Blood Grouping in Pregnancy, Guidelines and Foetal Genotyping

Kasia Ballard
28.02.2017
Guideline for blood grouping and red cell antibody testing in pregnancy

White, J1 Qureshi, H2 Massey, E3 Needs, M4 Byrne, G5 Daniels, G6 Allard S7 & British Committee for Standards in Haematology

1 UK National External Quality Assessment Scheme for Blood Transfusion Laboratory Practice, Watford. 2Department of Haematology, University Hospitals of Leicester. 3NHS Blood and Transplant & University Hospitals Bristol NHS Foundation Trust, 4Institute of Biomedical Sciences and NHS Blood and Transplant, 5Department of Haematology, University Hospitals of Leicester, 6International Blood Group Reference Laboratory, NHS Blood and Transplant, and 7Barts Health NHS Trust and NHS Blood and Transplant

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The purpose of the guideline is to make evidence-based recommendations for the application of blood grouping and red cell antibody testing in pregnancy and if possible to prevent, haemolytic disease of the foetus and newborn (HDFN).

The blood group and antibody status of a pregnant woman should be tested at booking and at 28 weeks gestation to identify the ABO group and D status and to detect red cell antibodies that have the potential to be clinically significant.
ABO/D typing

ABO and D grouping should be performed in accordance with the guidelines for compatibility procedures in blood transfusion laboratories (BCSH, 2012b)

- All not clear positive of RhD typing, should be classified as D negative until the D status is confirmed.

- All pregnant women found to be D negative should be given written information about their D-negative status and the importance of anti-D Ig prophylaxis. The D status should be clearly recorded in the notes to inform those responsible for their care of the need to offer prophylactic anti-D Ig.

Screening for red cell antibodies

Maternal antibody screening is undertaken to detect clinically significant antibodies, which might affect the foetus and/or newborn, and to detect antibodies that may cause problems with the provision of compatible blood components for the woman and for the foetus/newborn.

Approximately 1% of pregnant women are found to have clinically significant red cell antibodies (Howard et al., 1998; Koelwijn et al., 2008; Smith et al., 2013).

The concentration of each antibody capable of causing HDFN should be assessed independently. For specificities where there is a national standard preparation, quantification should be undertaken. Other antibody specificities should be measured using titration.
Antibody testing

Antibody quantification.

Quantification requires specific equipment and measures antibody concentration against a national standard [National Institute for Biological Standards and Control (NIBSC)].

Anti-D and anti-c are the only antibodies that are currently quantified, and they are reported as IU per millilitre.

Where possible, each sample should be tested in parallel with the previous sample and the results compared to identify significant change in antibody concentration.

Antibody titration.

Titration is used to assess the concentration of clinically significant red cell antibodies other than anti-D and anti-c.

Doubling dilutions (1 in 2, 1 in 4, etc) of plasma prepared in phosphate-buffered saline are tested by IAT using reagent red cells, where possible, showing heterozygous expression of the corresponding antigen(s).

Sometimes there are more than one antibody specificity is present (including prophylactic anti-D). The concentration of each specificity should be assessed independently, e.g. where anti-K+Fya are present titrate against K−, Fy(a+b+) and K+k+, Fy(a−) cells.
Protocol for patients with antibodies

- Samples from pregnant women with immune anti-D or anti-c should be assessed serologically at 4 weekly intervals to 28 weeks gestation and at fortnightly intervals thereafter until delivery. Such cases should be referred to a foetal medicine specialist if the antibody reaches the critical level and/or the level is rising significantly, where assessment of the need for further monitoring will be made.

- Pregnant women with anti-K or other Kell system antibodies (unless the father is confirmed to be negative for the corresponding antigen) should be assessed serologically at monthly intervals to 28 weeks gestation and at fortnightly intervals thereafter until delivery and referred to a foetal medicine specialist when the antibody is first identified.

Clinically significant antibodies, other than anti-D, -c or -K, should be excluded or, if present, assessed by titration at the booking appointment and at 28 weeks gestation. If deemed necessary based on a high titre (>32) and/or a past history of HDFN, referral to a specialist in foetal medicine should be made for further assessment.

