Case Report ISSN: 2689-1077

Genetics & Molecular Medicine

Alkaptonuria in Latina Populations: A Comprehensive Review of Genetics, Pathophysiology, and Clinical Outcomes

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Received: 05 Jan 2026; **Accepted:** 12 Feb 2026; **Published:** 23 Feb 2026

Citation: Ashley S Membreno Lopez, Cara Green, Camrynn Cutchin, et al. Alkaptonuria in Latina Populations: A Comprehensive Review of Genetics, Pathophysiology, and Clinical Outcomes. Genet Mol Med. 2026; 8(1): 1-7.

ABSTRACT

Alkaptonuria represents one of the first recognized inborn errors of metabolism yet remains an understudied rare genetic disorder with profound implications for chronic pain management and quality of life. This review examines the genetic architecture, pathophysiological mechanisms, psychological burden, and social determinants influencing clinical outcomes in alkaptonuria, with particular attention to epidemiological patterns in Latina populations. Despite global prevalence estimates of 1 in 250,000 to 1 million individuals, certain populations demonstrate markedly elevated disease frequency, most notably in the Dominican Republic where prevalence approaches 1 in 19,000. Understanding these population-specific patterns illuminates both founder effects and potential gene-environment interactions that shape disease expression. The progressive nature of alkaptonuria-related arthropathy creates a substantial chronic pain burden beginning in the third decade of life, necessitating multidimensional approaches to care that address not only biomedical mechanisms but also psychological adaptation and social determinants of health access.

Keywords

Alkaptonuria, Latina health, Chronic pain, Rare genetic disorder, Genetic epidemiology, Health disparities.

Introduction

In his landmark 1908 Croonian Lectures, Sir Archibald Garrod described alkaptonuria as an exemplar of the newly conceived concept of "inborn errors of metabolism," establishing foundational principles that would transform our understanding of genetic disease. More than a century later, alkaptonuria continues to provide critical insights into the intersection of monogenic disorders, chronic pain syndromes, and health equity [1]. The disorder arises from biallelic pathogenic variants in the homogentisate 1,2-dioxygenase (HGD) gene, leading to systemic accumulation of homogentisic acid (HGA) and its oxidized polymers in connective tissues throughout the body [2]. While the molecular defect produces a relatively straightforward biochemical phenotype characterized by markedly elevated urinary HGA excretion, the clinical manifestations unfold over decades in a pattern that transforms a biochemically silent childhood into a debilitating adult syndrome dominated by chronic musculoskeletal pain, progressive arthropathy, and multisystem complications.

The epidemiological landscape of alkaptonuria reveals intriguing population-specific clustering that speaks to historical migration patterns, founder mutations, and potentially gene-environment interactions. While the disorder affects all ethnic groups, the dramatically elevated prevalence in the Dominican Republic and Slovakia suggests complex evolutionary and demographic forces at work [2]. For Latina populations, the Dominican experience represents a critical natural experiment in disease epidemiology, offering insights into both genetic architecture and the social determinants that shape access to diagnosis and care.

Genetic Architecture and Molecular Pathogenesis

The genetic basis of alkaptonuria centers on mutations within the

HGD gene located on chromosome 3q21-q23. This gene encodes homogentisate 1,2-dioxygenase, an enzyme that normally catalyzes the conversion of homogentisic acid to maleylacetoacetic acid in the tyrosine degradation pathway [2]. The enzyme exhibits tissue-specific expression patterns, with highest activity in liver, kidney, prostate, small intestine, and colon, reflecting the distributed nature of tyrosine metabolism across organ systems. The HGD protein functions as a hexamer organized into two trimers, each containing an iron atom essential for catalytic activity [2]. Pathogenic variants may disrupt enzyme function through diverse mechanisms including alterations in protein folding, active site geometry, oligomerization capacity, or protein stability.

More than 212 distinct pathogenic variants have been identified across the HGD gene, with certain exons (particularly exons 6, 8, 10, and 13) representing mutational hotspots where recurrent pathogenic changes cluster [3]. The molecular genetics of alkaptonuria demonstrate the phenomenon of allelic heterogeneity, wherein different populations harbor distinct spectra of causative mutations reflecting their unique demographic histories. Notably, studies have consistently failed to establish clear genotype-phenotype correlations, as residual HGD enzyme activity ranging from 1% to over 30% shows no consistent relationship with either serum HGA levels or clinical disease severity [3]. This absence of correlation suggests that factors beyond simple enzyme deficiency modulate disease expression, potentially including genetic modifiers, epigenetic regulation, environmental exposures, or stochastic developmental processes [3].

