ThalassemiaNEWS

A quarterly newsletter keeping the medical and patient community in touch with thalassemia developments

Autumn 2023

IN PROFILE

An in-depth view of an organization or individual involved in thalassemia and sickle cell disease

In this Issue, we highlight The International Hemoglobinopathy Research Network (INHERENT)* which was established in 2020 to examine the role of genetic modifiers in hemoglobinopathies (NCT05799118).

INHERENT aims to recruit at least 30,000 hemoglobinopathy patients in order to undertake a large-scale multi-ethnic genome-wide association study (GWAS) to inform patient stratification and personalized treatment. Specifically, INHERENT aims to:

- Discover new genetic modifiers of hemoglobinopathies
- Validate previously-reported genetic modifiers
- Pool and analyze existing genomic data
- Standardize phenotypic descriptions
- Develop a standardized case report form for use across countries to gather high-quality data
- Develop a research resource of disease-specific data

The INHERENT network comprises nine existing consortia and participation is open to any group able to provide at least 30 DNA samples alongside a core phenotypic description. The network has grown rapidly and now spans 45 countries globally. The network's coordinator Dr Petros Kountouris from the Molecular Genetics Thalassemia Department, the Cyprus Institute of Neurology and Genetics in Nicosia, told us:

"INHERENT's emphasis on global collaboration, expanded sample size, and diverse population studies is poised to uncover novel insights that can have a profound impact on the field of hemoglobinopathies"

For more information about the INHERENT network, visit https://www.inherentnetwork.org/

*Partial support provided by Agios for Investigator Sponsored Research

IN-DEPTH

The value of patient registries and research networks in thalassemia

Thalassemia manifests as widely variable phenotypes with changing demographic features, all of which influence diagnostic and treatment decisions, and define prognostic evaluations. The inter-relationships between these variables and management response must therefore be characterized to enable optimal treatment to be tailored on an individual patient basis. The rarity of thalassemia means that few patients with a specific disease presentation will be encountered at a given center. Building patient registries and research networks, which collect and analyze patient data across multiple centers, enables robust analyses within a reasonable timeframe.

Registries have provided information and treatment insights related to thalassemia patients for many years[1-4] and new registries continue to be established, e.g., The International Registry of Patients with Alpha Thalassemia (Clinicaltrials.gov NCT04872179) is currently recruiting patients to evaluate treatment outcomes.

A recent evaluation of thalassemia registries worldwide between 1984 and 2016 identified sixteen that were operating on a multinational, national, or regional level[5].

Thalassemia registries were shown to be essential tools for large-scale collection of data needed to ensure that the needs of patients with thalassemia are being met effectively.

The power of patient registries can be further increased by collaboration between registries to form a larger network. Although the individual registries remain distinct, they are connected by a common infrastructure and standardized data collection to support broader research initiatives. A recently established international collaboration between thalassemia registries and databases is The International Hemoglobinopathy Research Network (INHERENT) that is designed to study the role of genetic modifiers in hemoglobinopathies[6]. Further information can be found in the 'In Profile' section of this newsletter.

The Thalassaemia International Federation (TIF) has recently implemented a web-based platform to host a global thalassemia registry with the aim of promoting the coordination and collaboration between existing thalassemia registries and the establishment of new ones[7].

Contributions from research networks to the thalassemia evidence base

Thalassemia networks are continually adding to the understanding of thalassemia disease knowledge. Indeed, research conducted by registry networks has already changed clinical practice. For example, the OPTIMAL CARE database, the first to be fully dedicated to patients with β-thalassemia intermedia at six comprehensive care centers in Lebanon, Italy, Iran, Egypt, United Arab Emirates, and Oman, had an essential role in establishing risk factors for morbidity in this patient population including advancing age, splenectomy, anemia, and iron overload[8,9]. Similarly, analyses of the Thalassemia Longitudinal Cohort conducted by the Thalassemia Clinical Research Network (including centers from the US and UK) provided valuable insights on several morbidities and treatment patterns in transfusion-dependent patients, which also provided the evidence base needed to establish monitoring guidelines for the management of patients with thalassemia in 2015[10].