All babies born to women who have clinically significant antibodies should be closely observed for evidence of HDFN. A DAT should be performed on a cord blood sample, and haemoglobin and bilirubin concentrations should be measured.

A positive DAT is not, in itself, diagnostic of HDFN. Where the DAT is positive and the baby shows signs of HDFN, a red cell eluate may be helpful to confirm the red cell antibody specificity. IgG ABO antibodies occasionally cause severe HDFN, and so, if the baby has a major ABO mismatch with the woman, the eluate should also be tested with A1 and/or B cells, negative for any other antigen against which the woman has made IgG alloantibodies. Regular assessment of bilirubin and haemoglobin concentrations is necessary, and hence, early discharge is not advisable.
At booking
All pregnant women
ABO + D* typing
Antibody screen

Clinically significant** antibody screen positive

Anti-D, -c or -K***
Consider paternal/fetal genotyping for corresponding antigen(s)
Test monthly until 28 weeks gestation
See figure 2

From 28 weeks gestation:
Test 2 weekly until delivery
See figure 2

Cord blood for:
DAT, Hb, bilirubin

No clinically significant** antibodies

All other clinically significant** antibodies
Consider paternal/fetal genotyping for corresponding antigen(s)

Repeat testing at 28 weeks gestation

Repeat antibody screen at 28 weeks gestation

No antibodies
No further action

Clinically significant antibodies
Anti-K detected
Titrate antibody

Anti-D detected
Quantify Antibody level
4-15 IU/mL mod risk HDFN
>15 IU/mL severe risk HDFN

Anti-c detected
Quantify Antibody level
7.5-20 IU/mL mod risk HDFN
>20 IU/mL severe risk HDFN

Non-invasive pre-natal diagnosis
Or
Test father

K Positive
Heterozygous expression

K Positive
Homozygous expression

K Negative

D Positive
Heterozygous expression

D Positive
Homozygous expression

D Negative

FETUS AT RISK OF HDFN

Refer to specialist unit
Fetus US, MCA Doppler, IUT if needed

Deliver at 37 weeks gestation.

Cord blood Hb, Bilirubin, DAT.

Management HDFN as needed

Legend
Ab = antibody
Bil = bilirubin
DAT = direct antiglobulin test
cffDNA = cell free fetal DNA
Hb = haemoglobin
HDFN = haemolytic disease of the fetus and newborn
IUT = intrauterine transfusion
MCA Doppler = middle cerebral artery Doppler
Pos/Neg = positive/negative
US = ultrasound

Chelsea and Westminster Hospital
NHS Foundation Trust
Anti-D is identified in maternal plasma at a level of \( \leq 0.4\text{IU/mL} \) in the absence of clear evidence of immune anti-D historically, and where anti-D Ig has been administered.

Is this sample after the 28 week routine sample?

- No it was taken prior to the 28 week sample
  - Anti-D detected at or before 28 weeks will only be identified in a relatively small proportion of pregnancies. It poses a greater risk of rising in level and causing significant HDFN if it is immune. Some will be however be passive anti-D Ig

- Yes it was taken after the 28 week sample
  - Was anti-D previously identified in the 28 week sample?
    - Yes
      - No it is \( \geq 0.2\text{IU/mL} \) & may be immune
    - No
      - Is the level \( < 0.2\text{IU/mL} \)?
        - Yes it is \( < 0.2\text{IU/mL} \)
          - It is almost certainly passive and if it does prove to be immune, its absence at 28/40 would make it unlikely to cause significant HDFN. Therefore no follow up testing for anti-D levels is required.
        - No it is \( \geq 0.2\text{IU/mL} \) & may be immune
          - This may be immune anti-D and should be monitored as such, i.e. quantification every 4 weeks to 28 weeks gestation and then every 2 weeks until delivery (unless anti-D is no longer detectable)

If the level of anti-D is \( \leq 0.4\text{IU/mL} \), anti-D Ig should be administered in accordance with the BSH guideline for the use of anti-D Ig to prevent HDFN, as the anti-D may be passive.
Anti-D immune and prophylaxis

Recommendation

• Blood transfusion laboratories should keep a record of anti-D Ig administration to provide a basis for distinguishing between immune anti-D and prophylaxis anti-D Ig.

