Harnessing the Power of Real World Data

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X Foresight Training Course

The European Medicines Regulatory Network: Present and Future

October 27, 2017

Topics

- About bluebird bio
- Real world data: What it is and why it's important in drug development
- Developing gene therapy for β-thalassemia: The role of real world data

Our Strategic Intent

Severe Genetic Diseases
Hematopoietic Stem Cells (HSCs)

Immunotherapy
T Cells

- ***Lentiviral Gene Delivery – Pure, Potent, Reproducible, Scalable***
  - ***Global Manufacturing Platform – Virus and Drug Product***
    - ***Genome Editing Platform – MegaTALs***

bluebird Pipeline Overview

Product Candidates	Program Area	Preclinical	Phase 1/2	Phase 2/3	Rights/Partner
	CNS Diseases				
Lenti-D™ Drug Product	Cerebral ALD				Worldwide
	Rare Hemoglobinopathies				
LentiGlobin® Drug Product	Transfusion-Dependent ß-thalassemia*				Worldwide
	Severe Sickle Cell Disease				Worldwide
	Oncology				
bb2121 BCMA	Multiple Myeloma				Celgene
Next Gen BCMA	Multiple Myeloma				Celgene
Five Prime Target	Undisclosed				Worldwide
HPV-16 E6 TCR	HPV-associated Cancers				Kite Pharma
Viromed Target	Undisclosed				Worldwide excluding Korea
Other Programs	Undisclosed				Worldwide
	Research				
Early Pipeline	Undisclosed + Gene Editing				Worldwide

*The current clinical trials for LentiGlobin are Phase 1/2 studies that may provide the basis for early conditional approval in some jurisdictions

About bluebird's Development Approach

Adaptive Pathways / PRIME

Breakthrough Therapy Designation

Orphan Drug Designation

Phase 1/2 and phase 2/3 studies

Open-label, open-database, single-arm studies

Patients First

Why are real world data important to patients?

- People living with disease don't live life in a clinical trial, nor do their doctors
- They want treatments—transformative ones, as soon as possible

In other words, for the same reasons they are important to us…

Real world evidence:
What it is and why it's important in drug development

Some Definitions

Real World **Data** (RWD)

Data routinely generated in the course of health care delivery

Alternatively defined as any data outside of clinical trials

Real World **Evidence** (RWE)

What you get when you apply rigorous analytics to real world data

--Dave Thompson, INC/Inventiv

RWE addresses needs in:

- Clinical Development
- Regulatory
- Medical Affairs
- Commercial

"A comprehensive data strategy, implemented prelaunch and in partnership with key stakeholders, can make the difference in a product's success or failure – and, more importantly, in patients' lives."

Mike Eaddy, Xcenda

From Data Strategy: The Connective Tissue Required to Bring Cell and Gene Therapies to Market

bluebird uses multiple sources of real world data to support development of gene therapy

Data sources

- Registries
- Observational studies
- Chart reviews
- etc....

