RARE INHERITED ANAEMIAS

Priority Setting Partnership

ABOUT THE COLLABORATORS

Congenital Anaemia Network is a group of patients, carers, doctors, and scientists who are all interested in patients with rare inherited anaemia.

DBA UK is a registered charity aiming to deliver support, research and hope to the Diamond Blackfan (DBA) community by bringing families together to share their experiences, communicating the latest medical information and raising funds to support those with DBA in the UK.

The James Lind Alliance brings patients, carers and clinicians together to identify and prioritise the unanswered questions they want health research to address through Priority Setting Partnerships.

Genetic Alliance UK is the national charity working to improve the lives of patients and families affected by all types of genetic conditions. Genetic Alliance UK is an alliance of over 200 patient organisations.

The National Institute for Health Research fund health and care research and translate discoveries into practical products, treatments, devices and procedures, involving patients and the public in all their work.

Published by: James Lind Alliance Priority Setting Partnership Steering Group along with JLA, DBA UK, CAN, Genetic Alliance UK and Oxford BRC Blood Theme

MRC Weatherall Institute of Molecular Medicine
University of Oxford
Oxford
OX3 9DS

Telephone: +44 (0) 1865 222346
Email: noemi.roy@nhs.net
Website: oxfordbrc.nihr.ac.uk/haematology-and-stem-cells/

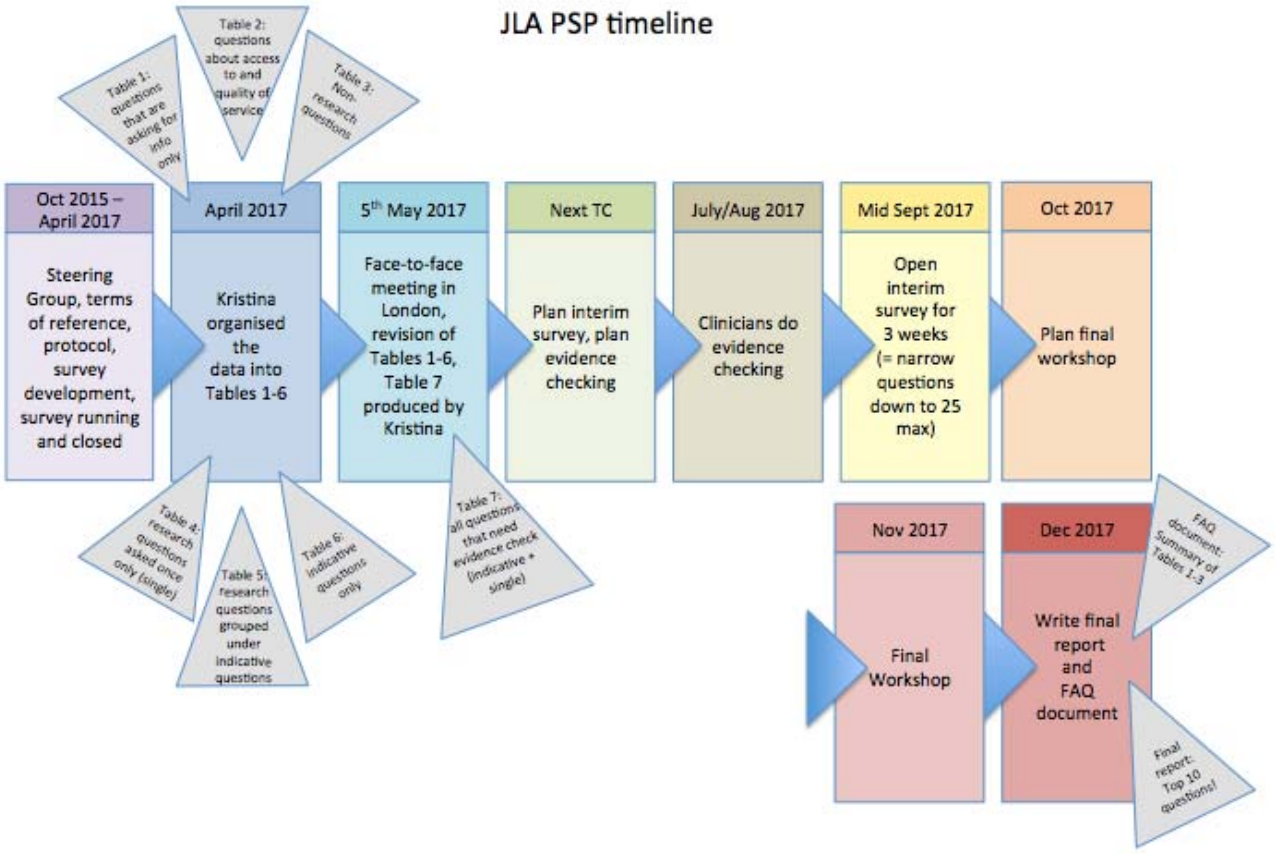
Photo accreditation: Oxford BRC Blood Theme
Published: June 2018

