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Application Form: 1574

Non-invasive prenatal testing for Rhesus D

# PART 1 – APPLICANT DETAILS

## Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant):

Corporation name: The Royal College of Pathologists of Australasia

ABN: 52 000 173 231

Business trading name: The Royal College of Pathologists of Australasia

**Primary contact name:** Dr Debra Graves

Primary contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

**Alternative contact name:** Ms Linda Mundy

Alternative contact numbers

Business: **REDACTED**

Mobile: **REDACTED**

Email: **REDACTED**

## (a) Are you a lobbyist acting on behalf of an Applicant?

Yes

No

## If yes, are you listed on the Register of Lobbyists?

Yes

No

# PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

## Application title

Non-Invasive Prenatal Testing (NIPT) for fetal Rhesus D genotype

## Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

Approximately one in seven women has a rhesus (Rh) D-negative blood group. RhD negative women carrying an RhD-positive fetus are at risk of becoming sensitised, producing antibodies against the RhD antigen if fetal cells enter the maternal circulation. Sensitisation places the RhD-positive fetus and future RhD-positive pregnancies at risk of haemolytic disease of the fetus and newborn (HDFN). If undiagnosed and/or untreated, HDFN carries significant risk of perinatal morbidity and mortality.1 In Australia, the current standard of care is the routine administration anti-D immunoglobulin to all RhD negative pregnant women at 28 and 34 weeks’ gestation, and within 72 hours of delivery of an RhD-positive fetus, or following other obstetric events associated with a risk of fetal-to-maternal haemorrhage.2

## Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

Cell-free fetal DNA (cffDNA) present in the maternal circulation is detected by high-throughput non-invasive prenatal testing (HT-NIPT), using real-time quantitative polymerase chain reaction (PCR). HT-NIPT is used to determine the RhD genotype of a fetus carried by a RhD-negative woman by detecting the presence of cffDNA fragments in the mother’s plasma. The presence of RhD-positive cffDNA would indicate the presence of a RHD gene, which suggests a RhD-positive fetus.3

## ****(a) Is this a request for MBS funding?****

Yes

No

## ****If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?****

Amendment to existing MBS item(s)

New MBS item(s)

## ****If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:****

N/A

## ****If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?****

1. **An amendment to the way the service is clinically delivered under the existing item(s)**
2. **An amendment to the patient population under the existing item(s)**
3. **An amendment to the schedule fee of the existing item(s)**
4. **An amendment to the time and complexity of an existing item(s)**
5. **Access to an existing item(s) by a different health practitioner group**
6. **Minor amendments to the item descriptor that does not affect how the service is delivered**
7. **An amendment to an existing specific single consultation item**
8. **An amendment to an existing global consultation item(s)**
9. **Other (please describe below):**

N/A

## ****If a new item(s) is being requested, what is the nature of the change to the MBS being sought?****

1. **A new item which also seeks to allow access to the MBS for a specific health practitioner group**
2. **A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)**
3. **A new item for a specific single consultation item**
4. **A new item for a global consultation item(s)**

## ****Is the proposed service seeking public funding other than the MBS?****

Yes

No

## ****If yes, please advise:****

## What is the type of service:

Therapeutic medical service

Investigative medical service

Single consultation medical service

Global consultation medical service

Allied health service

Co-dependent technology

Hybrid health technology

## For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

1. To be used as a screening tool in asymptomatic populations
2. Assists in establishing a diagnosis in symptomatic patients
3. Provides information about prognosis
4. Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
5. Monitors a patient over time to assess treatment response and guide subsequent treatment decisions
6. A service that tests for heritable mutations in clinically affected individuals to make a genetic diagnosis and thus estimate their variation in (predisposition for) future risk of further disease and, when also appropriate, cascade testing of family members of those individuals who test positive for one or more relevant mutations, to make a genetic diagnosis and thus estimate each family member’s variation in (predisposition for) future risk of developing the clinical disease.

## Does your service rely on another medical product to achieve or to enhance its intended effect?

Pharmaceutical / Biological

Prosthesis or device

No

## (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

Yes

No

## If yes, please list the relevant PBS item code(s):

## If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

Yes (please provide PBAC submission item number below)

No

## If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name:

Generic name:

## (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

Yes

No

N/A

## If yes, please provide the following information (where relevant):

Billing code(s):

Trade name of prostheses:

Clinical name of prostheses:

Other device components delivered as part of the service:

## If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

Yes

No

## Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

Yes

No

## If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

## Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumables: Laboratory consumables used to conduct quantitative polymerase chain reaction, such as primers, reaction tubes and laboratory pipette tips.