Uses of the data

Demonstrate outcomes of current therapies

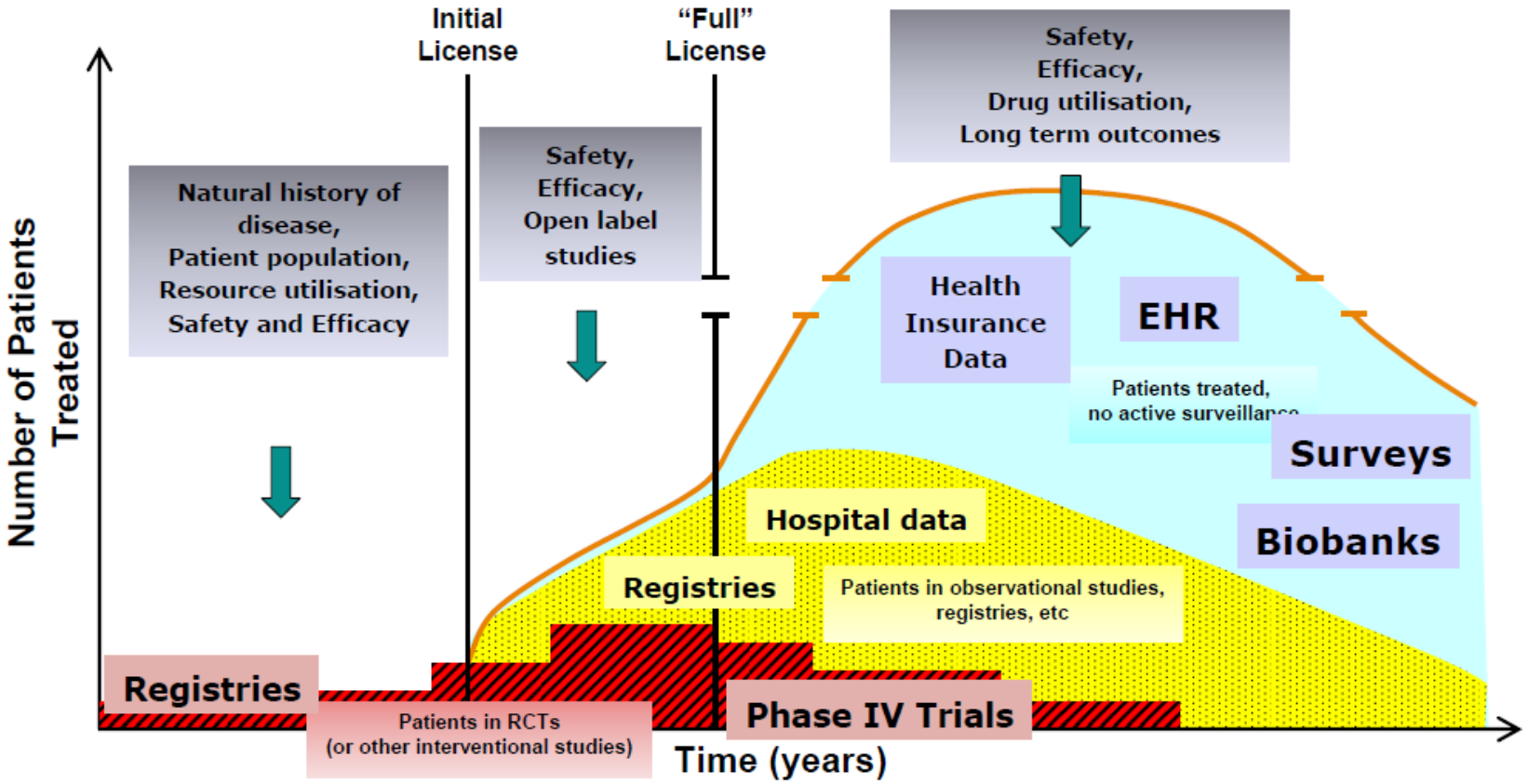
... to provide regulators and payers with context for gene therapy

Demonstrate long-term outcomes of gene therapy

... to aid in clinical decision-making for physicians and patients

... to fulfill regulatory obligations

RWE through the lifecycle
(from European Medicines Agency)



Harlet P. EMA, March 2016

Inheritance of β-Thalassemia

- People with β-thalassemia have little or no functional β globin due to a mutation in the *HBB* gene[1]
- Over 200 disease causing mutations have been identified and grouped into three categories[1,2]:

Notation	Description
β^0	No β globin production
β^+	Reduced β globin production
β^E	Reduced β globin production Primarily found in Southeast Asia

- Inheritance is autosomal recessive – meaning people with β-thalassemia inherit an affected copy of *HBB* from both parents[1]
  - A child of two carrier parents will have a 25% chance of being affected