CONTENTS

WHY SET PRIORITIES FOR RARE INHERITED ANAEMIAS RESEARCH?

Patients with a rare inherited anaemia may take years to receive a precise diagnosis, if at all. Lack of specialist knowledge, or poor access to the few centres of specialist expertise, means that not all patients will have access to the same standard of care. Few treatments have been developed because of the lack of research in this area. When treatments are available, not all patients can access them, and their doctors may not have full knowledge of how the treatment should be given.

This Priority Setting Partnership aimed to stimulate research on rare inherited anaemias by finding out what people with these conditions, their carers and health professionals believe to be the most important areas for future research.



THE TOP 10 PRIORITIES FOR RARE INHERITED ANAEMIAS RESEARCH

The James Lind Alliance (JLA) Rare Inherited Anaemias Priority Setting Partnership agreed the following Top 10 priorities for research:

1. **Would a national formal network of clinicians with expertise and /or a national MDT (multidisciplinary team meeting) improve care for patients with rare inherited anaemias?**
2. **Can the diagnostic pathways in rare inherited anaemias be improved to provide faster and more accurate diagnoses in a cost effective manner?**
3. **Could an understanding of the cellular and molecular processes in red blood cell production lead to new treatments?**
4. **Could the need for iron chelation be reduced? Could current approaches and monitoring be improved?**
5. **How do existing drugs for rare inherited anaemias work? Could this understanding lead to new treatments and new ways of delivering treatments?**
6. **How can the fatigue of severe anaemia be managed (apart from blood transfusions)?**
7. **Would a register of all rare inherited anaemia patients in the UK (including data and samples) improve care?**

8. **How is quality of life affected by rare anaemia and its treatment? How could this be improved for patients?**

9. **What factors indicate that a person with a rare inherited anaemia needs a transfusion, and what is the best regime to maintain safety and quality of life?**

10. **How can high quality care be sustained throughout a patient's lifetime (e.g. from child to adult and into old age)?**

'It soon became apparent that every person's perspective was valuable'
External observer

SETTING THE LIMITS OF THIS PRIORITY-SETTING EXERCISE

The Steering Group discussed the limits of this PSP and agreed that following rare inherited anaemias should be included:

- Diamond-Blackfan Anaemia
- Congenital Dyserythropoietic Anaemia
- Congenital Sideroblastic Anaemia
- Red cell Membrane disorders
- Red Cell Enzyme disorders
- Transfusion-dependent unexplained inherited anaemias

'There were several instances in which people changed their minds about the priorities of individual questions, having listened to the contribution of others with a totally different perspective.'

External observer

A number of other specific inherited anaemias (such as Sickle Cell Anaemia, Thalassaemia and aplastic anaemias, including Fanconi Anaemia) are relatively rare in the UK as a whole, but were not included in the PSP. This was because people with these conditions do not experience the same delays in diagnosis and treatment. In the case of people with aplastic anaemias, the natural history is very different (usually acute rather than chronic) and anaemia is not usually their main symptom.