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OPTIMAL CARE's lead author, Prof Ali Taher commented:

"This was the only way for us to gather a large sample and produce meaningful analysis, reflecting our real-life practice"

Registry networks continue to add valuable data from clinical practice to inform the management of thalassemia. The positive impact on patient care can be appreciated by considering some of the outputs from key ongoing research collaborations, such as the following ones.

WEBTHAL/DB-INTHEM*

The computerized clinical record, developed by the Turin Thalassemia Centre (WEBTHAL/DB-INTHEM) since the 80s and then developed by a multicenter board, has currently reached version 3.0. As of 2021, SITE, the Italian Thalassemia and Hemoglobinopathy Society, holds intellectual property, which makes it available to all centers. Funding to cover management and implementation costs has been provided by the ForAnemia Foundation. Webthal contains epidemiologic and clinical data for over 50% of all thalassemia patients in Italy[11]. This initiative involves 36 Italian thalassemia centers, including four regional ones (Cagliari, Genoa, Brindisi and Milan), and has been adopted by three centers in Brazil. It has archives for many aspects of the disease, including comorbidities and complications, transfusion therapy and iron chelation, and as such represents a rich data source for analysis.

One early analysis in 2013 evaluated the clinical practice of iron overload management and identified risk factors for suboptimal monitoring of hepatic and cardiac iron overload levels by MRI, even when resources are available[12]. More recent WEBTHAL analyses have provided valuable epidemiological data for thalassemia in Italy by highlighting overall and complication-free survival estimates[13], and establishing prevalence of and mortality from pulmonary arterial hypertension (PAH) in ß- thalassemia, one of the most worrisome disease-related complications[11,14,15].

Former SITE's President, Prof Gian Luca Forni commented:

"WEBTHAL has allowed to collect standardized information on a large group of patients as part of our day to- day practice, which addressed several data pitfalls that are commonly encountered in observational studies"

MIOT/E-MIOT

Another Italian thalassemia network, MIOT/E-MIOT (Myocardial Iron Overload in Thalassemia and an Extension Protocol), focuses on the high-quality quantification of tissue iron overload by MRI. It is a collaborative project involving 66 clinical centers and 11 radiological MRI centers involved in the care of patients with rare hemoglobinopathies. MIOT/E-MIOT has provided significant contributions to the understanding and quantifcation of iron burden by MRI and its impact on end-organ damage[16,17].

Very recently, this large dataset evaluated the impact of the COVID-19 lockdown on MRI monitoring to quantify iron overload in patients with thalassemia[18]. The evaluation of multi-organ iron accumulation by MRI was more than 80% lower in 2020 compared with 2019, and the reduction in T2* MRI scans approached 90% during the first lockdown from March to June 2020. The downstream impacts of the lack of tissue iron quantification remain to be determined.

IWG-THAL*

The International Working Group on Thalassemia (IWG-THAL), established in 2017 in Palermo, Italy by Prof. Aurelio Maggio, is a repository of historical thalassemia data dating back to 1997. It covers 13 international centers in Italy, Iran, US, Greece, Pakistan, Oman, and Saudi Arabia.

Analysis of data from more than 3000 patients enabled development of a complications risk score[19] and a more recent Thalassemia International Prognostic Scoring System (TIPPS) that stratifies patients with B-thalassemia according to classes of risk for mortality. Moreover, a DNA study using Low Pass Genomic Sequencing (LPGS) for detection of Copy Number Variants (CNV), to develop genetic markers of phenotype severity, has been implemented.

Overall, this study, allowing the stratification of patients into classes of risk using clinical and genetic markers, as in myelodysplastic syndromes, will provide crucial information for detecting ideal candidates for innovative treatments.

Lead Researcher Prof Aurelio Maggio commented:

"Our main aim was to gather data large enough to allow us to look into phenotypic distribution of thalassemia beyond the dichotomous classification of major and intermedia."

ICET-A

The International Network of Clinicians for Endocrinopathies in Thalassemia and Adolescence Medicine (ICET-A) was founded in 2009 by a core group of Endocrinologists from Italy, Egypt, Qatar, Cyrprus and UK. Their aim was to characterize endocrine complications due to thalassemia and describe the optimal care that should be provided to affected individuals[20].

ICET-A contributed a large number of articles that reshaped our understanding of endocrinopathy in thalassemia patients. Most recently, ICET-A has shown that abnormal glucose tolerance is common among patients with acquired hypogonadism, the most prevalent endocrine complication in thalassemia major, and those with iron overload, highlighting the importance of regular oral glucose tolerance tests to monitor glucose homeostasis[21,22].