• If anti-D is detected in an antenatal maternal sample (except for that taken immediately prior to delivery), testing should include a measurement of antibody concentration by CFA or similar technique that gives a result that is expressed in or can easily be converted to IU per millilitre of anti-D.

• When there is doubt as to the passive or immune nature of anti-D, the level should be monitored as if it could be immune. In this situation, anti-D Ig prophylaxis should continue to be offered, until the nature of the anti-D is established.

Table 1. The significance of levels of anti-D

<table>
<thead>
<tr>
<th>Anti-D concentration</th>
<th>Predicted clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 4 IU mL⁻¹</td>
<td>HDFN unlikely, continue to monitor</td>
</tr>
<tr>
<td>4–15 IU mL⁻¹</td>
<td>Moderate risk of HDFN, requiring referral to a fetal medicine specialist</td>
</tr>
<tr>
<td>More than 15 IU mL⁻¹</td>
<td>High risk of HDFN requiring referral, as above</td>
</tr>
</tbody>
</table>

Table 2. The significance of levels of anti-c

<table>
<thead>
<tr>
<th>Anti-c concentration</th>
<th>Predicted clinical outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 7.5 IU mL⁻¹</td>
<td>HDFN unlikely, continue to monitor</td>
</tr>
<tr>
<td>7.5–20 IU mL⁻¹</td>
<td>Moderate risk of HDFN, requiring referral to a fetal medicine specialist</td>
</tr>
<tr>
<td>More than 20 IU mL⁻¹</td>
<td>High risk of HDFN requiring referral, as above</td>
</tr>
</tbody>
</table>

Transfusion Medicine, 2016, 26, 246–263
Paternal testing

When a clinically significant antibody capable of causing HDFN is present in a maternal sample, determining the father’s phenotype can provide useful information to predict the likelihood of the foetus expressing the relevant red cell antigen and for counselling the couple regarding future pregnancies.

It should be recognised that in any pregnancy, the partner may not be the biological father (assisted conception with sperm donation from a donor panel, the pregnant woman’s partner will not be the biological father).

It is reasonable to avoid paternal testing and proceed directly to foetal genotyping using cffDNA.

Recommendation

If potentially clinically significant maternal antibodies have been identified, paternal testing should be considered to predict the risk to current and future pregnancies. This may be particularly relevant if non-invasive foetal genotyping is not available for the corresponding red cell antigen.

Foetal genotyping in alloimmunised pregnancies. Foetal genotyping is a useful diagnostic tool when:

a) A pregnant woman has a clinically significant antibody;

b) A pregnant woman has a history of HDFN;

c) The father’s antigen status is unknown or he expresses the corresponding antigen.
Taking part in the NHS cffDNA testing

Administer anti-D selectively, only to RhD Negative women with a RhD Positive baby

Improve patient pathway and satisfaction

Focus midwifery / obstetrician time on clinically indicated care

Cost neutral

Potentially save laboratory time
WHY Change the system??
Routine Antenatal Anti-D Prophylaxis (RAADP) has been hugely successful in UK:

1930’s  RhD antigens identified
1969  First use of anti-D as postnatal prophylaxis
1999  RAADP introduced

Maternal isoimmunisation reduced from 16% to 0.2%
Perinatal mortality  46 to 1.6 / 100000 births
### Potentially Sensitising events during pregnancy

<table>
<thead>
<tr>
<th>Timeframe</th>
<th>Action</th>
</tr>
</thead>
</table>
| 12 weeks  | At least 250 IU anti-D Ig if:  
  - surgical intervention  
  - termination of pregnancy (surgical or medical)  
  - unusually heavy bleeding  
  - unusually severe pain  
  - unsure of gestation  
  Kleihauer test not required |
| 12–20 weeks | At least 250 IU anti-D Ig  
  Kleihauer test not required |
| 20+ weeks  | At least 500 IU anti-D Ig  
  Take maternal blood for Kleihauer test  
  Further anti-D Ig if indicated by Kleihauer |

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**BCSH guideline for the use of anti-D immunoglobulin for the prevention of haemolytic disease of the fetus and newborn**

H. Qureshi, E. Massey, D. Kirwan, T. Davies, S. Robson, J. White, J. Jones & S. Allard
Facts

16% UK population RhD negative [lower in non Caucasian populations]

~40% of their babies will be RhD Negative = 40,000 women / year receive unnecessary anti D in UK

Introducing cffDNA testing potentially could reduce issuing of proph-D by 30%.