The inheritance pattern follows autosomal recessive Mendelian principles, requiring biallelic pathogenic variants for disease manifestation. Heterozygous carriers typically remain asymptomatic and may express 50% or greater normal enzyme activity, insufficient to produce clinical or biochemical abnormalities even under tyrosine loading conditions [4]. For couples who are both carriers, each pregnancy carries a 25% risk of producing an affected child, a 50% chance of producing a carrier, and a 25% probability of producing a child inheriting two wild-type alleles [4]. While extremely rare, autosomal dominant transmission patterns have been reported in isolated pedigrees, suggesting the possibility of dominant-negative effects or involvement of modifier loci that remain poorly characterized [4].

Pathophysiological Mechanisms of Tissue Damage

The pathophysiology of alkaptonuria flows directly from the enzymatic defect in tyrosine catabolism. Under normal conditions, dietary phenylalanine undergoes hydroxylation to tyrosine, which then proceeds through a multi-step catabolic pathway ultimately generating fumarate and acetoacetate [2]. Homogentisate 1,2-dioxygenase catalyzes a critical step in this cascade, and its absence creates a metabolic bottleneck resulting in HGA accumulation to levels 100-fold above normal [2]. While the kidneys actively secrete HGA and eliminate 1 to 8 grams daily in the urine, even this efficient clearance mechanism cannot prevent gradual tissue deposition over decades [2].

The molecular mechanism by which HGA causes tissue damage centers on oxidative polymerization. Upon exposure to oxygen, particularly under alkaline conditions, HGA undergoes spontaneous oxidation to benzoquinone acetic acid intermediates that further polymerize into melanin-like macromolecular pigments [5]. These ochronotic polymers bind avidly to collagen and other structural proteins within connective tissues, preferentially accumulating in cartilage, tendons, ligaments, and vascular tissues. The pigment deposition fundamentally alters the mechanical and biochemical properties of affected tissues [5]. In cartilage, HGA and its polymers inhibit crucial enzymes involved in collagen cross-linking, diminishing the structural integrity of the extracellular matrix and predisposing to premature degradation [5]. The pigmented cartilage becomes brittle, fragmented, and prone to calcification, setting the stage for the devastating arthropathy that defines the clinical syndrome [5].

Beyond direct effects on structural proteins, emerging evidence suggests that HGA may trigger inflammatory cascades and oxidative stress pathways within affected tissues. The accumulation of oxidized HGA metabolites potentially generates reactive oxygen species that damage cellular components and activate inflammatory signaling [6]. This inflammatory component may contribute substantially to the pain experience in alkaptonuria, as oxidative damage and inflammation are well-established drivers of chronic pain in degenerative joint diseases [6] Recent advanced imaging studies have identified high-density mineralized protrusions extending from subchondral bone into overlying cartilage in alkaptonuric joints, structures that may represent focal points of mechanical stress and nociceptive signaling [7].

The systemic nature of ochronosis means that virtually all collagen-rich tissues eventually sustain damage, though clinical manifestations vary by anatomical location. Spinal involvement typically appears earliest, with intervertebral disc calcification and degeneration producing the characteristic kyphoscoliosis and height loss [8]. Large peripheral joints including hips, knees, and shoulders follow, often necessitating joint replacement by the fifth or sixth decade [8]. Cardiac involvement manifests as aortic and mitral valve calcification with associated stenosis or regurgitation, complications that affect approximately 40% of patients and may require valve replacement in severe cases [9]. Renal and prostatic stone formation occurs in approximately 50% of individuals by age 64, resulting from HGA crystallization in urine [10]. Even soft tissues such as ear cartilage and sclera develop visible pigmentation, providing external clues to the internal pathological processes.

Epidemiology and Population-Specific Patterns

Global prevalence estimates for alkaptonuria range from 1 in 250,000 to 1 in 1,000,000 individuals, though the true frequency remains uncertain due to incomplete ascertainment and variable diagnostic practices [11]. The disorder affects all racial and ethnic groups, with slight male preponderance in disease severity rather than incidence. Two populations demonstrate dramatically elevated prevalence that has attracted sustained scientific attention: Slovakia with an estimated prevalence of 1 in 19,000, and the Dominican Republic where similar frequencies have been documented [11].

