# EQAS for Rare and Congenital Anaemias

Barbara De la Salle

UK NEQAS General Haematology

UK NEQAS



West Herts Hospitals NHS Trust

UK NEQAS

# Objectives

- Haematology WG proposal
- ENERCA
- Questionnaire Results
- New proposal – PK EQAS
- Problems of providing cross boundary EQAS
- Experience – UK NEQAS Molecular Haemoglobinopathies

# Haematology WG Proposal

***European survey of existing EQAS for rare diseases diagnostic tests***

**TITLE**

The provision of External Quality Assessment Schemes (EQAS) for the diagnostic tests associated with rare anaemias in Europe

**AIMS AND OBJECTIVES**

1. To survey EQA providers within European Union member states to determine the provision of EQAS for rare and congenital anaemias.
2. To discuss with EQA providers the use of reference methods for haematological parameters within EQAS and how IVDD companies use reference methods in the calibration and development of instruments and kits.
3. To work in collaboration with the European Network for Rare and Congenital Anaemias (ENERCA) to produce a collated catalogue of relevant EQAS.
4. To present the outcome of the survey at the EQALM annual meeting, 2011.

# enerca

European Network for Rare and Congenital Anaemias

**Rare anaemias (RA) :**
**Prevalence less than 5 per 10,000 individuals in a given community.**

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# enerca

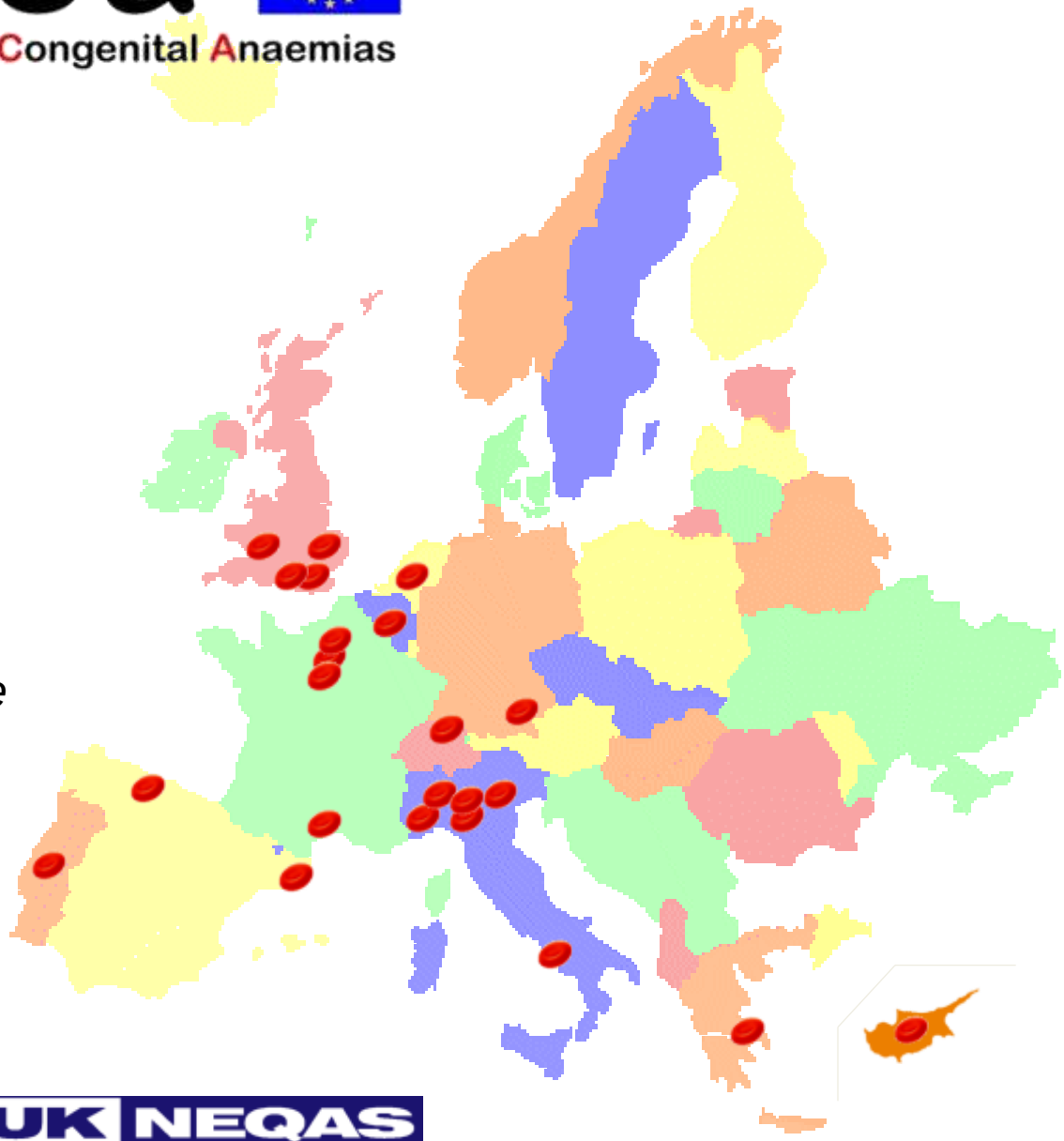
European Network for Rare and Congenital Anaemias