Considering implications:

- financial
- ethical
- safety
2002- Recommended further research into foetal RhD typing

1994: Fetal blood group genotyping introduced
2001: Fetal D typing on cffDNA
        Extended to K, C, c, E

2006-11 High throughput foetal RhD testing trials at different gestations:

Highly accurate from 11+2 weeks gestation

2013/14 Foetal RhD service pilot
- North Bristol
- UHs Bristol
- Weston Area

BMJ 2014;349:g5243 doi: 10.1136/bmj.g5243
DOI: 10.1111/1471-0528.13055 www.bjog.org
Clinical implications: Antenatal

RhD Negative pregnant women tested after 12 weeks’ gestation.

Possible results:

1. Baby Predicted RhD Positive – continue usual RAADP

2. Baby Predicted RhD Negative – no RAADP required;
   - no Kleihauer or anti-D for sensitising events and post delivery

3. Inconclusive – treat as if RhD Positive

4. Not tested (‘Rejected’)
Clinical implications: Postnatal

Options include:

1. Continue current policy of cord blood on all babies born to RhD Negative women, with anti-D dose determined by Kleihauer

2. Cord blood only on babies predicted to be RhD Negative

   Women delivering babies predicted to be RhD Positive given anti-D, without cord blood group testing.
Setting up the service

‘Self appointed’ multidisciplinary working party:

Obstetrician
Haematologist
Blood Transfusion Manager
IT expert
Experienced Midwife

Guideline and pathway writing; midwife champions identified; patient involvement; business case
Developing Protocol

Take routine booking blood samples for group & antibodies

Late bookers known to be Rh neg who have not had fetal testing in current pregnancy should have all routine blood samples taken and be offered cffDNA regardless of gestation unless delivery is expected

Woman RH D positive

Repeat blood group & antibody test at 28 weeks

ANC MW will check results. Post or give information leaflet about cffDNA testing to woman prior to 16 week appointment, record that she has done so. Place request form for cffDNA in hospital notes

Declines cffDNA screen

cffDNA sample taken after 11 weeks gestation, usually at first antenatal appointment after dating scan by community MW. Record in hospital and hand held notes that sample has been taken or declined

Baby RH D positive

Maternal blood group & antibody test
Offer routine anti D prophylaxis

28 Weeks

Maternal blood group & antibody test
Offer routine anti D prophylaxis +/- Kleihauer test

Sensitising Event

Offer routine anti D prophylaxis +/- Kleihauer test

Delivery

Cord blood for group & DAT
Maternal blood for antibody testing and Kleihauer
Offer Anti D if baby RH D positive

Cord blood for group & DAT
Maternal blood for antibody testing and Kleihauer
Offer routine Anti D prophylaxis

Maternal blood group & antibody test
Offer routine anti D prophylaxis

Baby RH D negative

Results entered on ICE notepad

West Middlesex University Hospital

Chelsea and Westminster Hospital NHS Foundation Trust
Concerns to make decisions relating to:

• Identifying the relevant women
• Ensuring sample taken, correctly
• Handling the samples on receipt
• Handling the results
• Availability of results to the clinical teams
• How to audit pathway and get patient feedback
How to identify relevant women… and what to do about ‘catch up’

Multipronged approach, all based around current ways of working

1. cffDNA test described in ‘Safe In Our Hands’ pregnancy information booklet given to all pregnant women at booking

2. All print outs of booking bloods received by ANC sisters and reviewed

3. Notes of RhD Negative women given PINK cover, information leaflet posted to her, name entered on secure spreadsheet

4. Target to take during ‘16 week’ midwife appointment, or at any other meeting if delivery ‘not imminent’
Taking the samples, correctly

Departmental education for all staff via monthly Maternity Forum, Newsletters, Team Leaders meetings etc

Midwife champions

HCAs working in ANCs ‘empowered’

Single full PINK top sample

at any clinical point from 14weeks
Handling samples in lab

Received in laboratory via standard pathways from all clinics; sample stable at room temperature

Entered into Laboratory IT system [Winpath]

- The new genetic RhD (cffDNA) is now active in Winpath.
- Code = GRHD
- Please inform Manny if you need the test to be available in ICE as well.