Multi-use consumables: Nil

# PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

## (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: In-vitro diagnostic test developed “in-house”

Manufacturer’s name: N/A

Sponsor’s name: N/A

## Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

Class III

AIMD

N/A

**Class 4 in-house IVD**

## (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

Yes (If yes, please provide supporting documentation as an attachment to this application form)

No

## If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

Yes (if yes, please provide details below)

No

ARTG listing, registration or inclusion number:

TGA approved indication(s), if applicable:

TGA approved purpose(s), if applicable:

## If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

Yes (please provide details below)

No

Date of submission to TGA:

Estimated date by which TGA approval can be expected:

TGA Application ID:

TGA approved indication(s), if applicable:

TGA approved purpose(s), if applicable:

## If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

Yes (please provide details below)

No

Estimated date of submission to TGA:

Proposed indication(s), if applicable:

Proposed purpose(s), if applicable:

# PART 4 – SUMMARY OF EVIDENCE

## Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

| - | Type of study design\* | Title of journal article or research project (including any trial identifier or study lead if relevant) | Short description of research (max 50 words)\*\* | Website link to journal article or research (if available) | Date of publication\*\*\* |
| --- | --- | --- | --- | --- | --- |
| 1. | Diagnostic accuracy | Determination of fetal RHD type in plasma of RhD negative pregnant women4 | The fetal RHD genotype was studied in 373 samples from RhD negative pregnant women (median gestational week 24). DNA extracted from plasma was analysed for the presence/absence of RHD exon 7 and 10 in a real-time PCR. The RHD genotype of the fetus was compared with the serological RhD type of the newborn. In 234 samples, the fetal RHD test was positive and in 127 samples negative. There was one false positive and no false negative results. In 12 samples, the fetal RHD type could not be determined, in all of them due to a maternal RHD gene. | <https://www.tandfonline.com/doi/pdf/10.1080/00365513.2018.1475681?needAccess=true> | 2018 |
| 2. | Systematic review and economic evaluation | High-throughput non-invasive prenatal testing for fetal rhesus D status in RhD-negative women not known to be sensitised to the RhD antigen: a systematic review and economic evaluation.3 | A systematic review of the evidence on the diagnostic accuracy, clinical effectiveness and implementation of high-throughput NIPT and the development of a cost-effectiveness model from the UK perspective. 8 studies were included in the diagnostic accuracy review, 7 studies were included in the clinical effectiveness review and 12 studies were included in the review of implementation. | <https://www.journalslibrary.nihr.ac.uk/hta/hta22130#/abstract> | 2018 |
| 3. | Cost-effectiveness analysis | High-throughput, non-invasive prenatal testing for fetal Rhesus D genotype to guide antenatal prophylaxis with anti-D immunoglobulin: a cost-effectiveness analysis.5 | A decision tree model was used to characterise the antenatal care pathway in England and the long-term consequences of sensitisation events. Five alternative strategies in which the use of HT-NIPT may affect the existing postpartum care pathway were considered. The diagnostic accuracy of HT-NIPT was derived from the systematic review above. | <https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1111/1471-0528.15152> | 2018 |