Take home messages

- Registries are essential tools for improving treatment approaches and outcomes in thalassemia.
- They enable timely evaluation of disease prevalence, patient health status, complications/comorbities, and treatment outcomes, which facilitates improvements in patient care.
- Registry networks have already contributed significantly to the characterization and treatment of thalassemia.
- Wider collaboration of registries, including the development of standardized data collection and storage approaches, will further increase the thalassemia evidence base. Ultimately, this will provide greater power to define best treatment practice and improve patient quality of life.

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CLINICAL RESEARCH UPDATE

Sharing the latest news on clinical research in thalassemia: The Adelphi Thalassemia Disease Specific Programme (DSP)*

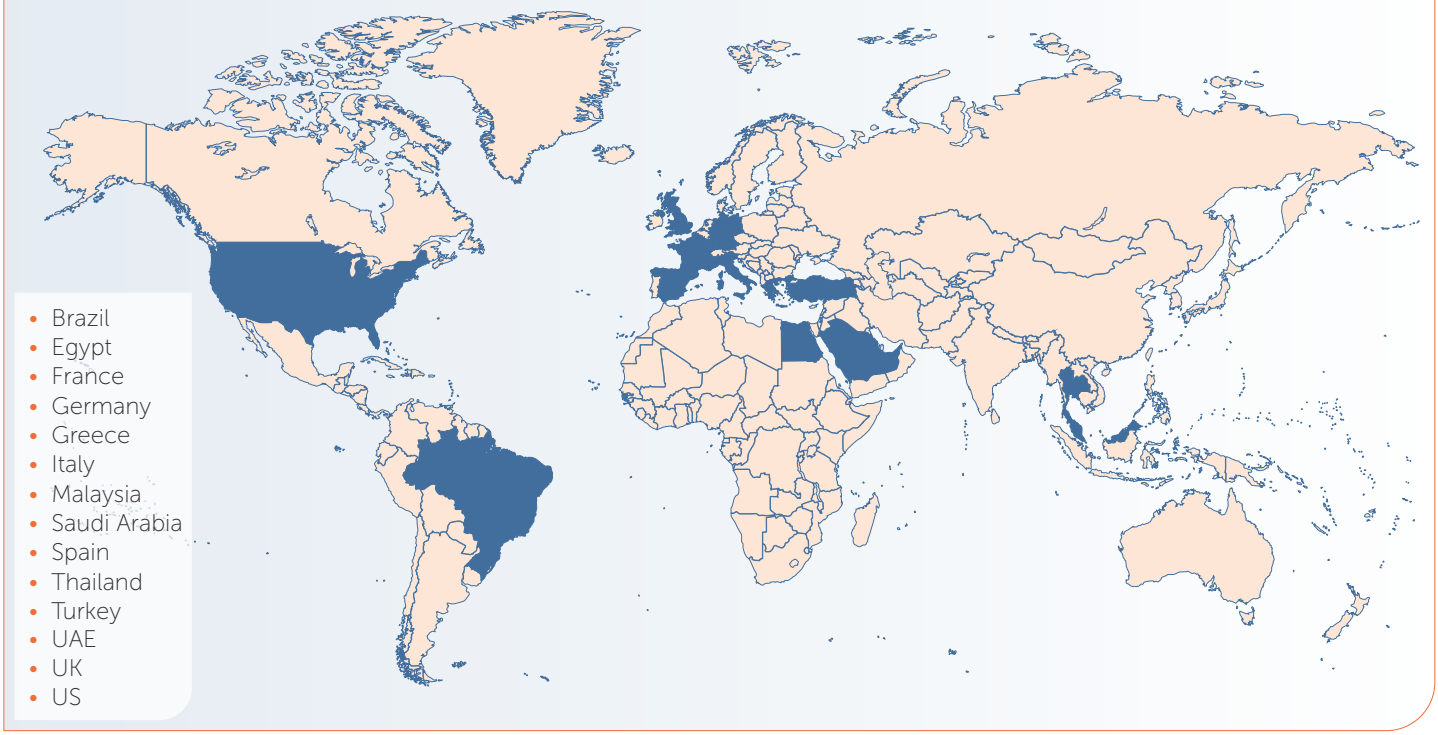
The overall objective of this survey is to capture real-world data to understand current standard of care, patient management, symptomatology, impact of thalassemia on healthcare systems and health-related quality of life, and overall unmet needs for patients with α- and β-thalassemia.