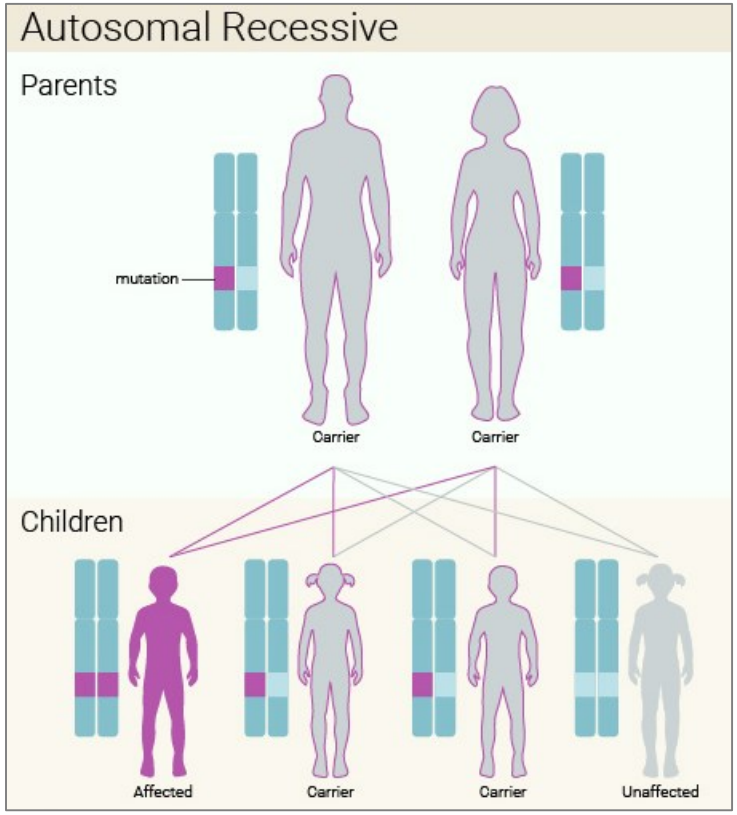
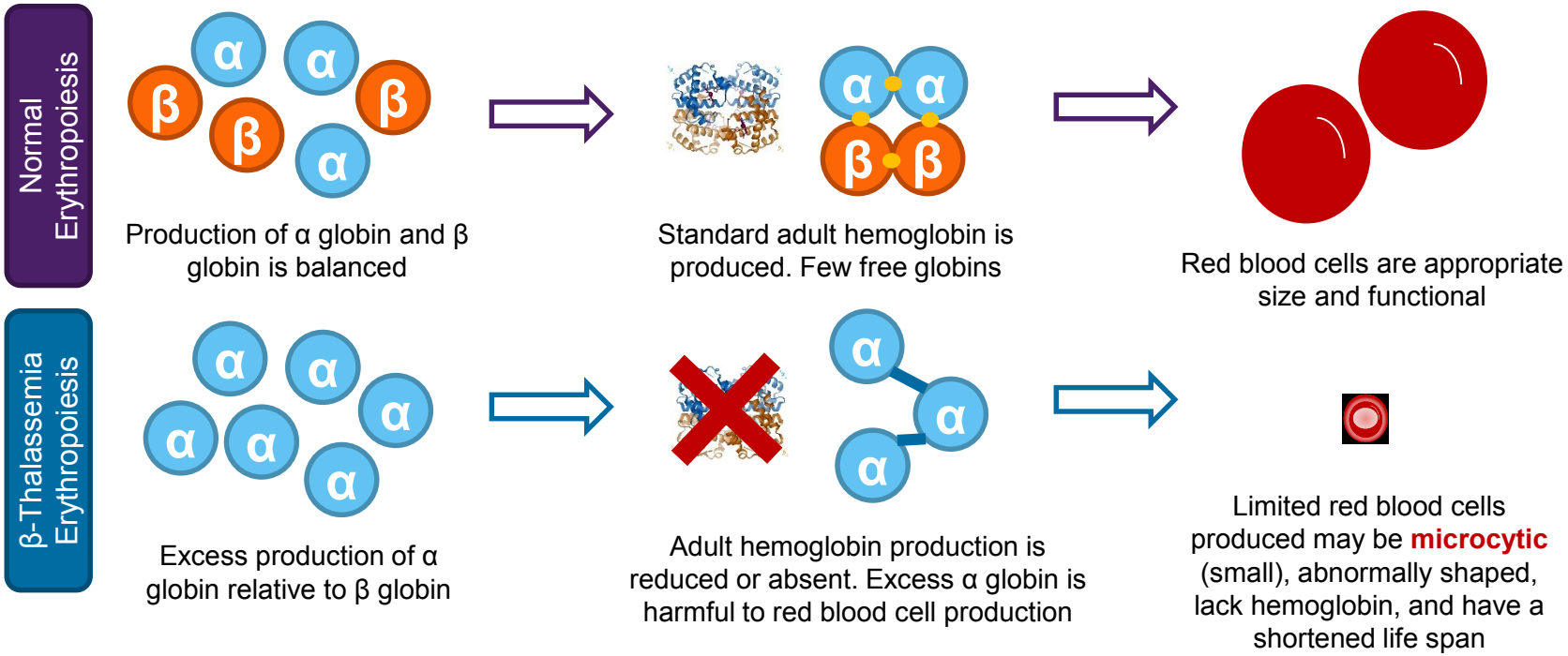


Image from https://ghr.nlm.nih.gov/handbook/illustrations/autorecessive

1. Cao A and Galanello R. *Genetics in Medicine*. 2010;12(2).
2. Thein SL and Wood WG. In *Disorders of Hemoglobin*. 2nd edition. 2009. Steinberg MH, et al. (Eds.) Cambridge University Press.

Pathophysiology of β-Thalassemia

- **Erythropoiesis** is the process of creating red blood cells, which are also called **erythrocytes**
- It typically takes place in bone marrow and requires similar levels of α and β globin chains



Cao A and Galanello R. *Genetics in Medicine*. 2010;12(2).
Rivella S. *Blood Rev*. 2012;26:S12–S15.