| 4. | Diagnostic accuracy | Prenatal non-invasive foetal RHD genotyping: diagnostic accuracy of a test as a guide for appropriate administration of antenatal anti-D immunoprophylaxis.6 | Cell-free foetal DNA was extracted from plasma of RhD-negative women between 11-30 weeks of pregnancy. The fetal RHD genotype was determined non-invasively by qPCR amplification of exons 5, 7 and 10 of the RHD gene. Results were compared with serological RhD cord blood typing at birth. The analysis of diagnostic accuracy was restricted to the period (24-28+6 weeks) during which fetal genotyping is usually performed for targeted antenatal immunoprophylaxis. Fetal RHD status was inconclusive in 9/284 samples, including 4 cases with RhD maternal variants. 2 false-positive results one false-negative result (in a sample collected at 18 weeks) were registered. After inclusion of samples at early gestational age (<23 week), sensitivity and accuracy were 99.6% and 95.5%, respectively. | <http://www.bloodtransfusion.it/articolo.aspx?idart=003194> | 2018 |
| 5. | Diagnostic accuracy | Non-invasive foetal RhD genotyping to guide anti-D prophylaxis: an external quality assurance workshop7 | An external quality assurance workshop in which 22 laboratories (including ones in Australia) participated in testing two plasma samples from pregnant RhD-negative women, with the aim of future development of standards for testing for foetal RhD genotype. | <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6034781/pdf/blt-16-359.pdf> | 2018 |
| 6. | Systematic review and bivariate meta-analysis | The accuracy of cell-free fetal DNA-based non-invasive prenatal testing in singleton pregnancies: a systematic review and bivariate meta-analysis8 | Determine accuracy of cffDNA-based NIPT for all conditions and to evaluate the influence of other factors on test performance. Included cohort studies reporting cffDNA-based NIPT performance in singleton pregnancies. For fetal rhesus D status, NIPT can be considered diagnostic. Bivariate meta-analysis demonstrated sensitivities and specificities, respectively for rhesus D, 0.993 (95% CI 0.982–0.997) and 0.984 (95% CI 0.964–0.993), 10 290 tests. | <https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1111/1471-0528.14050> | 2017 |
| 7. | Prospective cohort | Targeted antenatal anti-D prophylaxis program for RhD-negative pregnant women – outcome of the first two years of a national program in Finland9 | The aim of this study was to assess the accuracy of the non-invasive fetal RHD test at 24–26 weeks of gestation as part of the national Finnish antenatal screening program to target routine antenatal anti-D prophylaxis at 28–30 weeks for women carrying an RhD-positive fetus. A prospective cohort study involving all maternity care centres and delivery hospitals in Finland between February 2014 and January 2016. Fetal RHD genotyping using cell-free fetal DNA in maternal plasma was performed with real-time PCR with results compared with the serological newborn RhD typing. Fetal RHD was screened from 10,814 women. For the detection of fetal RHD, sensitivity was 99.99% and specificity 99.81%. One false-negative and 7 false-positive results were reported by the delivery hospitals in two years. The negative predictive value of the test was 99.97%. At the end of the study period, over 98% of the RhD-negative women participated in the new screening program. | <https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1111/aogs.13191> | 2017 |
| 8 | Cost-effectiveness analysis | Noninvasive fetal RHD genotyping of RhD negative pregnant women for targeted anti‐D therapy in Australia: A cost‐effectiveness analysis10 | A decision‐analytic model was constructed to compare RHD testing and targeted anti‐D prophylaxis, with current universal anti‐D prophylaxis among pregnant women with RhD negative blood type. | <https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1002/pd.5176> | 2017 |
| 9. | Retrospective cohort, diagnostic accuracy | Diagnostic accuracy of fetal rhesus D genotyping using cell-free fetal DNA during the first trimester of pregnancy11 | 416 serum samples from RhD-negative pregnant women were collected during the first trimester of pregnancy. Cell-free fetal DNA was extracted from maternal blood of both non-immunised and immunised women at 10-14 weeks of gestation. RHD sequence was determined by quantitative PCR, with amplification of exon 10. Results were compared with RhD phenotype data obtained by cord blood sampling of neonates. | <https://tinyurl.com/y8tyunqm> | 2016 |