The PSP included people of all ages, recognising that it might be difficult to engage young people in the surveys. People living outside the UK were invited to take part because these conditions are so rare. Their questions were only included if relevant to UK treatment and care.

Another PSP looking at Rare Musculoskeletal Diseases in adults was run at the same time. The questions from both PSPs were reviewed to see if there were common questions from people with rare conditions.

HOW WERE THE PRIORITIES IDENTIFIED?

Getting started

Key organisations, clinicians, and people with rare inherited anaemias were identified and invited to become partners in the project, and a steering group was formed to oversee the work. The partnership was officially launched in early 2016.

The first survey

A wide range of people with rare inherited anaemias, their friends and family members, and the health and social care professionals who support them, were asked to identify the questions they would like answered by research. They submitted their questions via an online survey between October 2016 and January 2017. A paper version of the survey was also made available.

The partners and Steering Group members sent the survey out to their networks, via email, newsletters, social media, websites and blogs. A total of 88 people responded. 23% of them have a rare inherited anaemia, 27% are carers, relatives or friends, 44% are health or social care professionals and 6% came from other organisations. Altogether, they asked 557 questions.

Processing the survey results

Some of the questions asked through the survey were not relevant to this project. Some people were asking for information or advice i.e.-, questions that do not need research to be answered. Answers to these questions have been collected in a FAQ document which can be found in Appendix 2 Other questions were about access to services or the quality of health professionals' training. These might need to be addressed through changing policy and practice rather than research, and again these questions were removed. The full list of removed questions is available on the JLA website (www.jla.nihr.ac.uk/priority-setting-partnerships/rare-inherited-anaemias/).

A total of 314 questions remained. Some of these questions were asked repeatedly by many people, in slightly different ways. Similar questions were grouped together and an overarching question was written which summarised all the questions in the group. A small number of questions were only asked once. These were added to a long list with all the summary questions. We then checked the published evidence from research that has been carried out in the past, and removed the questions that previous research had already

answered. At the end of this stage, we had 48 unanswered questions (see Appendix).

The second survey

The list of 48 questions went into a second survey, where we asked people to rank each question on a Likert scale to indicate the degree of importance of that question to them. The second survey went out to everyone from the first survey who wanted to stay involved, and to all the same networks. This time 120 people responded (between 26th Oct 2017 and 16th Nov 2017. 24% have a rare inherited anaemia, 28% are carers, relatives or friends, 41% are health or social care professionals and 7% came from other organisations. The questions in the survey were presented in 6 categories namely, Diagnosis, Treatment, Basic Biology, Psycho-social impact, Management and Health Services. Participants were asked to consider each question in each category, giving the questions a 'high priority' score of 5 points down to 'not a priority' score of 0. The points were then added up. We looked at the scores from each type of respondent (people with anaemia, carers, health care professionals etc), so that everyone could have an equal influence on the final outcome. A shortlist of 25 questions was agreed by the steering group, to include each of the groups' top priorities.

The priority setting workshop

The 25 shortlisted questions were discussed at a workshop held at Kassam Stadium Conference and Events Centre in Oxford on the 6th of Dec 2017. 31 people with different rare inherited anaemias, carers and health professionals came to the workshop – some Steering Group members, some people who had taken part in the surveys, and some people who were new to the project. They were recruited through the Steering Group's networks, via patient and clinician groups and through social media.