Image from http://www.sicklecellinfo.net/hemoglobin.htm.

Treatment of β-Thalassemia

- Blood transfusions to replace missing/defective red blood cells are the standard treatment for β-thalassemia[1,2]

Benefits

- Prolongs life – people with severe disease can live into adulthood
- Alleviates symptoms
- Improves how the transfused person feels
- Transfused people will have more energy and the ability to do more activities

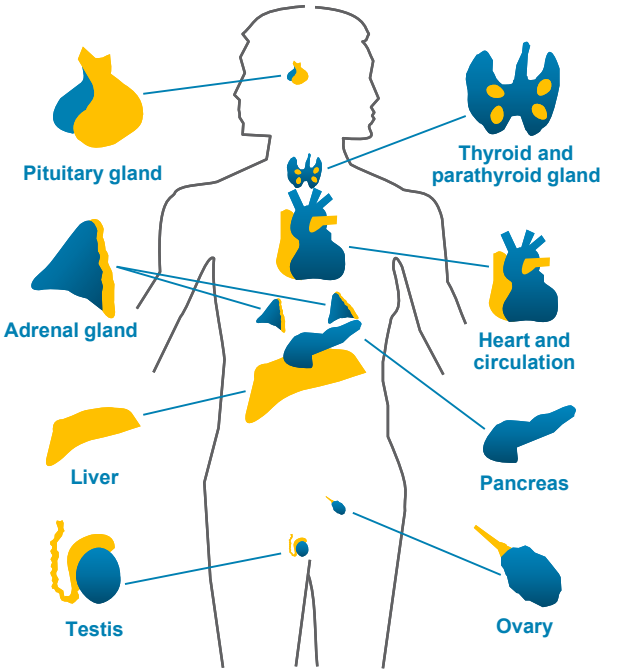
Limitations

- Process takes 1-4 hours or longer and requires travel to an infusion center (time off work and school)
- Effects are temporary, regular treatment every few weeks may be needed
- **Iron overload** needs to be managed with **chelation therapy**
- Expensive
- Risk for fever, alloimmunity, allergic reactions, and infection
- Despite improvements in care, treatment-associated complications are the primary challenge in medical management of people with TDT and the leading cause of mortality[3,4]

1. NHLBI. Online Available https://www.nhlbi.nih.gov/health/health-topics/topics/thalassemia/treatment
2. Cooley's Anemia Foundation. Online available: http://www.cooleysanemia.org/updates/pdf/GuideToLivingWithThalassemia.pdf
3. Tubman et al. J Pedatr Hematol Oncol. 2015;
4. Borgna-Pignatti et al. Ann NY Acad Sci. 2005; Ladis et al. Eur J Haematol. 2011

Iron Overload and Chelation Therapy

Organs that may be affected by iron overload



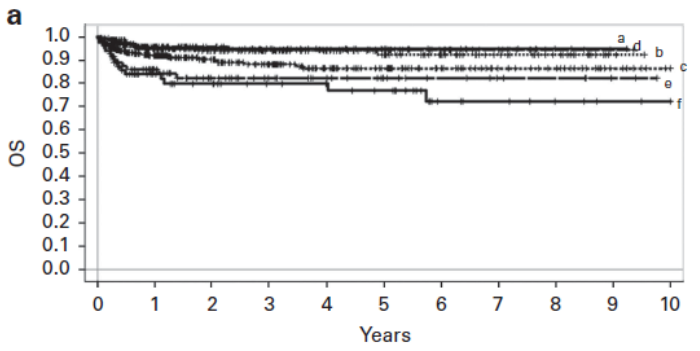
- Iron overload can cause serious, potentially fatal organ damage
- The chelation therapies have a high burden of treatment that may lead to poor compliance[1,2]
- Deferoxamine DFO
  - Subcutaneous administration with a pump for 8-12 hours a day, 5-7 days a week (or more)
  - May result in skin reactions, blurry vision, and hearing loss
- Deferiprone DFP
  - An oral tablet taken 3 times per day
- May result in nausea, vomiting, abdominal pain, joint pain, and reduction in immune cells
- Deferasirox DFX
  - Multiple oral formulations available, including once-daily oral tablet and dispersible tablets
  - May result in kidney, liver, and GI dysfunction

1. Children's Hospital and Research Center Oakland. Online Available http://thalassemia.com/documents/SOCGuidelines2012.pdf
2. Galanello R and Origa R. *Orphanet Journal of Rare Diseases*. 2010;5:11