| 10 | Cost-effectiveness analysis | Cost-effectiveness of first trimester non-invasive fetal RHD screening for targeted antenatal anti-D prophylaxis in RhD-negative pregnant women: a model-based analysis12 | Population-based (Sweden) cohort study to estimate the cost-effectiveness of first trimester non-invasive fetal RHD screening for targeted antenatal versus no routine antenatal anti-D prophylaxis (RAADP) or versus non-targeted RAADP. Intervention subjects in the underlying cohort study were RhD-negative pregnant women receiving first trimester fetal RHD screening followed by targeted anti-D in 2010–2011 (n = 6723). Historical comparators were RhD-negative women who delivered in 2008–2009 when standard care did not include RAADP (n = 7099). | <https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1111/1471-0528.13801> | 2016 |
| 11 | Diagnostic accuracy | Sensitivity of fetal RHD screening for safe guidance of targeted anti-D immunoglobulin prophylaxis: prospective cohort study of a nationwide programme in the Netherlands13 | Fetal RHD testing was performed with a duplex real time quantitative PCR, with cell-free fetal DNA isolated from maternal plasma and compared to serological cord blood typing. A fetal RHD test result and serological cord blood result were available for 25,789 pregnancies. Sensitivity and specificity for detection of fetal RHD was 99.94% and 97.74%, respectively. Nine false negative results for fetal RHD testing were registered, 2 of which were due to technical failures. False positive fetal RHD testing results were registered for 225 samples. Weak RhD expression was shown in 22 of these cases, justifying anti-D immunoglobulin use. The negative and positive predictive values were 99.91% and 98.60%, respectively. More than 98% of the women participated in the screening programme. | <https://www.bmj.com/content/bmj/355/bmj.i5789.full.pdf> | 2016 |
| 12 | Cost-benefit analysis | Costs and benefits of non-invasive fetal RhD determination14 | A decision analysis based on a theoretical population representing the total number of pregnancies in Alberta over a 1-year period (n=69 286). A decision tree was created that outlined targeted prophylaxis for unsensitised RhD-negative pregnant women screened for cffDNA (targeted group) vs routine prophylaxis for all unsensitised RhD-negative pregnant women (routine group). Probabilities at each decision point and costs associated with each resource were calculated from local clinical and administrative data. The estimated cost per pregnancy for the routine group was C$71.43 compared with C$67.20 in the targeted group. Sensitization rates per RhD-negative pregnancy were equal, at 0.0012, for the current and targeted programs. Implementing targeted antenatal anti-RhD prophylaxis would save 4,072 doses (20.1%) of RhIG over a 1-year period in Alberta when compared to the current program. | <https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1002/uog.14723> | 2015 |
| 13 | Diagnostic accuracy | Use of cffDNA to avoid administration of anti-D to pregnant women when the fetus is RhD-negative: implementation in the NHS15 | cffDNA testing was offered to all RhD-negative women at about 16 weeks’ gestation in 3 maternity centres (total number not stated). Uptake of testing increased over the time of the pilot study. 529 samples were received; 3 were unsuitable. The results were reported as RhD-positive (n = 278), RhD-negative (n = 185) or inconclusive, treat as positive (n = 63). Cord blood results were available in 502 (95%) and the only incorrect result was one case of a false positive (cffDNA reported as positive, cord blood negative – and so given anti-D unnecessarily). Audit showed that women who declined this service were correctly managed and that anti-D was not given when the fetus was predicted to be RhD-negative. The total use of anti-D doses fell by about 29% which equated to about 35% of RhD-negative women not receiving anti-D in their pregnancy unnecessarily. | <https://obgyn.onlinelibrary.wiley.com/doi/pdf/10.1111/1471-0528.13055> | 2015 |