Sent to NHSBT Colindale on standard daily transport

Transported from Colindale to Bristol on standard NHSBT transport
Handling Results

Results are expected within 2 weeks from receiving sample in Bristol:

- available immediately after authorisation on Specialist Services electronic reporting using the Sunquest ICE web browser (Sp-ICE) and can be seen by all Sp-ICE users, important for shared care patients
- Paper copy is sent in batches
- BMS must enter this manually to the WinPath system, and checked by second person before authorised on system, unable to use electronic transfer from Sp-ICE
- Results from WinPath are sent to ICE (hospital IT system).

Original report is send to ANC/Maternity

From 1 April NHSBT implementing additional charge £1 for every paper copy, therefore, we going to stop receiving paper copy and get thee results from Sp-ICE. This may be additional stretch for lab staff

Working process to build the result page on LIMs and Hospital IT systems
Fetal cfDNA Screen

Sample 00000336239 (TYPE UNSPECIFIED) Collected 12 Jul 2016 11:45 Received 12 Jul 2016 16:08

GENETIC RHD TESTING

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<td>15.07.16</td>
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<td>EDD</td>
<td>03.09.16</td>
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This result applies to pregnancy with EDD above.

cfDNA Comment

Fetal RhD typing predicts that his fetus is RhD POSITIVE.

NHSBT No 5535764625
NHS No 4623907929
Sample No 000 83 16 00 4665 0

End of report.
### Old setup

**Results Entry - C335235**

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<th>Age:</th>
<th>DoB:</th>
<th>Fasting: A</th>
<th>Urgent: N</th>
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<td>Clinician: NP</td>
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<tr>
<td>Tests: GRHD</td>
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Status: Incomplete

**Edit All** | **View All**
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<table>
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<tbody>
<tr>
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### New setup

**Results Entry - C000301**

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<th>Urgent: N</th>
<th>On-Call: N</th>
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<tbody>
<tr>
<td>Source: GYNAEOPD</td>
<td>Clinician: AJAJ</td>
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<tr>
<td>Tests: GRHD</td>
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<tr>
<td>NHS No</td>
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<td>Sample No</td>
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<td>EDD</td>
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<td>Special Requirements: None</td>
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### New request – 'GRHD'

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### Resulting entered from referral report

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<td>Complete</td>
<td>Unverified</td>
<td>Genetic RHD test (cHNA)</td>
<td>NEGATIVE</td>
</tr>
<tr>
<td>Source:</td>
<td>ANCHOR</td>
<td>Clinician: HULLS</td>
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<td></td>
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</tr>
</tbody>
</table>

### Comment auto-added below EDD

- This result applies to pregnancy with EDD above.
- Fetal RHD typing predicts that this fetus is RHD

### Once saved – Comment auto-added below EDD

<table>
<thead>
<tr>
<th>Hospital Number:</th>
<th>NHS No.</th>
<th>Verification:</th>
<th>Name:</th>
<th>Status:</th>
<th>Demographics:</th>
<th>Tests</th>
<th>Result:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1111111</td>
<td></td>
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<td>TESTPATIENT TESTPATIENT</td>
<td>Complete</td>
<td>Verified</td>
<td>Genetic RHD test (cHNA)</td>
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<tr>
<td>Source:</td>
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<td>Clinician: HULLS</td>
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</tbody>
</table>
Example request

**Results Lookup - C000062**

Hospital Number: NHS No. Verification: Name: TEST, TEST
Sex: M Age: DoB: Fasting: A Urgent: N On-Call: N
Source: MFMN Clinician: MIRZ