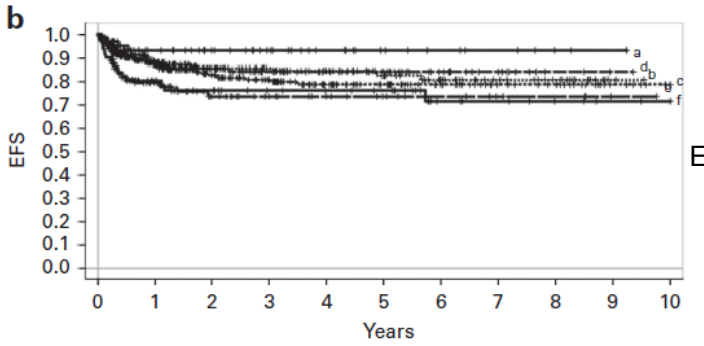
HSCT in Thalassemia

- HSCT is the only curative therapy for β-thalassemia, but is associated with serious risks
- Using modern regimens, transplant related mortality has fallen to ≤5% in low risk cases[1]
- **Rare**: >3000 transplants from 1981-2010[2], but hundreds of thousands of people with β-thalassemia born in that time period
- Why so few?
  - Risks of the procedure
  - No available HLA-matched donor
  - Patients may choose transfusion and chelation
  - Age and health status of the recipient
  - Cost and availability of transplant

Outcomes from 1493 HSCT, in TDT, between 2000 and 2010 (30 countries data)[2]



Overall Survival



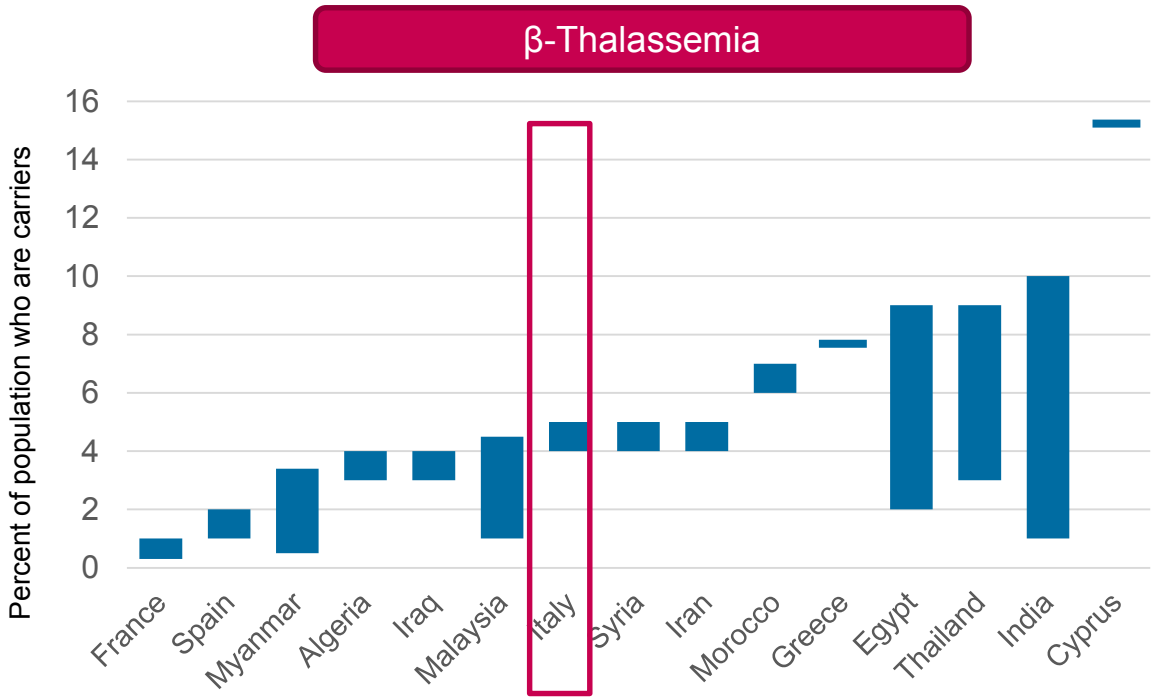
Event-free Survival

	Patients	A) OS Events	A) OS 2-yrs. OS	B) EFS Events	B) EFS 2-yrs. pEFS
a) < 2 years	66	3	0.95±0.03	4	0.93±0.03
b) 2-<5 years	266	13	0.94±0.02	32	0.86±0.03
c) 5-<10 years	352	33	0.90±0.02	52	0.83±0.02
d) 10-<14 years	197	8	0.96±0.02	24	0.86±0.03
e) 14-<18 years	97	14	0.82±0.04	20	0.74±0.05
f) ≥18 years	82	16	0.80±0.05	18	0.76±0.05
P-value (for trend)		<0.001		<0.001	