ENERCA 1  2002

ENERCA 2  2005

ENERCA 3  2009

WP1 –
WP2 – *Quality of patient care*
WP3 –
WP4 –
WP5 –
WP6 –



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# WP2 Specific Objectives 1

- To establish close collaborative links with recognised European and International organisations
- To improve the quality of laboratory data on RA by linking methods to higher order reference materials


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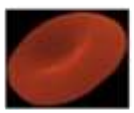
# WP2 Specific Objectives 2

- To facilitate the participation of Expert Centres in EQA
- To provide educational EQAS
- To prioritise the preparation of guidelines for the laboratory diagnosis of RA
- To develop a European Registry of RA



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European Network for Rare and Congenital Anaemias

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E·Q·A·L·M
European Committee for External Quality Assurance Programmes in Laboratory Medicine

enerca
European Network for Rare and Congenital Anaemias

May 2011

## QUESTIONNAIRE TO EUROPEAN EQA PROVIDERS

ENQUE-Harmonisation-2

Dear Colleague,

At last year's EQALM meeting, the Haematology Working Group adopted a new project to examine the provision of EQAS and the use of reference methods for the laboratory investigations used in the diagnosis of Rare Anaemias throughout Europe. This work is a collaboration with the European Network for Rare and Congenital Anaemias (ENERCA) with the objective of providing improved patient diagnostics through standardisation and harmonisation.

Sent June 2011

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# Core List of Tests


- Rare anaemia groups – ENERCA website
- Rationalised into disorders using same types of diagnostic testing
- Background research
  - Literature search for tests used
  - Abstracts

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PLEASE COPY THE Q1 SHEET AND COMPLETE FOR EACH ANALYTE/MEASURAND FOR WHICH YOU PROVIDE AN EQA SCHEME

| General Laboratory Tests | Hb disorders | Red cell enzyme disorders | RBC membrane disorders | PNH |
|---|---|---|---|---|
| Blood film morphology | Hb variant detection | Glucose-6-phosphate dehydrogenase (G6PD) deficiency | Demonstration of red cell membrane proteins by sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) (HS, HE, Stomatocytosis) | Ham test (acidified serum lysis test) |
| CBC (complete blood count) | HPLC | NBT spot test | Osmotic gradient ektacytometry (HS, HE, Stomatocytosis) | Sucrose lysis test (sugar-water test) |
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| Bilirubin | Iso-electric focusing | Cytochemical demonstration of G6PD deficiency | Tryptic digestion of spectrin (HE) | FLAER assay (fluorescently labeled aerolysin test) |
| Serum haptoglobin | Capillary electrophoresis | Quantitative assay for G6PD activity | Osmotic fragility test (OFT) (especially HS) | |
| LDL levels | Globin chain electrophoresis | Chromate inhibition test | Autohaemolysis test (HS) | |
| Serum LDH | Hb S screening tests<br>- whole blood sickling test,<br>- sickle solubility test | Molecular diagnosis<br>- RFLP<br>- ASO probes<br>- SSCP<br>- sequencing<br>- RT-PCR-DGGE<br>- HRM | Acidified glycerol lysis test (AGLT) (HS) | |
| Urine haemosiderin | Hb A2, Hb F, Hb S quantitation | Pyruvate Kinase deficiency | Pink test (HS) | |
| Haemoglobinuria | HPLC<br>Microcolumn chromatography<br>Electrophoresis and elution<br>Alkali denaturation | Spot test | Cryohaemolysis test (CHT) (HS, positive results also for SAO) | |
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| Cobalamin | Kleihauer test (Hb F distribution) | | | |
| Serum ferritin<br>*IRMA, RIA, ELISA, IFT, LIA*, nephelometric immunoassay, immunoturbidimetric assay; | Flow cytometry for Hb F cells | Other red cell glycolytic enzyme deficiencies<br>Quantitative assay: HK, GPI, PFK, Aldolase, TPI, PGK, BPGM, GSR, | | |
| (TIBC) | | | | |
| Liver iron concentration (SQID or MRT);<br>Myocardial iron concentration (MRT) | Electrospray ionisation mass spectrometry | Methemoglobinemia | | |
| Zinc-protoporphyrin | Globin synthesis in reticulocytes | Quantitative assay for methhaemoglobin reductase activity | | |
| Bone marrow iron stain | DNA analysis<br>Alpha thalassaemia mutations<br>Beta thalassaemia mutations<br>Structural variants | Molecular diagnosis | | |

General Laboratory Tests

PLEASE LIST ANY ADDITIONAL TESTS HERE - APPLICABLE TO RARE AND CONGENITAL ANAEMIA DIAGNOSIS

| General Laboratory Tests | Hb disorders | Red cell enzyme disorders | RBC membrane disorders | PNH |
|---|---|---|---|---|
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PLEASE COPY THE Q1 SHEET AND COMPLETE FOR EACH ANALYTE/MEASURAND FOR WHICH YOU PROVIDE AN EQA SCHEME