The participants were asked to look at the 25 questions before they came, and to think about how they would rank them in order of importance. Their priorities were obviously informed by their own experience. By coming to the workshop and taking part in a number of small group discussions, everyone got to hear other people's views on which questions were most and least important. This helped the group as a whole to reach an agreement on

which questions should be a priority. This is the aim of the JLA to build consensus and shared understanding between lots of very different groups with an interest in research.
The 15 questions (from the original 25 discussed at the workshop) that did not make the final Top 10 are listed below. They are listed in order of importance as agreed by the people at the workshop:

1. Are there existing drugs for anaemias (or other conditions) that could be used to treat rare inherited anaemias?

2. Could therapies that repair faulty genes cure rare inherited anaemias?

3. How can we predict which patients will respond to particular treatments and tailor treatments to the individual?

4. What are the psychological impacts of rare anaemias on patients and their families?

5. What are the long-term side effects of treatment and how can they be reduced?

6. What are the social impacts (on education, work-life and income) of rare inherited anaemia? How can these be improved?

7. What are the precise genetic mutations causing different types of rare inherited anaemia and variation between people with the same type of rare inherited anaemia?

8. What is the role of next generation sequencing (NGS) in the diagnostic pathway for rare inherited anaemias?

9. Would a registry of patients help provide accurate data on the number of people affected by rare inherited anaemias in the UK?

10. Are there biomarkers for rare anaemia? Could this be used to develop new treatments?

11. What are the risks in pregnancy (for mother and child) for women with rare inherited anaemia?

12. What factors determine which patients are best treated by bone marrow transplant?

13. Could new technology (e.g. phone apps and wearable trackers) be used to support self-management (e.g. to determine the need of transfusion)?

14. Are there non-invasive ways of measuring blood haemoglobin levels that could be accurate enough to be used in clinical practice?

15. What is the risk of cancer for people with rare inherited anaemia?

NEXT STEPS

The JLA Rare Inherited Anaemias Priority Setting Partnership hopes that by identifying these priority questions for research, we will ensure that future research is focused on the issues that matter most to people with rare inherited anaemias, their carers, relatives and friends and the health and social care professionals who support them.

'There are multiple ways to engage in good quality research on subjects that might be 'soft' but that produce evidence of immense significance to patients and carers.'

External observer

A call to action

Many people gave their time and effort to submit their questions and to work through the JLA process to identify the final top 10 questions for future research. We want to ensure that these efforts are respected and recognised and therefore:

- We encourage research funders to include these priorities in their research strategy and to target these topics for future research funding.

- We encourage researchers to focus their efforts on answering the highest priority questions and to mention the JLA Rare Inherited Anaemias PSP in their applications for funding. If a researcher receives funding to address any of the listed priorities, we ask that they please inform the JLA.

- We encourage funders, researchers and all interested parties to share this report with others and to raise awareness of the need for more research on rare inherited anaemias in the UK.

'The use of social media helped to engage patients that otherwise may not have had access to this kind of research project. This led to a surprisingly good response from the smaller rare anaemia groups such as CDA.'

Rachel Wearmouth

This PSP was supported by Genetic Alliance UK, the national charity working for patients and families affected by all types of genetic conditions. Genetic Alliance UK is an alliance of over 200 patient organisations and runs Rare Disease UK, the national campaign for people with rare diseases and all who support them. Two members of Genetic Alliance UK staff worked as members of the PSP steering group, and the charity helped develop the communications strategy for the surveys and report.

While each rare disease presents specific challenges to patients and their families and clinicians, there are also commonalities of experience across rare diseases. Research questions identified through this PSP that relate to such experiences have been collected – and will be collated with similar findings from the rare musculoskeletal PSP that is also due to complete in 2018, and with those from a new rare disease PSP that Genetic Alliance UK is about to launch. Thus a list of research priorities relevant across rare diseases will be identified, providing a valuable addition to the outputs from the individual PSPs.

If you have any queries or comments about this work, please sheelaupadhyaya@gmail.com

Further information about the project can be found at: www.jla.nihr.ac.uk/priority-setting-partnerships/rare-inherited-anaemias/

If you would like more information and advice about inherited anaemia, please contact noemi.roy@nhs.net

ACKNOWLEDGMENTS

Thanks to our partners who supported this project, the Steering Group members, the James Lind Alliance advisers and support staff who advised and facilitated the partnership, and the people who took part at all the different stages.