The Adelphi Thalassemia Disease Specific Programme™ (DSP) is an international point-in-time survey of thalassemia-treating physicians and the patients they see. Physicians complete a structured online survey for consecutive patients with α- or β-thalassemia seen during the survey period. The survey includes data on demographics, clinical characteristics, comorbidities, symptoms/complications, treatment, and healthcare resource utilization. Patients are also invited to complete a patient-reported survey while they are in the doctor's office. Patient-reported outcome assessments such as the Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue) and the Work Productivity and Activity Impairment (WPAI), and other questions about health-related quality of life, are included[23].

Inclusion criteria are as follows:

Physician inclusion criteria	Patient inclusion criteria
• Hematologist or hematologist-oncologist • Current involved in the treatment of patients with thalassemia • Currently manages at least one patient with α- or β-thalassemia • Consented to participate in the study	• Not currently participating in a mitapivat clinical trial • Diagnosed with α- or β-thalassemia • Adult (ages 18+)

Country participation:



The study will start recruitment across 14 countries in December 2023.

Health Care Providers interested in participation can contact Emily King
emily.king@adelphigroup.com

The Adelphi Thalassemia Disease Specific Programme is owned by Adelphi

KEY DATES

December 9-12, 2023
American Society of Hematology (ASH)
San Diego - USA

February 19-20, 2024
World Hematology Congress
London – UK

April 3-6, 2024
American Society of Pediatric Hematology/Oncology (ASPHO)
Seattle - USA

June 13-16, 2024
European Hematology Association (EHA)
Madrid - Spain

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COMMUNITY RESOURCES

Discover new resources for thalassemia healthcare providers, patients, and their caregivers

Fast Facts

A series of educational booklets and information sheets written by experts for patients, families, and healthcare providers on the key topics of thalassemia screening, α-thalassemia and β-thalassemia.

You can access and download the Fast Facts resources here:

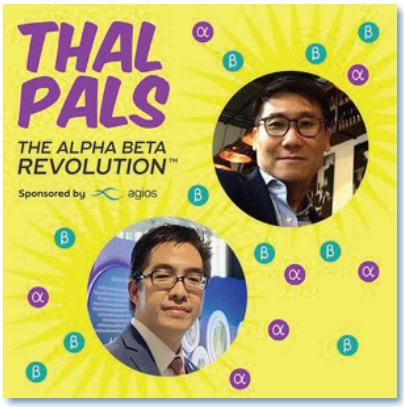
Thal Pals Podcasts

Replay: Dr. Nica Cappellini - Mother of Thalassemia

Cooley's Anemia Foundation Family Conference: A Teen Conversation

Thalassaemia International Federation Guidelines

Thalassemia: Perspectives from Thailand with Dr. Vip Viprakasit



The thalassemia podcasts *Thal Pals: The Alpha Beta Revolution™* aims to facilitate ongoing collaboration between patients, caregivers, and medical experts. The monthly broadcasts feature members of the thalassemia community from around the world discussing currents topics relevant to both α- and β-thalassemia.

Fourteen episodes are available and can be accessed here:

EDITORIAL POLICIES & TEAM

The objective of this newsletter is to provide updates on new scientific information, resources, and activities of interest to the thalassemia medical and patient community. The newsletter content is prepared by thalassemia experts in collaboration with Agios Pharmaceuticals. All of these experts serve as paid consultants for Agios Pharmaceuticals.

The following experts are involved in this initiative

- Khaled Musallam, MD, PhD
- Sujit Sheth, MD
- Thomas Coates, MD
- Vip Viprakasit, MD, DPhil
- Ali Taher, MD, PhD
- Hanny Al-Samkari, MD
- Kevin Kuo, MD
- Maria Dominica Cappellini, MD

Mitapivat is not approved for the treatment of thalassemia by any health authority. The safety and efficacy of mitapivat in thalassemia are under investigation and have not been established. There is no guarantee that mitapivat will receive health authority approvals or become commercially available in any country for the uses under investigation.

Contact:
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