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| Red cell folate | Heinz bodies | Pyrimidine-5'-nucleotidase deficiency Radiometric assay<br>Spectrophotometric assay<br>HPLC | | |
| Cobalamin | Kleihauer test (HbF distribution) | | | |
| Serum ferritin<br>*IRMA, RIA, ELISA, IFT, LIA*, nephelometric | Flow cytometry for Hb F cells | Other red cell glycolytic enzyme deficiencies | | |
| *immunonephelometric assay* | | | | |
| Serum iron and total iron binding capacity (TIBC) | Hb M detection using absorption spectra | Glutathione stability | | |
| Liver iron concentration (SQID or MRT);<br>Myocardial iron concentration (MRT) | Electrospray ionisation mass spectrometry | Methaemoglobinemia | | |
| Zinc-protoporphyrin | Globin synthesis in reticulocytes | Quantitative assay for methreductase activity | | |
| Bone marrow iron stain | DNA analysis<br>Alpha thalassaemia mutations<br>Beta thalassaemia mutations<br>Structural variants | Molecular diagnosis | | |

# Hb disorders

## Hb variant detection

PLEASE LIST ANY ADDITIONAL TESTS HERE - APPLICABLE TO RARE AND CONGENITAL ANAEMIA DIAGNOSIS

| General Laboratory Tests | Hb disorders | Red cell enzyme disorders | RBC membrane disorders | PNH |
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UK NEQAS

PLEASE COPY THE Q1 SHEET AND COMPLETE FOR EACH ANALYTE/MEASURAND FOR WHICH YOU PROVIDE AN EQA SCHEME

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| Serum LDH | Hb S screening tests<br>- whole blood sickling test,<br>sickle solubility test | Molecular diagnosis<br>- RFLP<br>- ASO probes<br>- SSCP<br>- sequencing<br>- RT-PCR-DGGE<br>- HRM | Acidified glycerol lysis test (AGLT) (HS) | |
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| Cobalamin | | | | |
| Serum ferritin<br>*IRMA, RIA, ELISA, IFT, LIA immunoassay, immunoturb* | | | | |
| Transferrin<br>*radial immunodiffusion, immunonephelometric assay, immunoturbidimetric assay* | | | | |
| Serum transferrin receptor<br>*immunoassay, RIA, IEMA, immunoturbidimetric assay, immunonephelometric assay* | 2,6 - Dichlorophenolindophenol test for Hb E | Reduced glutathione (GSH) assay | | |
| Serum iron and total iron binding capacity (TIBC) | Hb M detection using absorption spectra | Glutathione stability | | |
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| Bone marrow iron stain | DNA analysis<br>Alpha thalassaemia mutations<br>Beta thalassaemia mutations<br>Structural variants | Molecular diagnosis | | |

Red cell enzyme disorders

Glucose 6 phosphate D

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| Transferrin<br>radial immu<br>immunoep<br>immunofix | | | | |
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RBC membrane disorders

Demonstration of red cell membrane

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| Transferrin<br>*radial immunodiffusion, immunonephelometric ass immunoturbidimetric assay* | | | | |
| Serum transferrin recept *immunoassay, RIA, IEMA, immunoturbidimetric assay , immunonephelometric assay* | | | | |
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PNH

PLEASE LIST ANY ADDITIONAL TESTS HERE - APPLICABLE TO RARE AND CONGENITAL ANAEMIA DIAGNOSIS

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|---|---|---|---|---|
| | | | | |
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1.1 What is the name of the EQA programme or survey provided?

Full Blood Count

1.2 What tests from the 'core list of tests' are covered?

CBC - Hb, WBC, RBC, Hct, MCV, MCH, MCHC, Platelets

1.3 How frequently do you distribute specimens?

12 times per year

1.4 How many specimens are distributed each year?

24

1.5 What is the type of survey material provided?

Human whole blood - partially fixed

1.6 How many participants are registered?

1,300

1.7 Do you accept participants from outside your own country? Yes [x] No [ ]

1.8 Is there a higher order reference method for this test? Yes [ ] No [x]

*If yes, please give the reference if you can*

*Do you use the higher order reference method in your laboratory?* Yes [ ] No [x]

*Do you know if IVDD manufacturers use this reference method to calibrate their kits or equipment?* Yes [ ] No [x]

1.9 How do you establish your target value?

*Higher order reference method* [ ]
*Consensus of selected expert laboratories* [ ]
*Consensus mean or median of participants' results* [x]
*Other*

1.10 Do you provide performance assessment? Yes [x] No [ ]

1.11 Do you have document that describes how this is done? Yes [x] No [ ]

1.12 Is the programme accredited? Yes [x] No [ ]

1.13 If yes, please give the name of the accreditation body

CPA

1.14 Would you agree to your scheme being listed on the European Network for Rare and Congenital Anaemias website (www.enerca.org)? Yes [x] No [ ]

**FUTURE EQAS DEVELOPMENT**

2.1 Of the tests that you do NOT provide EQAS for, list the 5 that you think would benefit most from EQAS provision.

PK screen and assay
Transferrin
Flow cytometry for Hb F cells
PNH

2.2 Would you be prepared to offer EQAS for rare anaemias in collaboration with another EQAS provider? Yes [x] No [ ]

2.3 Are there any other tests that should be included in the core tests list?

No

**ABOUT YOUR EQA SCHEME**

2.4 Organisation name

UK NEQAS General Haematology

2.5 Nature of the organisation

*Private company* [ ]
*Government organisation* [x]
*Charity* [ ]
*Other* [ ]