'All in all it was a hugely enjoyable day and I was very impressed with the process. It really did feel as though all contributors were valued and that they all had shared ownership of the workshop outcomes.'

External observer

Members of the Steering Group were:

Carol Anderson, Anaemia Nurse Specialist, East Kent Hospitals NHS Trust

Elizabeth Blackmore, Congenital Anaemia Network

Subarna Chakravorty, Consultant Paediatric Haematologist, Kings College London

Caroline Clifford, Patient Representative

Amy Hunter, Genetic Alliance UK

Nick Meade, Genetic Alliance UK

Dominic Messenger, Diamond Blackfan Anaemia UK

Heather Paul, Patient Representative

Anupama Rao, Consultant Haematologist, Great Ormond Street Hospital

Irene Roberts, Professor of Paediatric Haematology, Paediatrics and MRC Molecular Haematology Unit, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford

Noémi Roy, Academic Clinical Lecturer & Haematologist, Weatherall Institute of Molecular Medicine, John Radcliffe Hospital, Oxford

Kristina Staley, Information Specialist

Sheela Upadhyaya, JLA Adviser

Rachel Wearmouth, Patient Representative

Jenny Welch, Consultant Paediatric Haematologist, Sheffield Children's Hospital

APPENDIX 1: THE FULL LIST OF QUESTIONS

These are the 48 unanswered questions sent in by people with a rare inherited anaemia, their carers, relatives and friends and the health and social care professionals who support them. People sent in their questions via a survey. The questions that were asked many times have been grouped and summarised into a single question. A full list of all questions asked, and the questions belonging to each group can be found on the JLA website (www.jla.nihr.ac.uk/priority-setting-partnerships/rare-inherited-anaemias/).

1. Are people with hereditary spherocytosis at risk of pulmonary hypertension (high blood pressure in the heart-lung system)?

2. Are there biomarkers for rare anaemia? Could these be used to develop new treatments?

3. Are there existing drugs for other types of anaemias or any other condition that could be used to treat rare inherited anaemias?

4. Are there non-invasive ways of measuring blood haemoglobin levels that could be accurate enough to be used in clinical practice?

5. Are there ways (such as medication) to reduce bilirubin levels in patients with inherited haemolytic anaemias (eg hereditary spherocytosis, PK deficiency, etc)

6. Can the diagnostic pathways in rare inherited anaemias be improved to provide faster and more accurate diagnoses in a cost effective manner?

7. Can we develop non-animal models of rare inherited anaemia to support laboratory based research?

8. Could an understanding of the cellular and molecular processes in red blood cell production lead to new treatments?

9. Could artificial blood be developed for transfusions?

10. Could life style changes (e.g. exercise, diet and/or supplements) help manage anaemia?

11. Could new technology (e.g. phone apps and wearable trackers) be used to support self-management (e.g. to determine the need for transfusions)?

12. Could the need for iron chelation be reduced? Could current approaches and monitoring be improved?

13. Could therapies that repair faulty genes cure rare inherited anaemias?

14. Could there be less invasive ways to assess bone marrow cells that don't involve sampling the bone marrow with a needle (for example imaging/X-ray techniques)?

15. For rare inherited anaemia patients who have had their spleen removed (splenectomy), are there risks of being on lifelong antibiotics?

16. How can high quality care be sustained throughout a patient's lifetime (e.g. from child to adult and into old age)?

17. How can the fatigue of severe anaemia be managed (apart from blood transfusions)?

18. How can we predict which patients will respond to particular treatments and tailor treatments to the individual?

19. How can you prevent gallstones forming because of the inherited anaemia?

20. How do existing drugs for rare inherited anaemias work? Could this understanding lead to new treatments and new ways of delivering treatments?

21. How is bone strength affected by rare inherited anaemias and how can it be optimised?

22. How is quality of life affected by rare anaemia and its treatment? How could this be improved for patients?

23. How likely are patients with hereditary spherocytosis who do NOT have splenectomy to develop gallstones?

24. If people with rare inherited anaemia receive blood transfusions that are better matched by blood type, does this reduce the risk of immune reactions to the transfusions?