*\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

*\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

*\**\*\* *If the publication is a follow-up to an initial publication, please advise.*

## Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

| - | Type of study design\* | Title of research (including any trial identifier if relevant) | Short description of research (max 50 words)\*\* | Website link to research (if available) | Date\*\*\* |
| --- | --- | --- | --- | --- | --- |
| 1. | **Nil** | Nil | Nil | Nil | Nil |

*\* Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

*\*\*Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

*\**\*\**Date of when results will be made available (to the best of your knowledge).*

# PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

## List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):

Royal College of Pathologists of Australasia (RCPA)

## List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):

Australian Red Cross Blood Service

Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Royal Australasian College of General Practitioners

## List the relevant consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):

Australian Red Cross Blood Service

## List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:

N/A

## Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):

Name of expert 1: **REDACTED**

Telephone number(s): **REDACTED**

Email address: **REDACTED**

Justification of expertise: **REDACTED**.

Name of expert 2: **REDACTED**

Telephone number(s): **REDACTED**

Email address: **REDACTED**

Justification of expertise: **REDACTED**.

*Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.*

# PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

## Define the medical condition, including providing information on the natural history of the condition and a high-level summary of associated burden of disease in terms of both morbidity and mortality:

Although the Rh system comprises 61 antigens, the D antigen is the most immunogenic and important, with routine Rh typing only testing for the presence or absence of the D antigen on red cells. The presence of RhD antigen confers Rh positivity; while people who lack RhD antigen are Rh negative.[[1]](#footnote-1) Approximately one in seven women has a rhesus (Rh) D-negative blood group. RhD negative women carrying an RhD-positive fetus are at risk of becoming sensitised, producing antibodies against the RhD antigen if fetal cells enter the maternal circulation.1 Although sensitisation can occur at any time during gestation, it usually occurs in the third trimester or during labour. In addition, sensitisation can result from medical interventions (e.g. chorionic villus sampling, amniocentesis or external cephalic version), terminations, late miscarriages, antepartum haemorrhage and abdominal trauma. Sensitisation has no adverse effect on the mother, and usually has no adverse effect on the RhD-positive fetus of the pregnancy during which it occurs. However, future RhD-positive pregnancies in women who have been sensitised to the RhD antigen are at risk of haemolytic disease of the fetus and newborn (HDFN) when the mother mounts an immediate immune response. The mother’s anti-D antibodies respond to the presence of RhD-positive blood in the fetus, cross the placenta and bind to fetal red blood cells, leading to haemolysis.3 If undiagnosed and/or untreated, HDFN carries significant risk of perinatal morbidity, including fetal anaemia and fetal heart failure, fluid retention, and generalised oedema which can be severe (hydrops fetalis), and possibly intrauterine death. In the newborn high levels of bilirubin (caused by the breakdown of red blood cells) can lead to severe neonatal jaundice with an increased risk of permanent brain damage.16 The risk of HDFN increases with each subsequent pregnancy with a Rh-positive fetus.10

The current standard of care is the routine administration anti-D immunoglobulin prophylaxis to all RhD negative pregnant women at 28 and 34 weeks’ gestation, and within 72 hours of the delivery of an RhD-positive fetus, or following other obstetric events associated with a risk of fetal-to-maternal haemorrhage.2

The Australian Red Cross Blood Service estimates that approximately 17% of Australian women who become pregnant are RhD-negative and would receive routine anti-D prophylaxis.[[2]](#footnote-2) However, of all RhD-negative pregnant women, approximately 40 per cent will be carrying an RhD-negative fetus and would receive unnecessary anti-D prophylaxis.17 Based on these figures and the number of births in Australia in 2016 the number of RhD-negative pregnant women and unnecessary anti-D treatments have been calculated as per Table 1.

Table 1 Estimated number of women who would be tested and estimated number of women receiving unnecessary anti-D (annually) based on 2016 ABS data[[3]](#footnote-3)

| **Total number of births 2016** | **Estimated number of RhD negative pregnant women (women who would be tested)a** | **Estimated number of women receiving unnecessary anti-D in the absence of NIPT  (RhD-negative fetus)b** |
| --- | --- | --- |
| 311,104 | 52,887 | 21,155 |

a 17% of total number of births

b 40% of pregnancies in RhD negative women

## Specify any characteristics of patients with the medical condition, or suspected of, who would be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

All pregnant women should undergo serological testing to ascertain their RhD status (positive or negative) in early pregnancy. RhD-negative women should also be tested for the presence of anti-D antibodies regardless if they have been known to be sensitised.2 As described above (Q24), all pregnant RhD-negative women should undergo non-invasive RhD testing to ascertain the RhD status of their fetus instead of receiving non-targeted anti-D prophylaxis.

## Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

As above

PART 6b – INFORMATION ABOUT THE INTERVENTION

## Describe the key components and clinical steps involved in delivering the proposed medical service:

RhD-NIPT is used to detect fetal RhD DNA circulating in maternal blood. Initial observations found that cffDNA was present at about 1–10% of the concentration of maternal DNA in maternal plasma18 The test requires a venepuncture to be performed on the pregnant woman for the collection of a blood sample that is referred to a pathology laboratory for genetic analysis.

