic diseases<sup>1</sup>
  - 0.77 mean score in patients with ulcerative colitis<sup>2</sup>
  - 0.79 mean score in patients with chronic obstructive pulmonary disease (COPD)<sup>3</sup>

Rating of Quality of Life Parameters Between Exacerbations by People with AHP (N=74)<sup>1</sup>



1. Gouya L et al. ICPP 2017. Presentation OC13. 2. Van Assche G et al. *Dig Liver Dis.* 2016;48:592-600. 3. Lin F-J et al. *BMC Med Res Methodol.* 2014;14:1-12.

# Recent Single-Center Study Demonstrated Diminished Quality of Life and Posttraumatic Stress Disorder Symptoms in Patients with AIP

## Background

- 27 female patients of reproductive age with genetically confirmed AIP from mainland China were evaluated
  - Median 1.7 exacerbations in the past year
  - Compared to 2410 healthy Chinese adults
- Quality of life assessment tool: Short Form-36 (SF-36, Chinese version)
- Posttraumatic stress disorder (PTSD) symptoms assessment: Impact of Event Scale–Revised (IES-R)

## Results

- AIP patients had significantly lower scores compared to the general population on 2 components of SF-36: physical functioning and mental health
- AIP patients had significantly higher scores on the IES-R ( $p < 0.001$ ), indicating PTSD symptoms
  - In a qualitative assessment, some patients stated that they were fearful of future exacerbations and even of menses as a potential precipitating factor

Yang J et al. *Biomed Res Int.* 2018;2018:1-6.

## Comparison of SF-36 Subscale Scores in 27 Women with Confirmed AIP vs Historical Healthy Controls

Scale	Score in AIP Patients*	Norm-Based Score* (N=2410)	p value
Physical functioning	85.74 ± 11.67	91.83	0.01
Role physical	64.81 ± 57.74	82.43	0.13
Bodily pain	77.96 ± 22.81	83.98	0.18
General health	51.67 ± 25.84	55.98	0.39
Vitality	57.96 ± 18.96	60.27	0.53
Social functioning	85.65 ± 23.44	91.19	0.23
Role emotional	69.13 ± 54.64	71.62	0.81
Mental health	65.19 ± 19.15	72.79	0.049

\*Scores for each category range from 0 to 100, where 100 represents the best health status.

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# Clinical and Lifestyle Burden of AHP

## Clinical burden of disease

- AHP—a group of rare genetic diseases almost universally associated with acute exacerbations involving severe, diffuse abdominal pain (neurovisceral pain)<sup>1,2</sup>

## Challenges with diagnosis

- Patients are frequently misdiagnosed with other more common diseases (26% in one recent study) or undiagnosed<sup>3,4</sup>
- Delay in diagnosis can result in multiple hospitalizations and unnecessary surgeries<sup>4</sup>

## Lifestyle burden of disease

- Patients with AHP can have a high burden of disease, which limits employment, daily functioning, and quality of life<sup>5-8</sup>

1. Bissell DM, Wang B. *J Clin Transl Hepatol*. 2015;3:17-26. 2. Ramanujam V-MS, Anderson KE. *Curr Protoc Hum Genet*. 2015;86:17.20.1-17.20.26. 3. Ko JJ et al. ACG 2018. Poster. 4. Bonkovsky HL et al. *Am J Med*. 2014;127:1233-1241. 5. Naik H et al. *Mol Genet Metab*. 2016;119:278-283. 6. Simon A et al. *Patient*. 2018;11:527-537. 7. Bylesjö I et al. *Scand J Clin Lab Invest*. 2009;69:612-618. 8. Gouya L et al. ICPP 2017. Presentation.