25. If there is a very high reticulocyte (immature red blood cells) count in hereditary spherocytosis, can this cause fatigue even with normal haemoglobin counts?

26. In DBA (Diamond–Blackfan anaemia) could understanding the role/reason for elevated ADA (adenosine deaminase activity) help better understand the condition?

27. Is it safe to play contact sports with an enlarged spleen?

28. Is splenectomy for haemolytic anaemia a more complicated procedure in older patients (middle age & beyond)?

29. Is there a difference between using MRI T2* scan vs ferriscan to monitor iron loading?

30. Is there a link between rare inherited anaemia and diabetes?

31. Would the benefits of a screening programme for rare inherited anaemias outweigh any risks?

32. What are the long-term side-effects of treatment and how can they be reduced?

33. What are the precise genetic mutations causing different types of rare inherited anaemia and variation between people with the same type of rare inherited anaemia?

34. What are the psychological impacts of a diagnosis of rare anaemia on patients and their families?

35. What are the risks of pregnancy (for mother and child) for women with rare inherited anaemia?

36. What are the social impacts (on education, work-life and income) of rare inherited anaemia? How can these be improved?

37. What factors determine which patients are best treated by a bone marrow transplant?

38. What factors indicate that a person with a rare inherited anaemia needs a transfusion, and what is the best regime to maintain safety and quality of life?

39. What is the best steroid treatment regime in DBA (Diamond–Blackfan anaemia)?

40. What is the likely course of rare inherited anaemia with or without treatment?

41. What is the risk of cancer for people with rare inherited anaemia?

42. What is the role of GPs in providing care to people with rare inherited anaemia and how could they be better prepared for this role?

43. What is the role of next generation sequencing (NGS) in the diagnostic pathway for rare inherited anaemias?

44. Would a national formal network of clinicians with expertise and/or a national MDT (multidisciplinary team meeting) improve care for patients with rare inherited anaemias?

45. Would a register of all rare inherited anaemia patients in the UK (including data and samples) improve care?

46. Would a registry help provide accurate data on the number of people affected by rare inherited anaemias in the UK?

47. Would care coordinated via a central specialist centre improve care for patients and be more cost effective?

48. Would patient-held records improve quality of care for patients with rare inherited anaemias?

APPENDIX 2: FREQUENTLY ASKED QUESTIONS

1. **Are MRI (magnetic resonance imaging) techniques able to replace invasive monitoring of iron loading by, for example, liver biopsy?**

   MRI, or magnetic resonance imaging, is a technique that is used to image the body. It does not use any radiation (unlike X-rays or CT scans) and relies on the natural magnetic properties of water in the body. Different tissues in the body will have different amounts of water, allowing each organ to be clearly visualised. Because iron overload in different organs change their magnetic properties, it is possible to get an idea of how much iron there is in each organ.

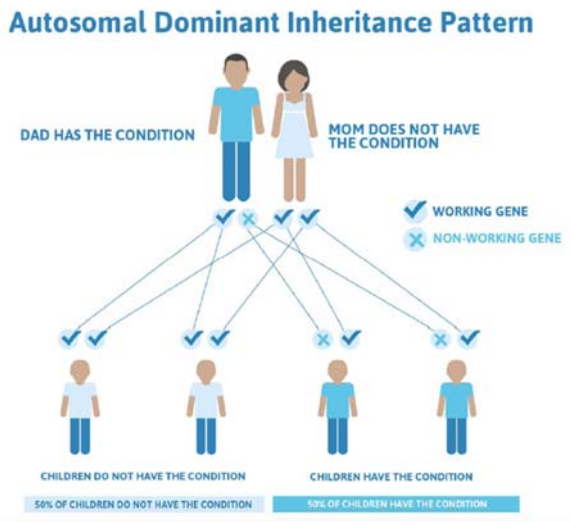
   For the liver, there is a direct link between the iron estimated by MRI and the iron that is found on liver biopsies. While this has mostly been looked at in patients with thalassaemia, it is accepted that this is also true for iron overload in all types of inherited anaemias, for patients on regular blood transfusions and for patients with a condition called genetic haemochromatosis. For this reason, liver biopsies are almost never done to assess iron anymore. Patients who are on iron chelation are now regularly monitored (~yearly) with an MRI.