High-throughput RhD NIPT is carried out using 4 ml to 6 ml of maternal anti-coagulated blood. DNA is extracted and amplified using real-time quantitative PCR. Primers and probes of the RHD gene are used, and the following controls are tested alongside the samples: RHD positive DNA; RHD negative DNA; RHD pseudogene positive DNA; and no DNA. The time to complete the test from sample receipt to report generation is 5 to 6 hours.19

RhD-NIPT should be offered to RhD-negative pregnant women prior to 28 weeks gestation, when prophylactic anti-D would normally be administered. The diagnostic accuracy of RhD-NIPT may vary according to different gestational ages at the time of sampling. Two meta-analyses found that the diagnostic accuracy of RhD-NIPT was higher in the first trimester than in the second and third trimester. However, a recent UK cohort study found that fetal RhD genotyping was more accurate for the prediction of RhD status if it was performed after, rather than before, 11 weeks’ gestation.3

The RhD-NIPT result would be reported to the treating medical practitioner/obstetrician who would advise the patient of the result and whether or not anti-D should be administered.

## Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

Various assays are available for NIPT using the same scientific principles and no single commercial or trademark product is endorsed in this application.

## If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

N/A

## If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

Once off diagnostic test for each pregnancy of a RhD-negative woman with the possibility of repeat testing in some instances where results are inconclusive, however women with an inconclusive result are usually treated as if positive and are administered anti-D.

## If applicable, identify any healthcare resources or other medical services that would need to be delivered at the same time as the proposed medical service:

None

## If applicable, advise which health professionals will primarily deliver the proposed service:

Testing would be provided by Approved Practising Pathologists in line with other tests in the MBS Pathology Table.

## If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

The Australian Red Cross Blood Service currently provide this service.

## If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

N/A

## If applicable, advise what type of training or qualifications would be required to perform the proposed service as well as any accreditation requirements to support service delivery:

Testing would be delivered only by Approved Practising Pathologists in Accredited Pathology Laboratories (as defined in MBS Pathology table) by referral only by registered Medical Practitioners (non-pathologists) in line with other tests in the MBS Pathology Table.

All RhD-negative pregnant women should be referred for RhD-NIPT by either their treating general practitioner or obstetrician.

## (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select all relevant settings):

Inpatient private hospital

Inpatient public hospital

Outpatient clinic

Emergency Department

Consulting rooms

Day surgery centre

Residential aged care facility

Patient’s home

Laboratory

Other – please specify below

1. **Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:**

N/A

## Is the proposed medical service intended to be entirely rendered in Australia?

Yes

No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

## Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

There is no true diagnostic comparator test administered at the same point of time in the care pathway. All pregnant women will have their Rhesus D status determined by a standard antibody test. If found to be RhD negative, they will be administered universal anti-D prophylaxis without the determination of the RhD status of the fetus. The Rhesus D status of the fetus can only be determined by cord blood sampling after the birth of the baby, or the invasive options of amniocentesis or chorionic villus sampling, which have the potential for adverse events. It is rare for these procedures to be conducted – usually for reasons other than determining RhD status. In the year July 2017 to June 2018, there were a total of 4,079 services performed using MBS item numbers 16606, 16600, and 16603. This represents 1.3% of all live births during the same period (311,104[[4]](#footnote-4)). NIPT enables the targeted administration of anti-D only to RhD negative women who need it, preventing the needless administration of anti-D to RhD-negative women carrying an RhD-negative fetus.

## Does the medical service that has been nominated as the comparator have an existing MBS item number(s)?

Yes (please provide all relevant MBS item numbers below)

No

**Item number 16606**: Fetal blood sampling, using interventional techniques from umbilical cord or fetus, including fetal neuromuscular blockade and amniocentesis (Anaes.). Fee: $243.25

**Item number 16600**: AMNIOCENTESIS, diagnostic. Fee: $63.50

**Item number 16603**: CHORIONIC VILLUS SAMPLING, by any route. Fee: $121.85

**Item number 65096**: Blood grouping (including back-grouping if performed), and examination of serum for Rh and other blood group antibodies, including:

(a) Identification and quantitation of any antibodies detected; and (b) (if performed) any test described in item 65060 or 65070. Fee: $41.00

**Item number 65090**: Blood grouping (including back-grouping if performed) - ABO and Rh (D antigen). Fee: $11.15

**Item number 65093**: Blood grouping - Rh phenotypes, Kell system, Duffy system, M and N factors or any other blood group system - 1 or more systems, including item 65090 (if performed). Fee: $22.00

## Define and summarise the current clinical management pathways that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards including health care resources):

According to current clinical practice guidelines, all pregnant women found to be RhD negative by a standard antibody test should be offered anti-D prophylaxis at approximately 28 week’s gestation and again at around 34 weeks gestation. Universal anti-D prophylaxis is administered without the knowledge of the RhD status of the fetus. Rh (D) Immunoglobulin should not, however, be given to women:

• with preformed anti-D antibodies (alloimmunisation), except where the preformed antibodies are due to antenatal administration of Rh (D) Immunoglobulin;

• who are Rh (D) positive;

• who are Immunoglobulin A deficient, unless they have been tested and shown not to have circulating anti-IgA antibodies;

• with a history of anaphylactic or other severe systemic reaction to Immunoglobulins.