The Slovak clustering has been extensively characterized at the molecular level, revealing not a single founder mutation but rather a constellation of 12 distinct pathogenic variants concentrated in specific mutational hotspots within the HGD gene [12]. This allelic heterogeneity suggests ancient origins predating recent population bottlenecks, with geographic concentration likely arising from restricted gene pools in northwestern Slovakia and subsequent regional migration patterns beginning in the 1950s [12]. The multiple independent mutations achieving elevated frequency speaks to the interplay of genetic drift, consanguinity patterns, and potentially selective pressures that remain incompletely understood.

The Dominican Republic presents a particularly illuminating case study for understanding alkaptonuria in Latina populations. Historical genetic investigations documented 58 affected individuals across eight generations of seven interrelated kindreds, establishing clear autosomal recessive inheritance within these extended family networks [13,14]. Molecular genetic analyses have identified founder mutations within the Dominican population, representing ancient genetic variants that achieved elevated frequency through founder effects during the island's complex demographic history. The Dominican population reflects admixture among indigenous Taíno peoples, Spanish colonizers, and African populations, creating a unique genetic landscape [14]. The high frequency of alkaptonuria in this admixed Latina population demonstrates how historical population movements, genetic bottlenecks, and reproductive isolation can concentrate rare alleles to clinically significant levels [14].

For broader Latina populations across the Caribbean, Central America, and South America, reliable epidemiological data on alkaptonuria prevalence remains scarce. The disorder's rarity delayed clinical presentation, and requirement for biochemical testing create substantial ascertainment bias. Many cases likely go undiagnosed or are misattributed to common forms of osteoarthritis, particularly in resource-limited settings where access to genetic testing and specialized metabolic evaluation remains constrained [15]. The dark urine that represents an early diagnostic clue often goes unrecognized, either because the color change occurs only after prolonged air exposure or because it appears in infancy when symptoms are otherwise absent and medical surveillance may be limited [15].

Chronic Pain

The natural history of alkaptonuria follows a characteristic temporal progression that belies the constitutional nature of the enzymatic defect. From birth through early adulthood, individuals remain largely asymptomatic aside from urine that darkens upon standing [15]. This prolonged latent period reflects the slow accumulation of ochronotic pigment over decades, as HGA deposits gradually reach pathological thresholds in target tissues [16]. However, once symptomatic disease emerges in the late third or early fourth decade, progression becomes relentless and disabling [16].

The dominant clinical feature that drives morbidity and healthcare utilization is chronic musculoskeletal pain. Back pain typically emerges first, often beginning in the late twenties or early thirties as progressive lumbar spine involvement [17]. The pain originates from multiple pathological processes including intervertebral disc degeneration, calcification, and collapse, along with facet joint arthropathy and paraspinal soft tissue involvement [17]. As spinal disease advances, patients develop progressive kyphoscoliosis, reduced spinal mobility, and diminished respiratory reserve from restricted thoracic cage expansion [2]. Spinal stenosis and cord compression may supervene in advanced cases, producing myelopathic symptoms and further compromising function [2,17].

Large peripheral joints follow a similar degenerative trajectory, with hips, knees, and shoulders bearing the greatest burden. The arthropathy of alkaptonuria shares features with primary osteoarthritis including joint space narrowing, cartilage loss, and subchondral changes, but occurs at earlier ages and progresses more rapidly, particularly in males [18]. Pain in affected joints demonstrates both mechanical and inflammatory characteristics, worsening with activity but also present at rest and during the night. Joint effusions and acute inflammatory flares can occur, though the underlying process remains primarily degenerative rather than autoimmune [17]. By the fifth or sixth decade, many patients require joint replacement surgery, often involving multiple joints sequentially as disease progresses [8].

The pain experience in alkaptonuria extends beyond simple nociception to encompass complex biopsychosocial dimensions. Chronic pain fundamentally alters patients' relationship with their bodies, their social roles, and their future prospects. The progressive nature of disability creates anticipatory distress as patients witness their functional capacity eroding year by year [19]. Sleep disruption from nocturnal pain compounds daytime fatigue and cognitive difficulties. The visible pigmentation changes in eyes and ears, while medically benign, serve as constant external reminders of internal pathology and may contribute to body image concerns and social self-consciousness [19].

