# RAINBOW SHINES ON RARE

*Cushing's community poised to benefit from expanding research focus on inequities in access to rare disease diagnosis and care*

**By William Looney**

A common thread in the treatment experience of Cushing's patients is discovering how little mainstream medicine understands about the condition. Even compared to other rare diseases, diagnosis of Cushing's is slow. Its characteristic symptoms are often mistaken for more common ailments or lifestyle behaviors that can resolve without specialized medical intervention. A recent meta-analysis from clinical records of over 5,000 Cushing's patients found the mean time from first symptoms to an accurate diagnosis was nearly three years, a lag that the study authors concluded was excessive and needed to be improved.[i]

The question, though, is how? While science continues to make progress in identifying heritability and the complex biologic interactions behind uncontrolled hypercortisolism in humans, much less is known about the many non-medical factors that influence the treatment that Cushing's patients actually receive. The impact of these so-called "social determinants of health" has been hard to quantify using standard statistical measures.

Nevertheless, there is a growing consensus in the rare disease community that something as simple as a patient's zip code may explain the persistence of sharp variations in individual outcomes from disease. Such disparities in diagnosis and access to care are especially prevalent in the Cushing's patient population even though a clinically validated practice guideline covering care for both the disease and its underlying condition, hypercortisolism, has been in place since 2008. [ii]

**New Cohort Study on Cushing's: Are Minorities Missing Out on Modern Science?**

As interest in health disparities builds among key patient advocacy groups like the National Organization for Rare Disorders (NORD), a number of small-scale research studies are investigating whether implicit barriers to access and treatment can affect outcomes and overall quality of life for patients with Cushing's. The current edition of the *Journal of the Endocrine Society* features a retrospective study on the effect racial identity has on presentation and post-

operative outcomes in African-American and white adults with Acromegaly (ACM – another rare disease caused by a pituitary tumor) and Cushing's Disease. [iii] The authors cite their work as "the first report that underlines significant differences in clinical and biochemical presentation between African-American and white patients with ACM."

The research analyzed the pre- and post-operative course of 241 male and female patients from the metropolitan Atlanta area who received standard-of-care transsphenoidal surgery (TSS) treatment at the Emory University Pituitary Center, a leading, high case-volume academic medical facility.

Key findings from the study are as follows:

- Despite having an equivalent proximity to Emory's Pituitary Center, black patients with ACM were less likely to undergo TSS treatment than white patients. The ratio increased when household income and medical insurance were taken into account. Together with differences involving clinical and biomedical presentation, which may be attributable to later diagnosis of ACM among black patients, the study finds a significant underrepresentation of black ACM patients in TSS operative care treatment at this world-class center for surgical pituitary interventions.

- With respect to the study cohort with Cushing's, no major racial disparities were identified, but the peak age for TSS was 10 years later for African-Americans than for whites, and a comparatively small number of black patients at Emory were diagnosed with Cushing's after age 50.

- Policy-related remedial measures to address these imbalances should include patient education outreach and targeted health delivery measures aimed at shortening the diagnostic delay for blacks, such as increasing minority population access to referral centers. Intermediating issues like access to public transportation and level of education remain to be explored.

- Larger studies are required to confirm the race impact on treatment access and outcomes involving patients with ACM and Cushing's Disease. Work here could be assisted by the development of disease-specific regional and national data registries.

Other recently published peer-review studies have confirmed a discrepancy between white people and Hispanic and African-American populations in the severity of Cushing's; again, this is largely due to the white cohort's experience of earlier diagnosis as well as better ability to access facilities with expertise in neuroendocrine interventions. An August 2017 study looking at 129

pediatric Cushing's Disease patients age 18 or younger, divided between non-Hispanic white and Hispanic/African-Americans, found a disproportionately higher severity of Cushing's in the latter, at both the pre-operative (later diagnosis) and post-operative stages (a threefold higher risk of recurrence of Cushing's after TSS surgery). [iv]

Specifically, it cited a higher prevalence of obesity among Hispanic and African-American children as one factor explaining the severity of Cushing's in this group compared to whites. The rationale was that clinicians were less likely to single out obesity as a presenting symptom of Cushing's, further delaying time to diagnosis. Instead, it was usually attributed to the lifestyle and cultural behaviors present in low-income communities where many of the Hispanic/African-American survey population live.