For women with severe thrombocytopenia or a coagulation disorder that contraindicates intramuscular injection, the intravenous preparation of Rh (D) Immunoglobulin should be used.20

The National Blood Authority currently supplies RhD immunoglobulin, which is manufactured by CSL Behring, Australia.

All pregnant women presenting to their care providor should be typed for ABO and Rhesus D status and antibody status.
RhD negative women who are found to be TRUE antibody positive do not require Anti D.
RhD negative women who are antibody negative should receive Anti D either as prophylaxis at 28 and 34 weeks, and at birth, OR less than 72 hours after  a sensitising event.
Women who are RhD positive do not require Anti D

Figure 1 Current care pathway for determining the RhD status in pregnant women20

## (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

in addition to

instead of

## If instead of, please outline the extent of which the current service/comparator is expected to be substituted:

Rhesus D NIPT will only be offered to RhD-negative women, with anti-D prophylaxis only offered to RhD women carrying an RhD-positive fetus.

## Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service including variation in health care resources (Refer to Question 39 as baseline):

The main difference in the care pathway of pregnant women who undergo RhD NIPT is the avoidance of the unnecessary administration of RhD immunoglobulin in women carrying an RhD negative fetus.

All pregnant women presenting to their care providor should be typed for ABO and Rhesus D status and antibody status.
RhD negative women who are found to be TRUE antibody positive do not require Anti D.
Women who are RhD positive do not require Anti D
RhD negative women who are antibody negative should be offered NIPT to determine RhD status of fetus. 
If the fetus is RhD negative, Anti D is not required. If the result is unequivocal or the fetus is RhD positive, then the mother shoudl receive  Anti D either as prophylaxis at 28 and 34 weeks, and at birth, OR less than 72 hours after  a sensitising event.

Figure 2 Care pathway for pregnant women with fetal RhD status determined by NIPT

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

## Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

When using the comparator, cord blood testing, the Rhesus D status of a fetus can only be determined after birth. As a consequence, anti-D prophylaxis is administered universally. It is ethically unacceptable to continue routine anti-D prophylaxis when fetal RHD genotyping using maternal blood is available and could identify those women who do not need this product.21 Women should be aware and appropriately informed of all the risks and benefits of treatment with anti-D. In Australia, anti-D is manufactured from plasma collected from a small pool (less than 200) of RhD negative male plasma donors, who are injected with RhD-positive red blood cells to stimulate sensitisation and antibody production.[[5]](#footnote-5) Blood products prepared from multiple donors carry the risk of infection, and although the theoretical risk of transmission of viruses and prions is small, it is a risk that may be avoided if anti-D is only used when indicated.21

The Australian Red Cross Blood Service estimates that approximately 17% of Australian women who become pregnant are RhD-negative and would receive routine anti-D prophylaxis.5 However, of all RhD-negative pregnant women, approximately 40 per cent will be carrying a RhD-negative fetus and would receive unnecessary anti-D prophylaxis.17 If RHD NIPT was offered to all RhD negative pregnant women it would assist them to make an informed choice about whether or not to have antenatal anti-D.22

In addition, the domestic supply of anti-D is threatened due to an ageing donor population, gradual decline in people available with anti-D antibodies. Australia is almost self-sufficient in the supply of anti-D, with the majority manufactured by CSL Behring, however, it has been necessary to import some product to meet demand, making supply vulnerable due to a world-wide shortage of anti-D.

## Please advise if the overall clinical claim is for:

Superiority

Non-inferiority

## Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

**Safety Outcomes:**

Sensitisation events

Rate of fetal adverse events including fetal anaemia and fetal heart failure, oedema, hydrops fetalis, neonatal jaundice and mortality.