2.6 Name of the Scheme Organiser/Director

Professor Keith Hyde

2.7 Address

PO Box 14, Watford, WD18 0FJ, UK

2.8 Telephone number

44 1923 217878

2.9 Fax number

44 1923 217879

2.10 Email

haem@uknegas.org.uk

2.11 Website

www.uknegash.org.uk

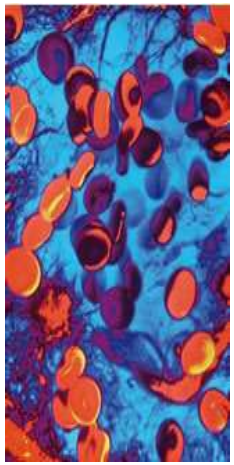
2.12 Name of the person completing this form

Barbara De la Salle

UK NEQAS

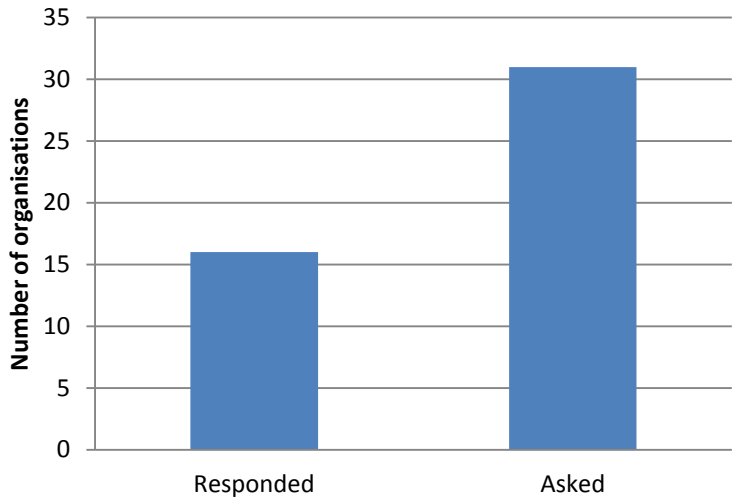
# Questionnaire

- Analytes
- Frequency
- Type of survey material
- Number of participants
- Performance monitoring
- EQAS ‘wishlist’
- Potential for collaboration
- Accreditation status



# Responses by September 2011

## Response rate

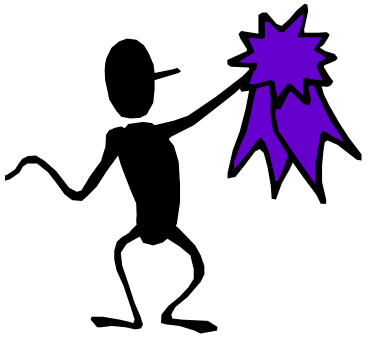



## Countries (some sent 2 replies)

- Slovenia
- Denmark
- Romania
- France
- Spain
- Canada
- Sweden
- UK
- Switzerland
- Norway
- Ireland
- Russia
- Czech Republic
- Croatia

50%

(16/31)