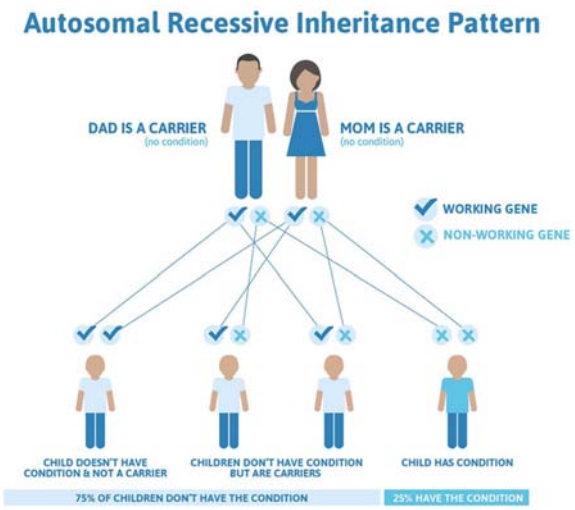
   In the heart, there isn't a direct link like there is for the liver. However, there are two cut-offs which identify "moderate iron overload in the heart" and "severe iron overload in the heart". Patients whose MRI shows moderate or severe iron in the heart are at risk of heart failure and even death if the iron is not removed by intensive chelation.

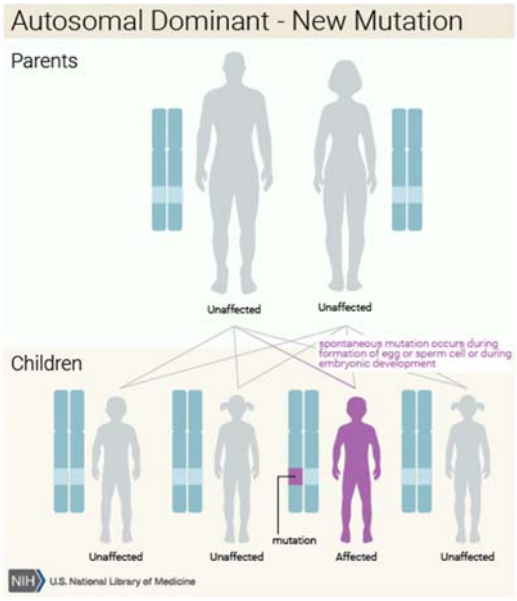
2. **What are the risks of other family members having rare inherited anaemia when one family member has been diagnosed?**

   There are different ways that different rare inherited anaemias can get inherited. Some are always inherited in the same way (autosomal recessive in the case of CDA-1 and CDA-2), and some can vary (autosomal dominant or new mutation/de novo in DBA; autosomal dominant or recessive in hereditary spherocytosis).

   Because the inheritance patterns can vary so much, finding the correct mutation for each patient's condition can help give accurate information about risks of passing on the condition to the next generation.







Source: geneticsupportfoundation.org

https://ghr.nlm.nih.gov/primer/inheritance/riskassessment

3. **What is the best way to support patients and families through the diagnosis (e.g. peer support groups)?**

Receiving the diagnosis of a life-long condition can be a very stressful time for patients and their families. This can be particularly so in rare anaemias as sometimes the diagnosis can be uncertain for months or even years although hopefully this is changing as diagnostic tests improve. Managing this uncertainty and trying to carry on with normal life is challenging. It's important for patients and families to have easy access to their healthcare team and important for the team to keep them well informed of any results or new developments. When the diagnosis is made there may be many questions and the clinicians will provide suitable written material and guide patients and families to the best on line resources. Getting in touch with a peer support group at this stage can make all the difference to how you view your condition. Contact with other people who have experienced the same challenges gives confidence and hope. There are a number of national and international organisations such as Congenital Anaemia Network (CAN), DBA Foundation, Rare Disease UK, Hereditary Spherocytosis UK, Genetic Alliance UK, Pyruvate Kinase Deficiency Support Group, European Network of Rare or Congenital Anaemias (ENERCA) details of all can be found on line.