Status: Incomplete

*EH Genetic RhD test (cffDNA)*
Result expected in 14 days

*EH cffDNA Report Date*

*EH NHSBT No*

*EH NHS No*

*EH Sample No*

*EH EDD*

*EH cffDNA Comment*

*AH*

Foetal RhD typing predicts that this foetus is RhD

Screenshot below confirms the comment was auto-added by the ‘SYSTEM’

**Results Entry - C000062**

Sex: M Age: DoB: Fasting: A Urgent: N
Source: MFMN Clinician: MIRZ

Tests: GRHD

Status: Incomplete

<table>
<thead>
<tr>
<th>Tests</th>
<th>Results</th>
<th>User</th>
<th>Authorisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>EH Genetic RhD test (cffDNA)</td>
<td>{ to send BRI }</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EH cffDNA Report Date</td>
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<td>NH Sample No</td>
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<td>NH EDD</td>
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<td>AH cffDNA Comment</td>
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<tr>
<td>AH RhD</td>
<td>SYSTEM</td>
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</tr>
</tbody>
</table>
Creating comments

![Creating comments screenshot](image)

**Comments**

- **Code**: Code for the comment
- **Comment**: Text of the comment
- **Section**: Section of the comment
- **Subsection**: Subsection of the comment

- **GP1**: Sample haemolysed so not suitable for antibody screen or crossmatch. Please send repeat.
- **GP2**: Sample not acceptable for crossmatch due to sensitivity.
- **ABO**, **Rh group acceptable for first sample**

**Result Rules**

- **Rule**: Rule for the criteria
- **Criteria**: Criteria for the rule
- **Test**: Test for the rule
- **U'list**: U'list for the rule
- **Queue**: Queue for the rule

- **7400**: [IF TLC] GRHD
- **[IF TEST STATUS] EDDR (a)**
- **EDDR <$$> 0EDDR**
- **[THEN] ADD COMMENT EDDR below TLC EDDR**
Ongoing audit and patient questionnaire

Started 1st June 2016, in 1st 4 months:

- 375 Letters sent to RhD Negative women re testing
- 235 Results received back
- 87 Babies predicted to be RhD Negative [37%]
Service Problems

Relatively few…

● Occasional wrong labelling and wrong sample size
● Occasional missed opportunity to take sample
● Likely some cord samples taken unnecessarily
● IT issues were complex to set up, but have been trouble free in clinical practice
● Typing results rather receiving electronically directly from Bristol

● From 1 April 2017, no paper copy (additional charge), could be more challenging for hospital laboratory staff
## Costs

Estimated that 15% RhD Neg women have 1 or more sensitising event, mostly >20wks

<table>
<thead>
<tr>
<th></th>
<th>£</th>
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</thead>
<tbody>
<tr>
<td>ffDNA</td>
<td>19.58</td>
<td></td>
</tr>
<tr>
<td>Anti D</td>
<td>35 / 22.95</td>
<td></td>
</tr>
<tr>
<td>Kleihauer</td>
<td>25</td>
<td></td>
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<tr>
<td>Cord blood group</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>
Accuracy of the cffDNA results?

**Predicted RhD Negative** – <1 in 1000 inaccurate

ie actually RhD Positive

check cord blood group for confirmation

1 in 86,000 chance of isoimmunisation

**Predicted RhD Positive** - 2% inaccurate

ie given anti D un necessarily

**Indeterminate** - ~8% may fall as technology improves

80-90% actually RhD Positive
Laboratory findings re: discrepant results

• **Predicted RhD Positive** - confirmed after birth RhD Negative - October 2016

  Note: unable to get more discrepant results as the protocol was changed and there is no Cord blood taken for Predicted RhD Positive babies

• **Predicted RhD Negative** - confirmed after birth RhD Positive - January 2017, investigation in process, sample was sent to Bristol
Summary

Implementation of cffDNA RhD testing is:

• Relatively straightforward

• Cost effective/neutral

• Saving time in midwifery area (less patients in clinic and less worrying if patients has PVB)

• Could save time on KL tests and issuing the anti-D, but BMS spend more time on booking sample for testing, packing, and sending to Bristol

• Also BMS spend more time typing and checking results

• Well received by Maternity staff and patients
Thank You for Listening... any questions?