1. Angelucci E. *ASH Education Book*. 2010;1:456-462
2. Angelucci et al. *Haematologica*. 2014;99(5).
3. Baronciani D et al, *Bone Marrow Transplantation* (2016) 536 – 541

Epidemiology of β-Thalassemia

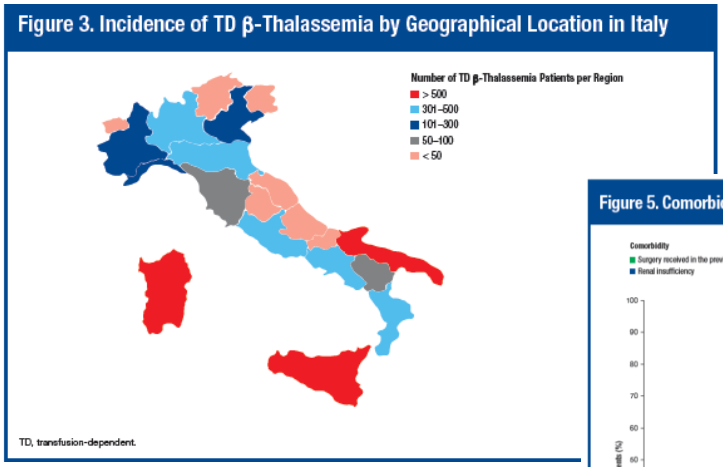
- Globally, 80-90 million people (1.5% of the population) are carriers of β-thalassemia[1]
- More than 40,000 babies with β-thalassemia are born each year[2]
- Migration is changing the distribution of people with the disease[3]

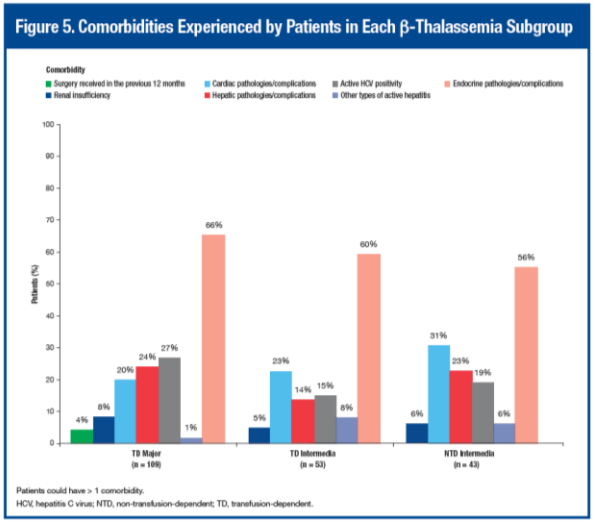


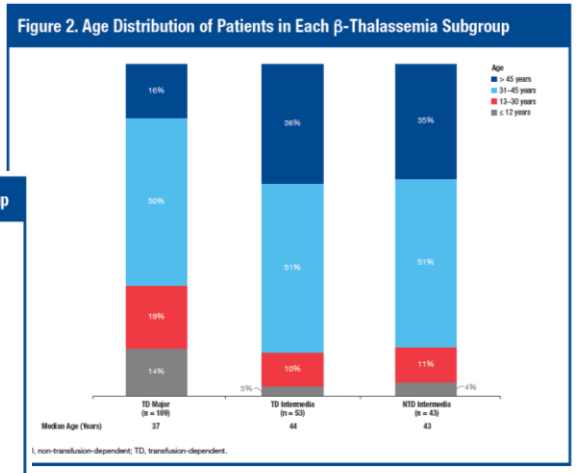
Data from Colah R, et al.

1. Colah R, et al. *Expert Rev Hematol*. 2010;3(1):103-117.
2. Modell B and Darlison M. *Bulletin of the World Health Organization* 2008;86:480–487
3. Angastiniotis M, et al. *The Scientific World Journal*. 2013. Online available http://dx.doi.org/10.1155/2013/727905

