What is Alkaptonuria (AKU)?

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AKU is an ultra-rare genetic metabolic disorder that prevents the breakdown of homogentisic acid (HGA), which is naturally produced during protein catabolism.[1]

Cause of AKU

AKU is caused by mutations that affect the function of homogentisate 1,2-dioxygenase (HGD), which impairs the tyrosine degradation pathway at HGA.[2]

The deposition of HGA leads to osteoarthritis and ochronosis, discoloration in skin and cartilage, among other complications affecting the kidney, heart and connective tissue. While AKU does not seem to affect life expectancy, it can impact a patient's quality of life significantly through developed pain, and reduced joint mobility.[2,3]

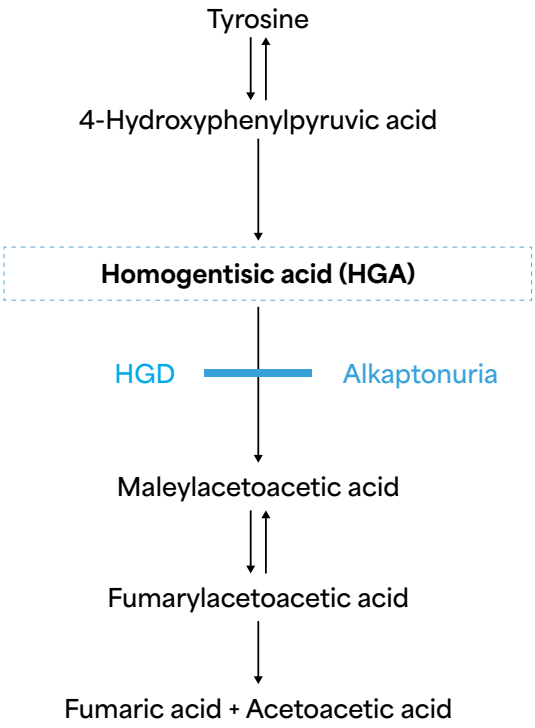

Fig. 1. Tyrosine catabolism pathway. 4-HPPD, 4-hydroxyphenylpyruvate dioxygenase; HGD, homogentisate 1,2-dioxygenase.[4]

Also known as Black Bone Disease

Typically diagnosed in adulthood[5]

1 in 250,000 people are estimated to have AKU in the US[1]

Inherited as an autosomal recessive trait

Affects both men and women

Often mistaken for other types of arthritis or skin conditions[2]

Symptoms

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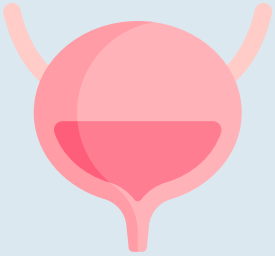
Symptoms of AKU are driven by the accumulation of HGA, which results in:

Osteoarthritis

- Over time, the build-up of HGA leads to severe early-onset osteoarthritis. HGA builds up around the bones and cartilage, turning them black and brittle.[1]
- Adult patients experience severe pain in their daily lives and can go on to require multiple joint replacements.[1]
- Typically, patients start complaining of back pain in their 30s, and knee pain in their 40s, while hip and shoulder pain often occurs later by their 50s.[1]

Black spots in the eyes and discoloration of the ears

- AKU patients can develop black spots in their eyes and a blue/black discoloration of cartilage (e.g. on the ears or around the nose).[1]
- These black spots will not affect vision, cause any pain, or other complications.[1]
- The black eye spots can appear at different ages, but they will eventually appear in almost all patients living with AKU.[1]



Other symptoms

- Dark urine after it has been exposed to air.[6]
- Kidney and bladder stones.[1]
- Skin can take on a blue/black speckled discoloration.[1]
- Sweat can stain clothes brown.[1]
- Cardiac complications.[6]