4. **What are the best ways to support patients and families in the day-to-day management of the condition (e.g. peer support groups)?**

Once your condition has been diagnosed and a management plan put in place by your healthcare team you may find that you only see your clinician infrequently. It's important you know how to contact the team with any health queries you have and you feel that they listen to your concerns.

However even the best most dedicated teams cannot supply the same helpful practical advice and reassurance as someone who has already faced the same challenges as you. This is why Peer support groups can be so successful. People in support groups have a wealth of knowledge and expertise that they are happy to pass on. Hopefully you too will be able to do this in future. The groups allow discussion of the practical problems that really matter and provide a space for you to 'be yourself' without having to constantly explain your condition. Learning about your condition, becoming an expert patient and possibly advocating for others with the same diagnosis can be a way of fighting with the challenges of a lifelong anaemia.

Support groups are useful forums for discussing symptoms and their management but it's important if you're thinking of trying a new treatment or management plan to discuss it with your Health care team first.

5. **What factors indicate that a person requires their spleen to be removed in inherited haemolytic anaemias?**

The spleen may be removed in some patients with inherited haemolytic anaemias to improve their anaemia and other symptoms of a large spleen. Removing the spleen increases the risk of sepsis and in some cases increases the chances of developing blood clots later in life. Hence surgery to remove the spleen should only be offered to patients in whom the benefits outweigh the risks. The most common reason for recommending spleen-removing surgery is when patients develop severe anaemia, or are red blood cell transfusion dependent, or have large, painful and uncomfortable spleens or have low platelet counts or white blood cell counts as a result of their large spleens. Spleen-removing surgery is not recommended in patients with mild forms of hereditary haemolytic

anaemias. As far as possible, surgery is delayed until age 6 to avoid severe infection soon after surgery. Spleen removing surgery should not be undertaken in a rare form of haemolytic anaemia called hereditary stomatocytosis as patients develop severe blood clots in later life.

6. **Why do many parents of children not know about pre-implantation diagnosis or about pre-implantation diagnosis with HLA (human leukocyte antigen) match?**

Pre-implantation genetic diagnosis (PGD) is an assisted reproduction technique that involves in vitro fertilisation (IVF) for couples who are at risk of passing a serious genetic condition to their offspring. This technique allows couples to have babies free of a genetic disease that they are at risk of passing to their children. PGD is highly regulated in the UK and is available in a few specialised centres and are only available to couples who fulfil several pre-determined criteria. More than 400 serious genetic conditions can be prevented using this technique in the NHS. In some cases, couples who have an affected child with a serious genetic blood disorder, PGD and HLA tissue typing can be used to allow the couple to give birth to a child free from a serious genetic disorder, but also an HLA match to their affected older sibling, allowing the new baby to donate cells to their affected sibling to undergo a Haematopoietic Stem Cell Transplant. PGD/HLA typing has a lower rate of success compared to PGD alone. It is not clear why information about these procedures is not widely known among parents with affected children. Fairly detailed information is available on the internet through the Human Fertilisation and Embryology Authority in the UK and through charities such as Genetic Alliance UK.


Yes We Can
CONGENITAL
ANAEMIA
NETWORK


dbaUK
Diamond Blackfan Anaemia (DBA) charity


James
Lind
Alliance
Priority Setting Partnerships


GENETIC
ALLIANCE UK


NHS
National Institute for
Health Research