Transfusion-dependent Thalassemia (TDT) in Italy







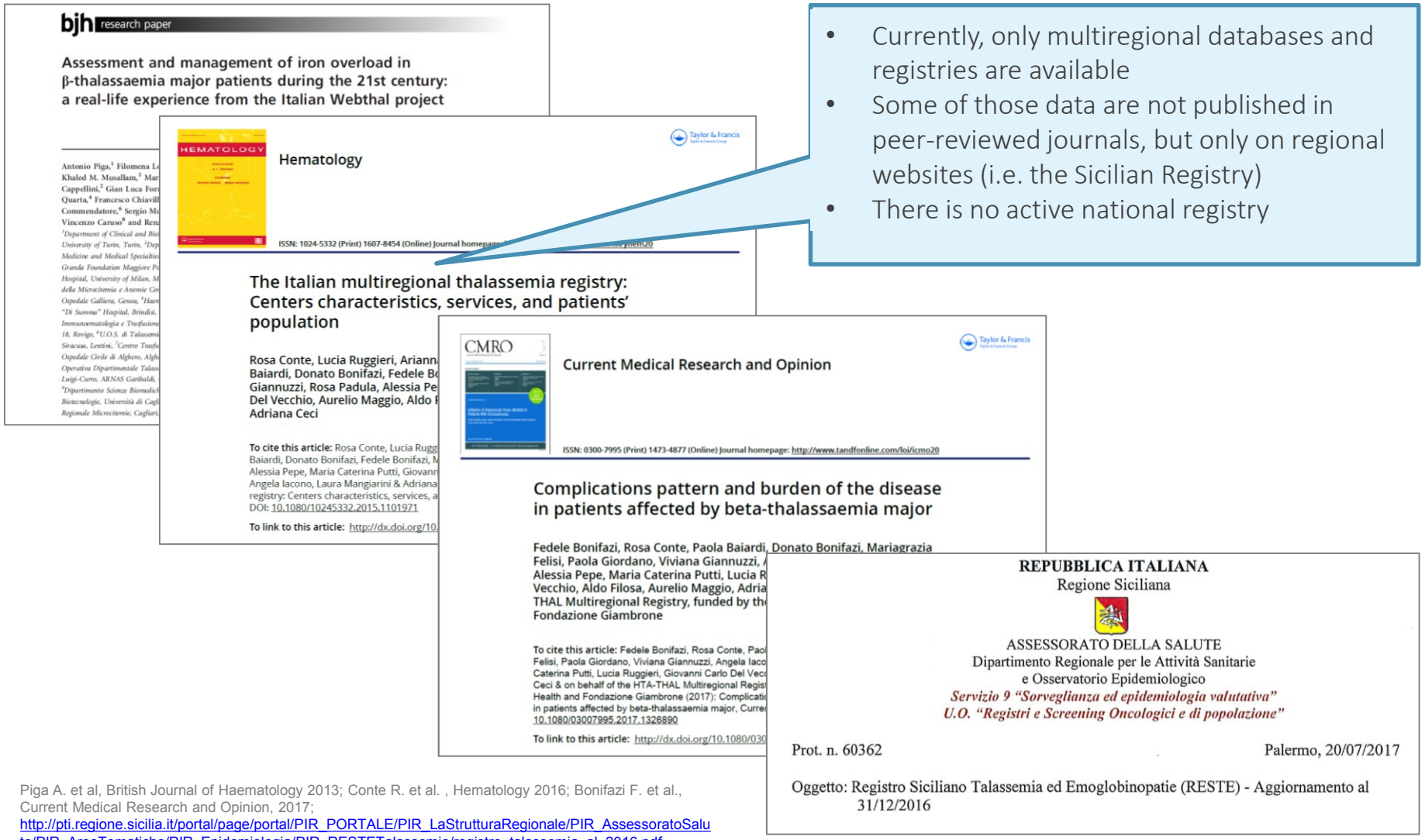
Images adapted by Angelucci E, ASH 2016

- β-Thalassemia is an important public health challenge in Italy; > 7,000 β-thalassemia patients in Italy require transfusion[1]
- TDT is most prevalent in Sicily, Sardinia, and Puglia
- However, TDT patients are presents in other 10 Italian Regions

1.Osservatorio Malattie Rare. http://www.osservatoriomalattierare.it/talassemia. Accessed October 28, 2016.

Italian Thalassemia clinical and registry landscape

- Currently, only multiregional databases and registries are available
- Some of those data are not published in peer-reviewed journals, but only on regional websites (i.e. the Sicilian Registry)
- There is no active national registry



bjh research paper

Assessment and management of iron overload in β-thalassaemia major patients during the 21st century: a real-life experience from the Italian Webthal project

Hematology

The Italian multiregional thalassemia registry: Centers characteristics, services, and patients' population

Rosa Conte, Lucia Ruggieri, Ariann… Baiardi, Donato Bonifazi, Fedele B… Giannuzzi, Rosa Padula, Alessia Pe… Del Vecchio, Aurelio Maggio, Aldo … Adriana Ceci