Diagnosing AKU

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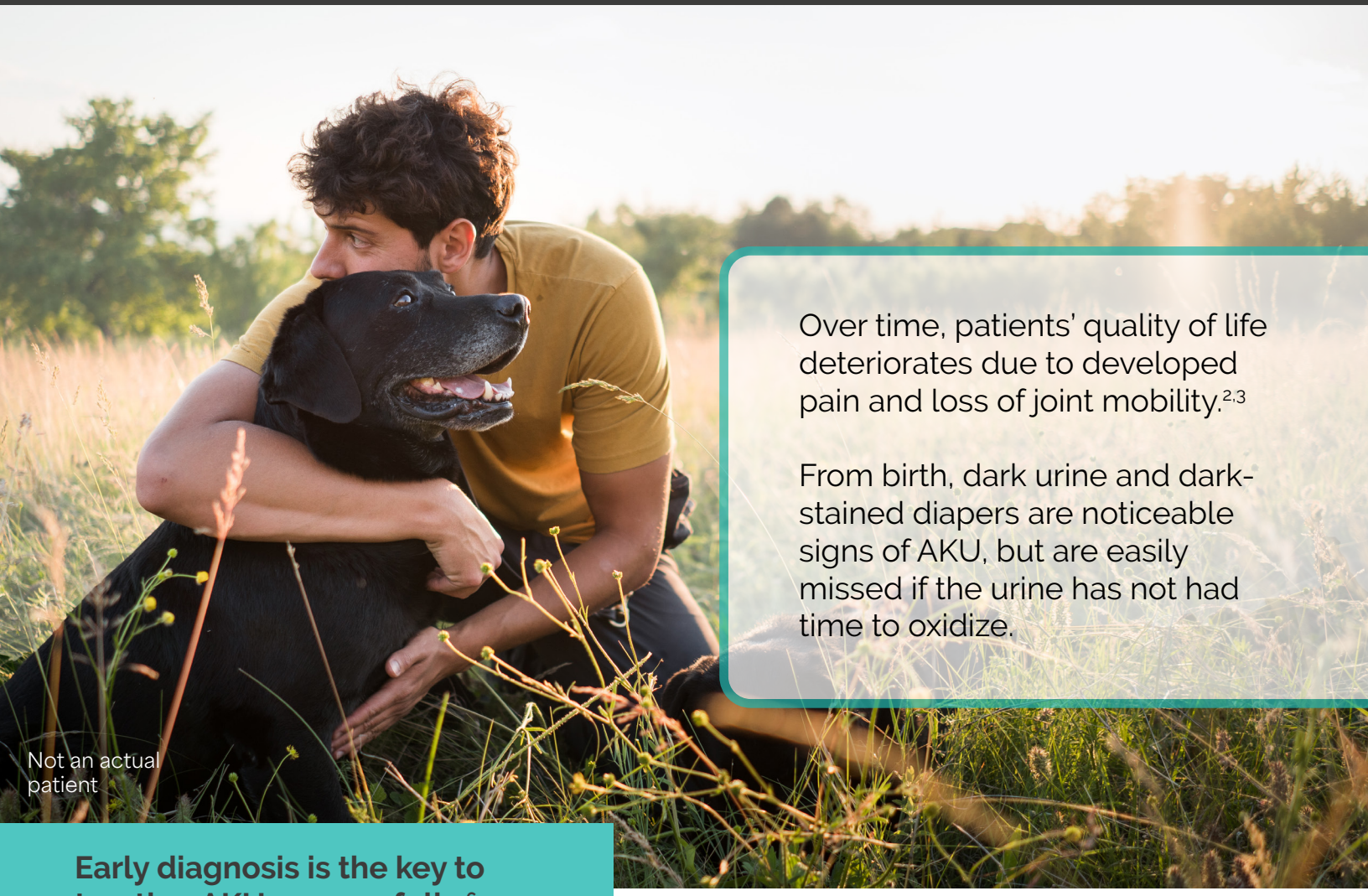

Over time, patients' quality of life deteriorates due to developed pain and loss of joint mobility.[2,3]

From birth, dark urine and dark-stained diapers are noticeable signs of AKU, but are easily missed if the urine has not had time to oxidize.

Early diagnosis is the key to treating AKU successfully.[6]

Given how rare the condition is, its slow progression, and variable presentation, AKU diagnosis is challenging.

AKU is not included in newborn screening programs in the US. Typically, patients are diagnosed in adulthood, when tissue damage manifests clinically.[5]

AKU can be determined by:

- Testing urine for HGA[6]
- Genetic testing to identify biallelic abnormalities in HGD[6]
- Patient history
- Physical examination

The sooner adult patients initiate treatment, the greater the potential to slow the progression of the non-reversible symptoms of ochronosis.[7]

Diagnosing AKU

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More Information

Watch this webinar from National Institutes of Health (NIH) experts, Dr Wendy J. Introne, MD, and Dr William A. Gahl, MD, PhD. They will guide you through diagnostic strategies and the latest developments in evidence-based treatment for AKU: **harliku.com/hcp/aku-webinar/**

The following sites have more information about AKU*:

AKU Society of North America - https://akusocietyna.org/

AKU Society - https://akusociety.org/

National Organization for Rare Disorders (NORD) - https://rarediseases.org/rare-diseases/alkaptonuria/

Alkaptonuria by Wendy J Introne, MD, et al - https://www.ncbi.nlm.nih.gov/sites/books/NBK1454/

Alkaptonuria by Alaa F. Sharabi, et al - https://www.ncbi.nlm.nih.gov/books/NBK560571/

Alkaptonuria: Current Perspectives by Andrea Zatkova, et al - https://pubmed.ncbi.nlm.nih.gov/32158253/

Natural History of Alkaptonuria by Chanika Phornphutkul, et al - https://www.nejm.org/doi/full/10.1056/NEJMoa021736

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References: 1. AKU Society. Available at https://akusociety.org/ (Accessed December 16, 2025). **2.** Introne WJ, Perry M, Chen M. 2003 (updated 2021). Alkaptonuria. Available at: https://www.ncbi.nlm.nih.gov/sites/books/NBK1454/ [Accessed: May 29 2025]. **3.** Zatkova, A., et al (2020). Alkaptonuria: Current Perspectives. The application of clinical genetics, 13, 37–47. doi:10.2147/TACG.S186773. **4.** Sharabi, A.F. and Goudar, R.B. (2023). Alkaptonuria. [online] PubMed. Available at: https://www.ncbi.nlm.nih.gov/books/NBK560571/. **5.** NORD, Alkaptonuria, Available at (online) (https://rarediseases.org/rare-diseases/alkaptonuria/ (Accessed March 13, 2025). **6.** Phornphutkul, C., et al. (2002). Natural history of alkaptonuria. The New England Journal of Medicine, [online] 347(26), pp.2111–2121. doi:https://doi.org/10.1056/NEJMoa021736. **7.** Ranganath L, et al, 2018, Nitisinone arrests ochronosis and decreases rate of progression of Alkaptonuria: Evaluation of the effect of nitisinone in the United Kingdom National Alkaptonuria Centre .Mol Genet. https://pubmed.ncbi.nlm.nih.gov/30055994/

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