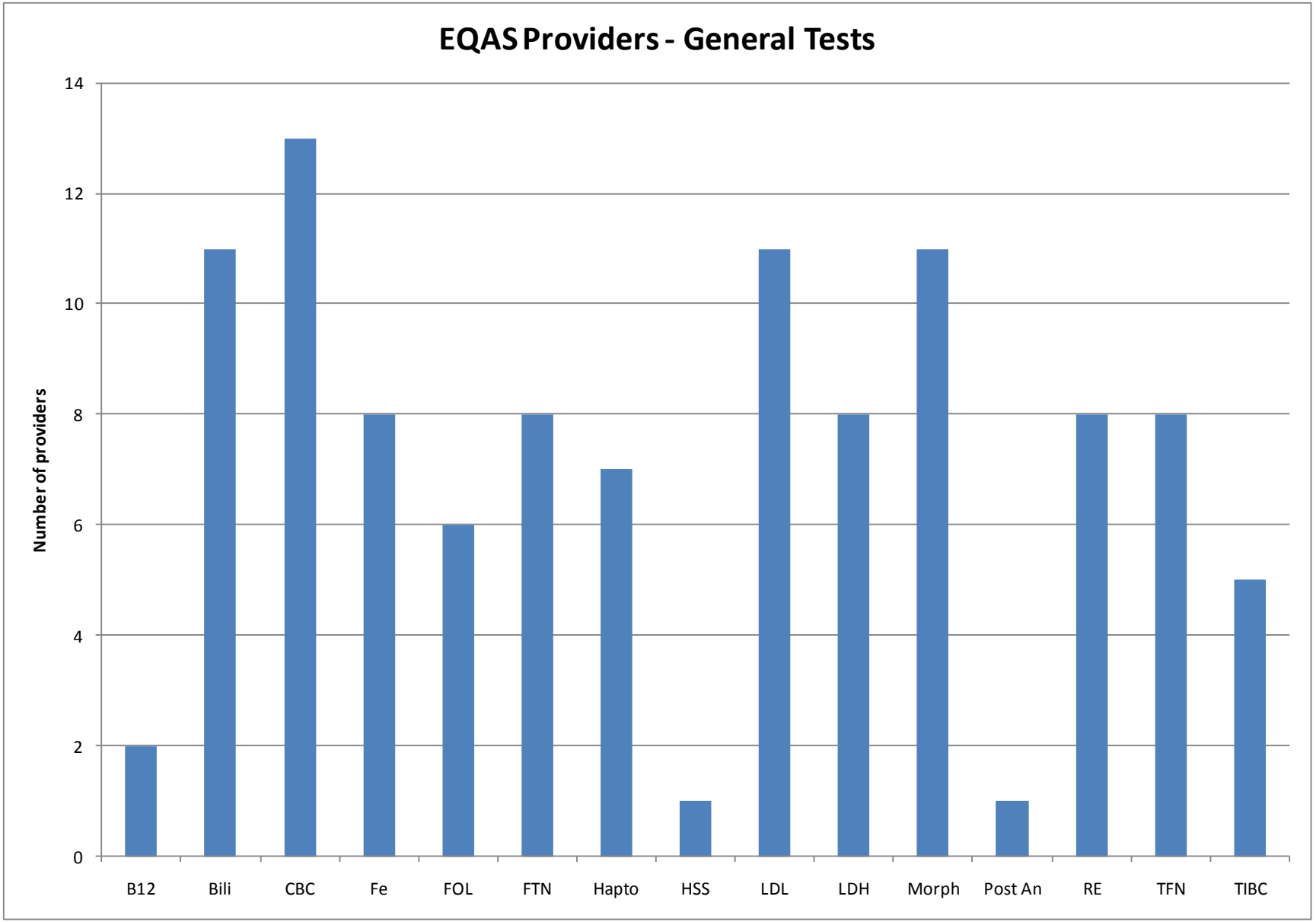



UK NEQAS

# EQAS Available for General Laboratory Tests

- Vitamin $B_{12}$
- Bilirubin
- CBC
- Serum Fe
- Folate
- Ferritin
- Haptoglobins
- Urinary haemosiderin
- Bone marrow Fe
- LDL
- LDH
- Blood morphology
- Post analytical interpretation
- Reticulocytes
- Transferrin
- TIBC

UK NEQAS


EQAS Providers - General Tests
Number of providers
14
12
10
8
6
4
2
0
B12
Bili
CBC
Fe
FOL
FTN
Hapto
HSS
LDL
LDH
Morph
Post An
RE
TFN
TIBC

UK NEQAS

# What's not provided from the core list?

| General Laboratory Tests |
| --- |
| Blood film morphology |

- Urine ferrioxamine iron
- Serum Transferrin Receptor
- Liver iron
- Myocardial iron
- Zinc protoporhyrin

**But……**

Are all tests clinically useful?

# EQAS Available for Hb Disorders

- Sickle cell solubility
- Hb variant identification
- Hb $A_2$ %
- Hb F %
- Hb S %
- Hb H bodies
- Newborn sickle screening
- Molecular Haemoglobinopathies (DNA)