Because early diagnosis and treatment can mitigate the severity of disease, Cushing's patients stand to benefit from researchers' increased attention to disparities in access. There is also movement on the policy front to promote health equity and outreach involving affected populations. In 2021, the National Institutes of Health (NIH) announced a new grant program, *Transformative Research to Address Health Disparities and Advance Health Equity*, to expand financing for study projects focused on minority-serving institutions and the ways that community barriers to access can be addressed and resolved. [v]

Likewise, the federal Centers for Disease Control and Prevention (CDC) recently adopted a *Health Equity Science and Intervention Strategy* that elevates health disparities as a core priority for the organization, with a shift from simply documenting their existence to actions involving the design, implementation, and evaluation of its entire research, data, surveillance, and disease intervention capabilities.[vi]

**NORD's New Message to Members: Share Your Colors**

But perhaps the most important development in this space is the embrace of the disparities agenda by the National Organization for Rare Disorders (NORD), representing 260 advocacy groups working for 30 million rare disease patients across the US. NORD, which has a Patient Assistance Program (PAP) covering drugs and related treatments for Cushing's Syndrome, has made health disparities the theme of this year's 25th annual Rare Disease Day on February 28.

"Share your Colors" [https://rarediseaseday.org] will set the tone for NORD's public advocacy over the next year. It will incorporate high-profile events, encounters with political and social leaders, shared personal stories on social media, and promotion of a diversity-focused research agenda spotlighting inequities in access and treatment for minorities based on race, gender, age, income, urban/rural status as well as other underrepresented communities.

NORD will be supported by the new Rare Disease Diversity Coalition (RDDC*), launched in February 2021 on a campaign to prioritize rare diseases in a more global and inclusive way, attracting support from professional associations and trade groups. Said a spokesman for RDDC, "no patient should face health disparities, particularly those fighting the burdens of a rare disease. The communities we serve are diverse and some of them face challenges in accessing a diagnosis, specialty care, or the treatments they need. We are determined to change that." [vii]

As the chief advocate for patients with Cushing's, CSRF will continue follow the emerging research and policy agenda on rare disease disparities as it unfolds.

**The RDDC was spearheaded by the early grassroots work of the Black Women's Health Imperative, founded in 1983 in Atlanta as the first non-profit created to help advance the health and well-being of 22 million black women and girls in the US. Other members of the RDDC include the American Medical Association, the federal Patient Centered Outcomes Research Institute (PCORI), the National Hispanic Medical Association, and Retrophin Inc.*

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[i] Rubinstein, German *et al*, "Time to Diagnosis in Cushing's's Syndrome: A Meta-Analysis Based on 5,367 Patients," *Journal of Clinical Endocrinology & Metabolism*, March 2020.

[ii] Nieman, Lynette *et al,* "The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline," *Journal of Clinical Endocrinology & Metabolism*, May 2008.

[iii] Ioachimescu, Adriana *et al*, "Racial Disparities in Acromegaly and Cushing's's Disease: A Referral Center Study in 241 Patients," *Journal of the Endocrine Society*, Vol.6, No.1, 2022.

[iv] Gkourogianni, Alexandra, *et al*., "Pediatric Cushing's Disease: Disparities in Disease Severity and Outcomes in the Hispanic and African-American Populations," *Pediatric Research*, August 2017.

[v] "New, highly innovative NIH research awards to address health disparities and advance health equity," *National Institutes of Health News Release*, October 13, 2021.

[vi] "CDC Core Health Equity Science and Intervention Strategy," *US Centers for Disease Control and Prevention,* October 20, 2021.

[vii] Dube, Eric, "Seizing the Moment for Change – Rare Disease Diversity Coalition Takes Action to Reduce Disparities in Rare Diseases," www.travere.com