Psychological Functioning

The psychological dimensions of living with alkaptonuria have received limited systematic investigation despite clear evidence of substantial mental health burden. Case reports document patients presenting with dysthymia characterized by social isolation, diminished interest in previously pleasurable activities, feelings of worthlessness, and chronic irritability [20]. While not meeting formal diagnostic criteria for major depressive disorder in all cases, these subsyndromal depressive symptoms nonetheless reflect significant psychological distress and impaired quality of life.

Multiple converging factors contribute to psychological vulnerability in alkaptonuria. The diagnostic delay that characterizes many cases means that patients often endure years of progressive symptoms before receiving accurate diagnosis and explanation. This diagnostic odyssey creates frustration, medical invalidation, and erosion of trust in healthcare systems. Even after diagnosis, the lack of disease-modifying treatments (until recent regulatory approval of nitisinone) leaves patients facing progressive disability with limited therapeutic options [20]. The chronic, unremitting nature of pain serves as a persistent stressor that taxes psychological coping resources and increases risk for mood and anxiety disorders [20].

Loss of functional capacity strikes at core aspects of identity and self-worth. Patients in their forties and fifties find themselves unable to maintain employment in physically demanding occupations, unable to participate in recreational activities that previously provided meaning and social connection, and increasingly dependent on others for basic activities of daily living [20]. The role transitions forced by progressive disability—from worker to disability recipient, from active parent to dependent adult, from autonomous individual to person requiring assistance—can precipitate identity crises and existential distress.

Survey data from patient populations reveal that pain and disability represent the symptoms with highest impact on quality of life, followed closely by emotional and mental health complications [21]. The inability to perform normal routines emerged as a particularly salient concern, highlighting how disease-related limitations ripple outward to affect all life domains. Interestingly, the visible pigmentation changes that might seem cosmetically significant were rated as lower impact by most patients, suggesting that functional limitations and pain overshadow appearance concerns in determining quality of life [21].

Social isolation represents both a consequence of and contributor to psychological distress. As mobility becomes limited and pain increases, patients withdraw from social engagements, recreational activities, and community participation [21]. This contraction of social networks reduces access to emotional support precisely when it becomes most needed. Furthermore, the rarity of alkaptonuria means that patients often feel uniquely afflicted, unable to find others who share their experience and understand their struggles. The emergence of patient advocacy organizations such as the AKU Society provides crucial platforms for connection, education, and mutual support, partially mitigating the isolation inherent in rare disease experience.

The limited research on psychological interventions in alkaptonuria represents a critical gap in the evidence base. While psychotherapy and lifestyle counseling have been proposed as potentially beneficial approaches to enhance coping and quality of life, rigorous trials evaluating these modalities remain absent. The multidimensional nature of alkaptonuria—encompassing progressive physiological deterioration, neurological complications from spinal disease, and psychological sequelae—demands equally multidimensional treatment approaches that integrate biomedical, rehabilitative, and psychosocial interventions.

Social Determinants of Clinical Outcomes

The framework of social determinants of health provides essential context for understanding disparities in alkaptonuria diagnosis, treatment access, and clinical outcomes. Social determinants encompass the conditions in which people are born, grow, live, work, and age, including economic stability, educational access, healthcare quality, neighborhood environments, and social community contexts [22]. These upstream factors exert profound influence on health outcomes through multiple pathways, creating systematic differences in disease burden across social groups.

For rare genetic disorders like alkaptonuria, several social determinants prove particularly salient. Healthcare access and quality emerge as critical determinants of diagnostic timeliness and treatment initiation. The diagnosis of alkaptonuria requires clinical suspicion, specialized biochemical testing for urinary HGA quantification, and often molecular genetic confirmation. In healthcare systems with limited access to genetic and metabolic specialists, or in populations facing geographic, financial, or linguistic barriers to specialized care, diagnosis may be substantially delayed or missed entirely [15]. Even when dark urine is noted in infancy, the finding may be dismissed or attributed to benign causes without triggering appropriate metabolic evaluation [15].

Economic stability influences multiple aspects of the alkaptonuria journey. The progressive disability characteristic of the disorder often forces patients out of the workforce during peak earning years, creating financial strain precisely when medical expenses increase. The need for joint replacement surgeries, pain management, physical therapy, and potentially cardiac interventions generates substantial healthcare costs [17,22]. For individuals without adequate health insurance coverage or financial resources, these costs may lead to delayed or forgone care, accelerating disability progression. The relationship between socioeconomic status and health outcomes in chronic diseases demonstrates consistent gradients, with lower-income populations experiencing earlier disease onset, more rapid progression, and higher complication rates.