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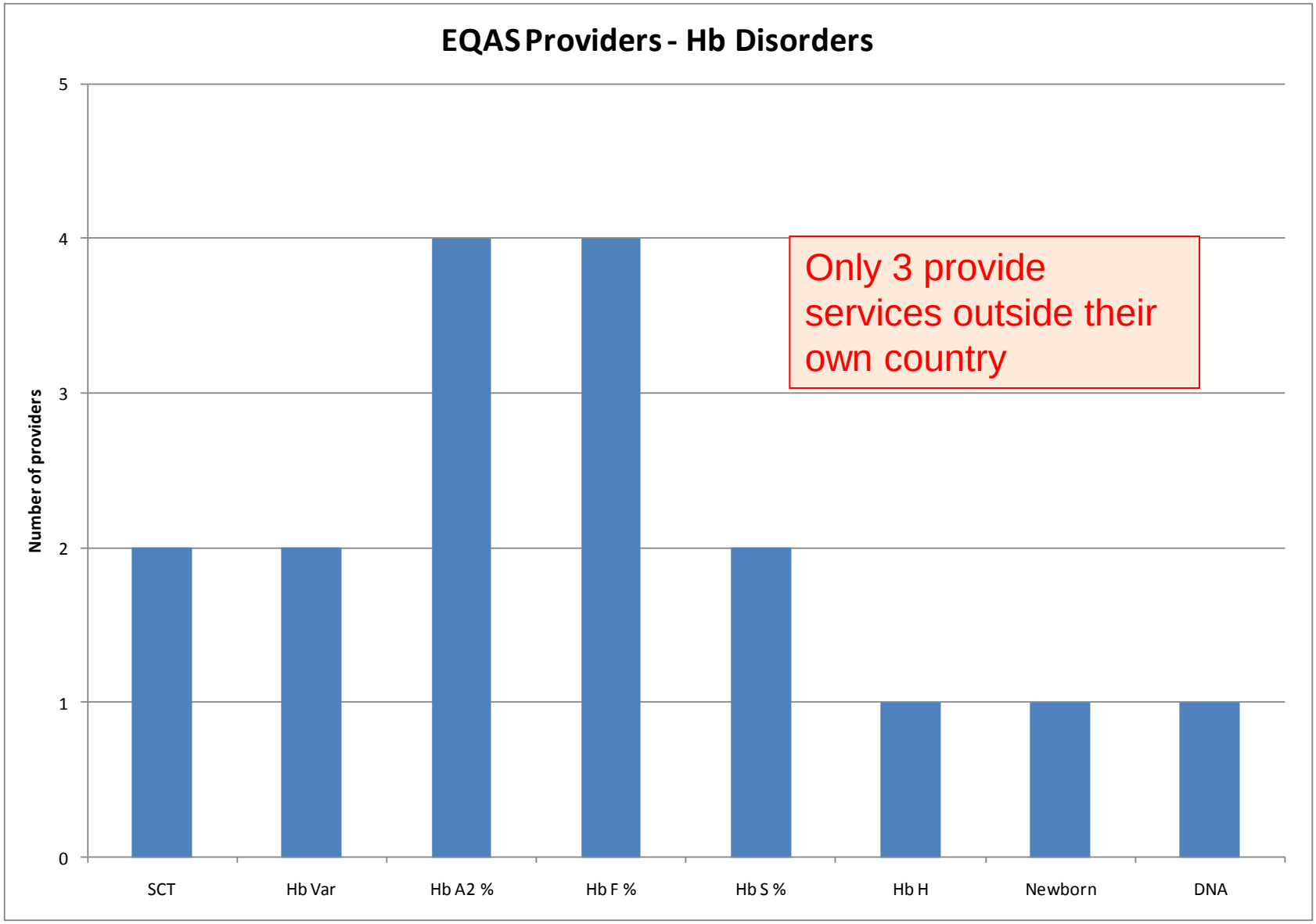
EQAS Providers - Hb Disorders
Number of providers
5
4
3
2
1
0
SCT
Hb Var
Hb A2 %
Hb F %
Hb S %
Hb H
Newborn
DNA
Only 3 provide services outside their own country

# What's not provided?

| Hb disorders |
| --- |
| Hb variant detection |

- Unstable haemoglobins
- Heinz bodies
- p50 for altered oxygen affinity
- Globin chain synthesis

# What's not provided?

| Red cell enzyme disorders | |
|---|---|
| Glucose 6 phosphate | D |

| RBC membrane disorders | |
|---|---|
| Demonstration of red cell membrane | H |

| PNH |
|---|
| [illegible] |

EQAS FOR MOST TESTS

.....Except: Hb F by flow, Kleihauer,

Methaemoglobin, Haemoglobinuria, PNH by flow

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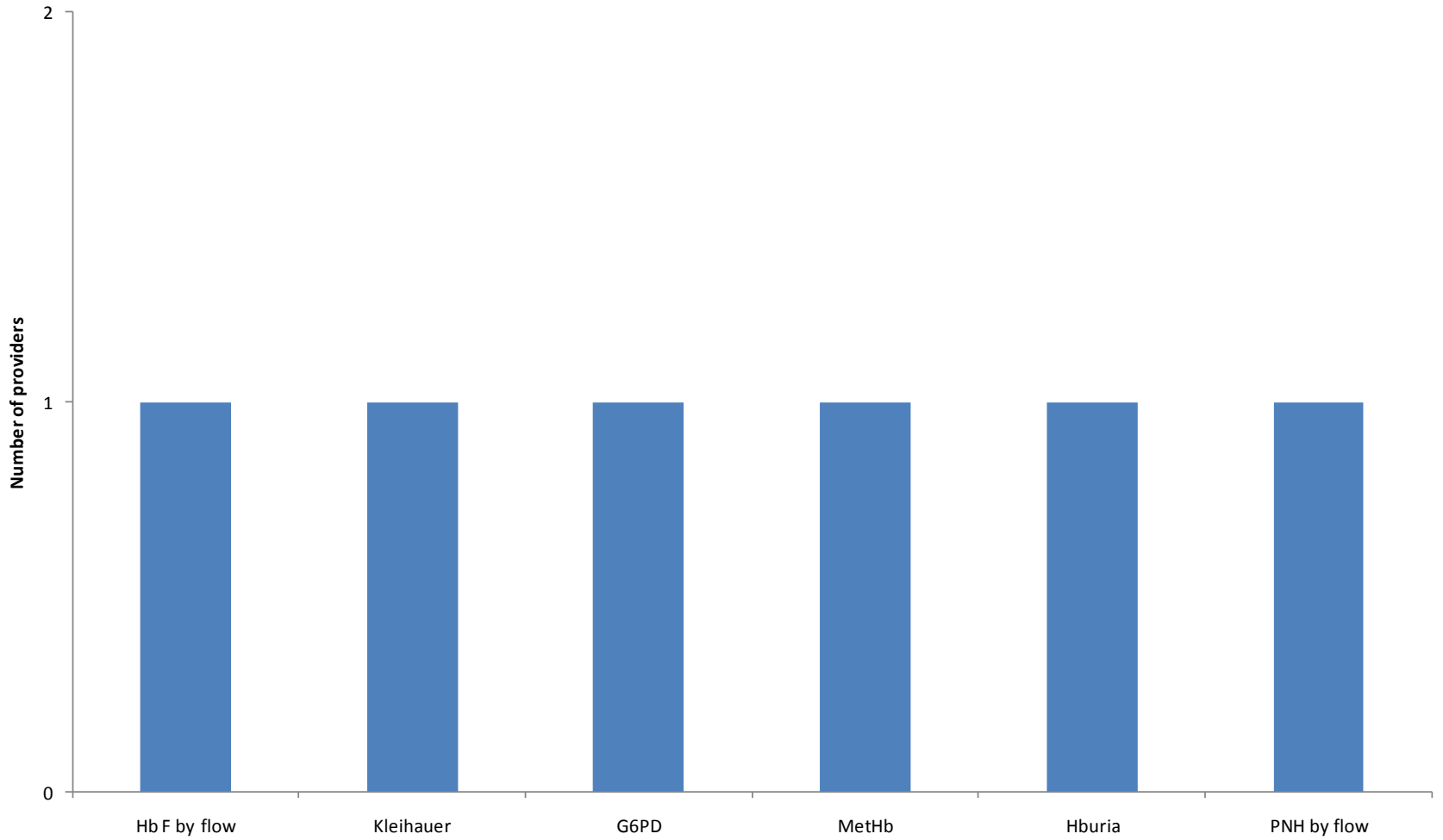
# EQAS Providers - Other tests