To cite this article: Rosa Conte, Lucia Rugg… Baiardi, Donato Bonifazi, Fedele Bonifazi, … Alessia Pepe, Maria Caterina Putti, Giovann… Angela Iacono, Laura Mangiarini & Adriana… registry: Centers characteristics, services, a… DOI: 10.1080/10245332.2015.1101971

To link to this article: http://dx.doi.org/10…

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Complications pattern and burden of the disease in patients affected by beta-thalassaemia major

Fedele Bonifazi, Rosa Conte, Paola Baiardi, Donato Bonifazi, Mariagrazia Felisi, Paola Giordano, Viviana Giannuzzi, … Alessia Pepe, Maria Caterina Putti, Lucia R… Vecchio, Aldo Filosa, Aurelio Maggio, Adria… THAL Multiregional Registry, funded by th… Fondazione Giambrone

To cite this article: Fedele Bonifazi, Rosa Conte, Paol… Felisi, Paola Giordano, Viviana Giannuzzi, Angela Iaco… Caterina Putti, Lucia Ruggieri, Giovanni Carlo Del Vec… Ceci & on behalf of the HTA-THAL Multiregional Regist… Health and Fondazione Giambrone (2017): Complicati… in patients affected by beta-thalassaemia major, Curre… 10.1080/03007995.2017.1326890

To link to this article: http://dx.doi.org/10.1080/030…

REPUBBLICA ITALIANA
Regione Siciliana

ASSESSORATO DELLA SALUTE
Dipartimento Regionale per le Attività Sanitarie
e Osservatorio Epidemiologico
Servizio 9 "Sorveglianza ed epidemiologia valutativa"
U.O. "Registri e Screening Oncologici e di popolazione"

Prot. n. 60362 Palermo, 20/07/2017

Oggetto: Registro Siciliano Talassemia ed Emoglobinopatie (RESTE) - Aggiornamento al 31/12/2016

Piga A. et al, British Journal of Haematology 2013; Conte R. et al. , Hematology 2016; Bonifazi F. et al., Current Medical Research and Opinion, 2017;
http://pti.regione.sicilia.it/portal/page/portal/PIR_PORTALE/PIR_LaStrutturaRegionale/PIR_AssessoratoSalute/PIR_AreeTematiche/PIR_Epidemiologia/PIR_RESTETalassemie/registro_talassemia_al_2016.pdf

Developing Gene Therapy for TDT in the EMA's Adaptive Pathways Program

About the Program

A prospectively planned, iterative approach to bringing medicines to market. It initially targets development to a well-defined group of patients likely to benefit most, then uses iterative phases of evidence gathering and progressive licensing adaptations to expand use to a wider population.

Purpose

Improve timely access for patients to new medicines

Three Main Elements

1. Iterative development
2. **Gathering evidence through real-life use to supplement clinical trial data**
3. Early involvement of patients and health-technology-assessment bodies

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000601.jsp

Example Project:
Retrospective Database Analyses of Current TDT Therapies

Key Questions about Current TDT Therapies

- What are the outcomes of transfusion/chelation therapy and allo-HSCT?
- What is the disease burden and progression during these treatments?
- What risk factors predict disease progression?

Overview of Study

Design

Retrospective, longitudinal data analyses

Inclusion Criteria

- Confirmed diagnosis of β-thalassemia
- Known transfusion status
- Retrospective data available for 2+ years

Data Elements

- Patient demographics
- Treatments (allo-HSCT, transfusion/chelation)
- Clinical outcomes
- Quality of life

Collaborators

- several centers of thalassemia care in EU
- European Society for Blood & Marrow Transplant
- Thalassemia Longitudinal Cohort (Primarily US)

Example Project:
Retrospective Database Analyses of Current TDT Therapies

Project steps and approximate duration

Step	Duration
Develop protocol and statistical analysis plan	2-3 months
Ethics and institutional approvals	4-6 months
Data extraction	2-4 months
Data analyses	2 months
Report development	2 months
Publication: To be determined in consultation with the investigators	

Example Project:
Retrospective Database Analyses of Current TDT Therapies

Collaborating Centers in Italy

M.I.O.T.
Myocardial Iron Overload
in Thalassemia

HTA-Thal
Italian Multiregional
Thalassemia Registry

Retrospective database analyses are challenging

- Pre-existing informed consents may limit or prohibit access
- Lengthy processes for institutional and ethical reviews require advance planning
- Many academic centers have limited resources to support these types of projects
- Aggregating data across multiple centers requires clinical insights from each center and careful interpretation

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… but may help improve patient lives

Thank you!

Gabriella Pasciullo
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