Geographic location shapes both disease risk and healthcare access in complex ways. The elevated prevalence in the Dominican Republic reflects historical population genetics, but also intersects with contemporary healthcare infrastructure, economic development, and social resources [14]. Rural populations globally face greater barriers to specialized medical care, requiring long-distance travel to access genetic and metabolic expertise [23]. For Latina populations distributed across the Caribbean, Central America, and South America, substantial heterogeneity exists in healthcare system capacity, with implications for rare disease management [14].

Educational attainment and health literacy influence patients' ability to navigate complex healthcare systems, advocate for appropriate diagnostic evaluation, understand genetic inheritance patterns, and engage in shared decision-making regarding treatment options. Lower educational attainment correlates with reduced health literacy, which in turn predicts poorer disease self-management, medication adherence, and health outcomes across chronic conditions [24]. For genetic disorders with autosomal recessive inheritance, family planning decisions require understanding of carrier status and recurrence risks, understanding that may be compromised by limited genetic literacy.

Social and community context encompasses the networks of support, discrimination, and cultural beliefs that shape health behaviors and healthcare utilization. For Latina populations, cultural factors including familialism (strong family orientation), personalismo (preference for personal relationships in healthcare), and traditional health beliefs may influence healthcare seeking and adherence [25]. Language barriers in non-Spanish-dominant healthcare settings create additional obstacles to effective communication and care coordination. Discrimination and implicit bias within healthcare systems may contribute to diagnostic delays and suboptimal care quality for minority populations [25].

The intersection of rare disease status with health inequity creates particular vulnerability. Rare diseases receive less research attention, fewer approved therapies, and more limited clinical expertise compared to common conditions. When rare disease overlaps with already-marginalized populations facing structural inequities, the combination amplifies disadvantage. Latina women with alkaptonuria thus navigate multiple axes of potential marginalization—rare disease status, gender, ethnicity, and potentially socioeconomic disadvantage—each contributing incremental barriers to optimal care.

Clinical Management

Until recently, alkaptonuria management remained entirely palliative, focused on symptomatic relief rather than disease modification. Pain management strategies employed analgesics ranging from acetaminophen and nonsteroidal anti-inflammatory drugs to opioids in severe cases, though none address underlying pathology [2]. Physical and occupational therapy aimed to preserve strength, flexibility, and function despite progressive joint damage. Surgical interventions including joint replacement and spinal fusion addressed mechanical complications but could not halt disease progression. Dietary protein restriction was proposed to reduce tyrosine and phenylalanine load, theoretically limiting HGA production, though adherence challenges and uncertain efficacy limited widespread adoption [2].

The therapeutic landscape shifted dramatically with investigation of nitisinone, a potent inhibitor of 4-hydroxyphenylpyruvate dioxygenase, the enzyme immediately upstream of the HGD deficiency [26]. By blocking this earlier step in tyrosine catabolism, nitisinone prevents formation of homogentisic acid, dramatically reducing HGA accumulation. Initial proof-of-principle studies demonstrated 95% reduction in urinary HGA excretion with nitisinone treatment, establishing biochemical efficacy [27]. However, translating biochemical efficacy into demonstrable clinical benefit proved challenging given the slow progression of alkaptonuria and the advanced disease stage at which most patients present.

A landmark randomized controlled trial conducted over three years compared nitisinone-treated patients to untreated controls, using hip range of motion as the primary outcome parameter. While the trial conclusively demonstrated sustained 95% reduction in HGA levels with excellent tolerability, the primary endpoint of improved hip mobility did not reach statistical significance [28,29]. This finding initially appeared to indicate limited clinical utility, leading to regulatory hesitation regarding approval. However, subsequent reanalysis focusing on patient-reported outcomes and functional assessments revealed significant benefits that were obscured by the selected primary endpoint [28,29].

Post-hoc analyses demonstrated that nitisinone-treated patients reported significant improvements in physical functioning on standardized quality of life instruments compared to untreated patients, along with gains in functional measures including the six-minute walk test. Domains of bodily pain showed near-significant improvement, suggesting that nitisinone may ease arthritic pain and improve function in meaningful ways not captured by hip range of motion measurements. The wide-ranging improvements across multiple quality of life domains indicated broad clinical benefit extending beyond any single anatomical site. Perhaps most compellingly, none of the nitisinone-treated patients without baseline aortic valve disease developed new aortic sclerosis or stenosis during the trial, whereas seven of seventeen control patients without baseline valve disease progressed to aortic pathology, suggesting that nitisinone may prevent cardiac complications [28,29].