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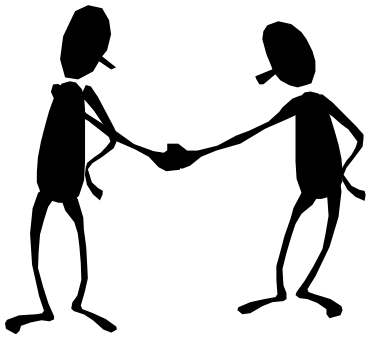
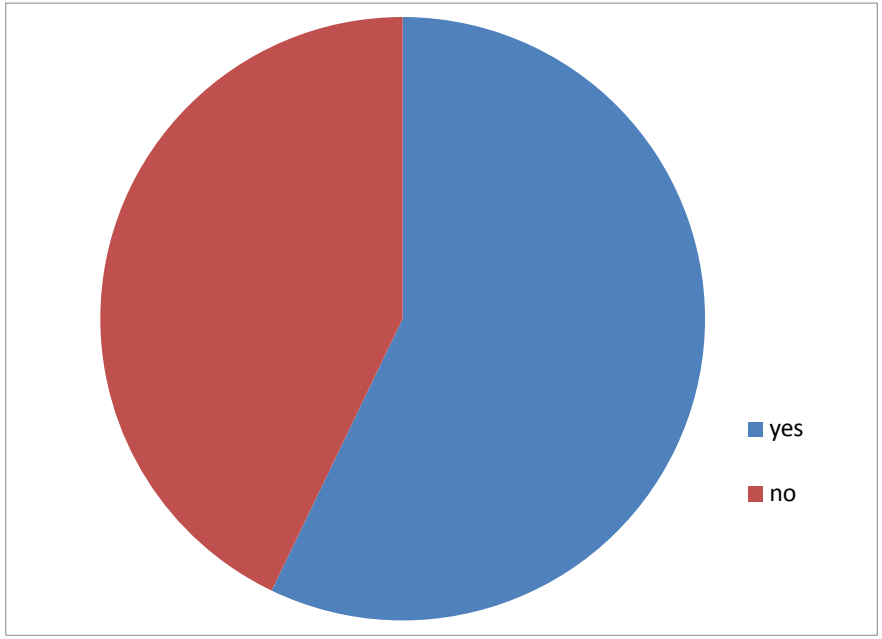
# Availability

