Tony Evers
Governor

Kirsten L. Johnson
Secretary

State of Wisconsin

Department of Health Services

DIVISION OF PUBLIC HEALTH

1 WEST WILSON STREET
P O BOX 2659
MADISON WI 53701-2659

608-266-1251
FAX: 608-267-2832
TTY: 888-701-1253
dhs.wisconsin.gov

November 2023

Hemoglobinopathy Subcommittee Newborn Screening Program State of Wisconsin

Re: Bart's Hemoglobin

Dear Colleague:

Your patient was recently found to have the presence of Fetal (F), Adult (A) and Bart's hemoglobin on their newborn screen. The presence of Bart's hemoglobin indicates that your patient likely has a form of **alpha thalassemia** (deficient production of alpha globin chains).

Fetal hemoglobin is composed of 2 alpha chains and 2 gamma chains ($\alpha_2\gamma_2$). When there is an insufficient number of alpha chains produced, 4 gamma chains combine to form Bart's hemoglobin (γ_4). Alpha-thalassemia is caused by decreased production of alpha-globin chains. Normally, four alpha-globin genes are present (2 on each chromosome 16). In people who have alpha thalassemia, 1, 2, 3, or 4 alpha-globin genes may be deleted or, less commonly, contain variants. Deletions account for approximately 90% of disease-causing alleles in alpha thalassemia. The diagnosis and phenotypic severity of disease expression depends on the number of genes affected as follows:

- Deletion of 1 alpha globin gene results in the patient being a **silent carrier** of alpha thalassemia. This may be accompanied by mild red blood cell (RBC) microcytosis.
- Deletion of 2 alpha globin genes results in the patient having **alpha thalassemia trait**. This may be accompanied by mild anemia and RBC microcytosis, but typically results in no major clinical difficulties.
- Deletion of 3 alpha globin genes results in the patient having **Hemoglobin H disease**. Patients with Hemoglobin H disease may have anemia, RBC microcytosis, hemolysis, jaundice and hepatosplenomegaly. Deletion of two alpha genes along with inheritance of a variant called Hemoglobin Constant Spring results in a more severe form of alpha thalassemia called Hemoglobin H Constant Spring.
- Deletion of all 4 alpha globin genes results in a condition known as **Hemoglobin Bart's hydrops fetalis**. Unless recognized and managed during the pregnancy, this condition almost invariably leads to *in utero* demise.

For your patient, the presence of fetal, adult and Bart's hemoglobin indicates the deletion of one, two, or (much less commonly) three alpha globin genes.

The RBC microcytosis associated with alpha thalassemia will be a lifelong characteristic and **will not** respond to iron supplementation. It's important to note, however, that both alpha thalassemia and iron deficiency are causes of anemia and RBC microcytosis. The two conditions can co-exist. If iron deficiency is a clinical concern or if screening is indicated, we recommend

obtaining a CBC with reticulocyte count and ferritin around the age of 6-9 months. Supplemental iron should only be provided if iron deficiency is objectively proven.

We recommend you **strongly consider a Pediatric Genetic Counseling referral** for your patient/family to receive genetic education and counseling**.** Genetic sequencing of the alpha globin genes is necessary to establish a precise and accurate diagnosis. Pediatric Hematology referral should be considered for patients with more severe anemia (hemoglobin 6-9 gm/dL), as this may suggest a diagnosis of hemoglobin H disease.

If you have questions, please contact one of the Pediatric Hematologists listed below who are members of the Wisconsin Department of Public Health advisory subcommittee for hemoglobinopathy screening.

Sincerely,

Amanda Brandow, DO, MS Milwaukee 414-955-4170

John Hill, MD Green Bay 920-433-8670

Jennifer Orozco, MD LaCrosse 608-775-1194

Anne Marsh, MD Madison 608-263-6420

Jon Brandt, MD Marshfield 715-387-5251