Subsequent larger trials confirmed these findings, demonstrating that nitisinone 10 mg daily effectively reduces urinary HGA excretion, decreases ochronosis progression, and slows clinical deterioration as measured by validated disease severity instruments. European regulatory authorities approved nitisinone for adult alkaptonuria in 2020, and the U.S. Food and Drug Administration granted approval in 2025, representing the first approved disease-modifying therapy for this ancient metabolic disorder. The approval was based substantially on the reanalyzed patient-reported outcomes demonstrating improvements in pain, energy levels, and physical functioning.

The optimal timing of nitisinone initiation remains an active question. Treatment begun after severe arthropathy develops cannot reverse existing joint damage, though it may slow further progression and prevent cardiac complications. Earlier treatment, ideally before significant ochronosis accumulates, might prevent the devastating arthropathy altogether. However, demonstrating such preventive benefit requires longitudinal studies spanning decades, a challenging proposition for any rare disease. The favorable safety profile of nitisinone—with hypertyrosinemia representing the primary adverse effect, manageable through dietary protein restriction—supports consideration of early treatment initiation.

Future Directions

Substantial knowledge gaps persist across all dimensions of alkaptonuria research, from molecular mechanisms to optimal care delivery. At the basic science level, fundamental questions regarding how HGA causes tissue damage, why certain tissues prove more vulnerable than others, and what factors modulate individual variability in disease expression remain incompletely answered. The absence of genotype-phenotype correlations suggests involvement of genetic modifiers or environmental factors that warrant systematic investigation. Animal models of alkaptonuria exist and have provided valuable insights, though they fail to recapitulate the full spectrum of human disease, particularly the severe arthropathy that dominates clinical presentation.

Clinical research priorities include defining optimal nitisinone dosing strategies across different age groups and disease stages, establishing biomarkers that predict treatment response and disease progression, and developing sensitive outcome measures capable of detecting clinically meaningful change over practical trial durations. The field would benefit from natural history studies that characterize disease evolution in diverse populations, identify prognostic factors that predict rapid versus slow progression, and document patterns of comorbidity and mortality. Comparative effectiveness research examining nitisinone against best supportive care in real-world settings would complement efficacy data from controlled trials.

The psychological and social dimensions of alkaptonuria merit dedicated research attention. Systematic characterization of mental health burden, identification of risk and resilience factors for psychological adaptation, and development and testing of psychosocial interventions represent critical gaps. Understanding how social determinants influence diagnosis, treatment access, and outcomes across diverse populations could inform targeted interventions to reduce disparities. For Latina populations specifically, research examining cultural factors that influence healthcare utilization, exploring genetic epidemiology across different Latino subgroups, and documenting barriers and facilitators to optimal care would advance health equity goals.

Implementation science approaches could accelerate translation of evidence into practice, particularly for rare disorders where clinical expertise remains concentrated in specialized centers. Strategies to improve early diagnosis, enhance primary care provider knowledge, facilitate referral to appropriate specialists, and ensure equitable treatment access merit investigation. Patient registries and international collaborative networks have proven valuable for rare disease research, pooling data across geographic boundaries to achieve adequate sample sizes and capturing diverse perspectives.

Conclusion

Alkaptonuria stands as a paradigmatic rare genetic disorder whose study illuminates fundamental principles of metabolic disease, chronic pain pathophysiology, and health equity. The dramatically elevated prevalence in the Dominican Republic situates this disorder at the intersection of population genetics and social determinants, providing a natural laboratory for investigating how genetic architecture and social context jointly shape disease burden in Latina populations. The progressive arthropathy that defines clinical presentation creates substantial chronic pain burden that demands comprehensive biopsychosocial approaches integrating biomedical treatments, psychological support, and rehabilitation.

Recent therapeutic advances with nitisinone offer genuine disease modification for the first time in over a century of research, though optimal deployment of this treatment requires addressing social determinants that shape access and adherence. Moving forward, the alkaptonuria field must embrace multidisciplinary approaches that span molecular genetics through population health, recognizing that rare diseases occur not in laboratory isolation but in real patients embedded in families, communities, and societies whose structures profoundly influence outcomes. By attending equally to bench science, clinical research, and health equity, we can transform the trajectory of this ancient metabolic disorder and improve lives across all affected populations.

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