**Do you accept participants from outside your own country?**






**ALSO** - 11 out of 15 EQAS providers would be prepared to offer new specialist services in collaboration

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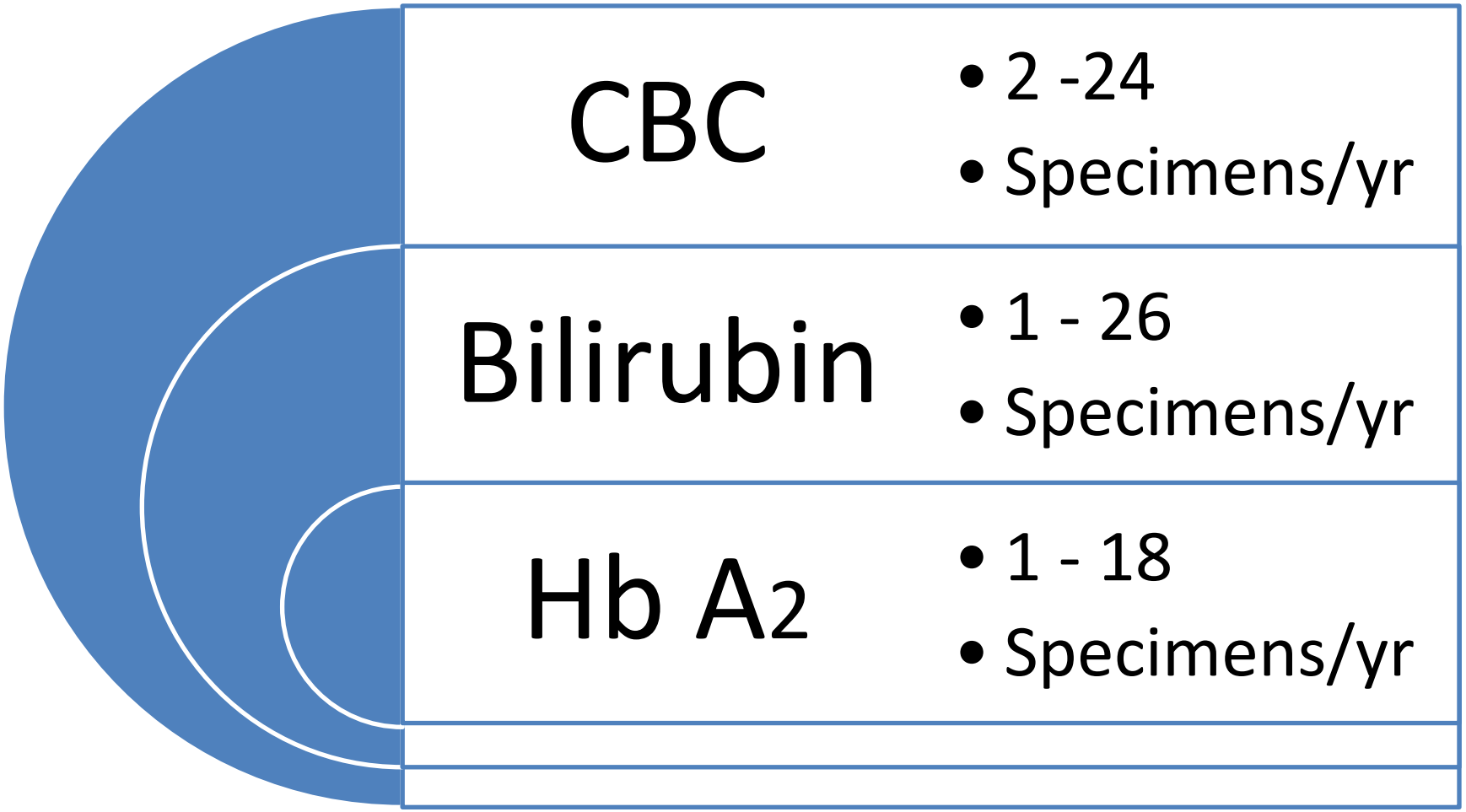
# Frequency of Provision



# EQA Wishlist

## Available within EQALM

- Hb Variant detection
- Hb A2, Hb F, Hb S
- G6PD
- Kleihauer
- Flow cytometry for Hb F
- Retics
- Red cell folate
- Serum folate
- Cobalamin
- Serum ferritin
- Serum Haptoglobin
- Blood Film Morphology

## Not available within EQALM

- Unstable Hbs
- Heinz bodies
- Serum transferrin receptor
- PK activity

**QUESTION**
Of the tests that you do NOT provide EQAS for, list the 5 that you think would benefit most from EQAS provision?

?

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# Barriers to EQAS provision

- **Survey material**
  - **Availability**
  - **Stability**
- **Insufficient demand in a single country**
- **Restriction of services to own country only**
  - **Funding restrictions**
- **Cost of transportation**
- **Customs difficulties**
- **Local medical practice**
- **Language**

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# New PK scheme proposal

- European collaboration
- Normal and PK deficient patient material
- Development phases:
  - Survey material development
    - Storage, stability, volumes etc.
  - Small scale survey with selected labs
  - Recruitment of interested participants
  - Pilot exercise(s) to refine scheme design
  - Performance assessment methods

# How will we provide pan-European services?

- Direct sale and delivery to individual participants
- Provision via an intermediary agent or distributor
- In collaboration with another EQA provider
  - Supported by ¾ responders to questionnaire

# UK NEQAS Molecular Haemoglobinopathies Scheme

- Approximately 9 labs in the UK
- Boosted to 25 with European labs
- Survey material – development of cell line library of cases
- Problems
  - Cost
  - Survey material
  - Matching EQA cases to local incidence
  - Performance assessment

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# Summary

- **For rare anaemias**
  - Adequate provision of most general tests within EQALM
  - Some provision for specialist / rare anaemias:
    - Haemoglobinopathy EQAS
    - PNH EQAS
    - G6PD EQAS
- **EQALM next steps**
  - Facilitate participation and collaboration
  - Offer guidance on new provision
  - Help recruit specialist laboratories to ENERCA

# Acknowledgements


- Professor J L Vives Corrons
- ENERCA Executive Committee
- Professor Andrea Mosca
- Vasilis Rapanakis (database specialist)
- EQALM members

# Thanks!

**Any more responses?**

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**Full report to EQALM and ENERCA at end 2011**

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