**Clinical Effectiveness Outcomes:**

Assessment of diagnostic/test accuracy: sensitivity, specificity, number of false positives, number of false negatives, number of inconclusive results

Assessment of clinical outcomes

**Cost-effectiveness**

Reduction in the administration of anti-D

# PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

## Estimate the prevalence and/or incidence of the proposed population:

The Australian Red Cross Blood Service estimates that approximately 17% of Australian women who become pregnant are RhD-negative and would receive routine anti-D prophylaxis.[[6]](#footnote-6) However, of all RhD-negative pregnant women, approximately 40 per cent will be carrying an RhD-negative fetus and would receive unnecessary anti-D prophylaxis.17 Based on these figures and the number of births in Australia in 2016 the number of RhD-negative pregnant women and unnecessary anti-D treatments have been calculated as per Table 2.

Table 2 Estimated number of women who would be tested and receive unnecessary anti-D, annually (based on 2016 ABS data[[7]](#footnote-7))

| **Year** | **Estimated number of  births each yearc** | **Estimated number of RhD negative pregnant women who would be testeda** | **Estimated number women receiving unnecessary anti-D in absence of NIPT (RhD-negative fetus)b** |
| --- | --- | --- | --- |
| 2016 | 311,104 | 52,887 | 21,155 |
| 2017 | 316, 921 | 53,876 | 21,550 |
| 2018 | 322, 847 | 54,884 | 21,954 |
| 2019 | 328, 884 | 55,910 | 22,364 |
| 2020 | 335, 034 | 56,956 | 22,782 |
| 2021 | 341, 299 | 58,021 | 23,208 |

a 17% of total number of births

b 40% of pregnancies in RhD negative women

c Estimates based on an increase in the number of births from 2015 to 2016 of 1.87%

## Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

Rhesus D NIPT should be performed for every pregnancy of an RhD negative mother.

## How many years would the proposed medical service(s) be required for the patient?

The number of tests performed will be based on the number of pregnancies per women – in 2016, Australia's total fertility rate was 1.79 babies per woman.[[8]](#footnote-8)

## Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

The number of births increased by 1.87% from 2015 to 2016. Based on the number of births in 2016, it would be expected that approximately 55,910 RhD negative pregnant women should be tested in 2019 (Table 2).

## Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of ‘leakage’ to populations not targeted by the service:

The estimated number of RhD negative pregnant women for 2019-2021 is summarised in Table 2 (Question 46).

# PART 8 – COST INFORMATION

## Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

An Australian cost-effectiveness analysis was conducted by Gordon et al in 2017, and estimated that the mean cost per person for the RHD gene test was AU$45.48. This figure was based on the large-scale testing of 46,000 women – based on an RhD negative prevalence of 15 percent. The analysis took into account the physical space required by a laboratory to conduct the test, staffing requirements, ancillary equipment in addition to consumables used in the testing (including a discount for bulk purchase). The study took a health system perspective including direct costs incurred by hospitals, the National Blood Authority, and the Australian Red Cross Blood Service.10 The cost of the test would likely increase slightly from that quoted by Gordon et al if performed by several smaller laboratories.

The results of the analysis found that the mean cost for a pregnancy in an RhD negative woman under universal anti‐D prophylaxis was $7,495 compared with 7,471 for NIPT, representing a small cost-saving per person to the health system. With NIPT, 13 938 women would avoid unnecessary antenatal anti‐D prophylaxis at a total cost savings to the National Blood Authority of $2.1 million per year. To the health system, net cost savings of $159,701 per year (0.05%) were predicted for total health care costs.10 A full summary of the costs of universal versus targeted anti-D prophylaxis can be found in Figure 3. The cost of RhD immunoglobulin in Australia in 2015 was $29.38 for 250 IU and $73.41 for 625 IU (manufactured by CSL Behring, Australia). In 2018, the National Blood Authority lists prices as follows:

* RhD immunoglobulin (plasma derived – imported) Rhophylac – 1500 IU = $411.22
* RhD immunoglobulin (Glycine Formulation, plasma derived - domestic) – 250 IU = $29.79, 625 IU = $74.44 23

It is expected that RhD NIPT will deliver savings to the Australian health system from the reduction in the widespread and unnecessary use of anti-D, in addition to reducing the potential reliance on an overseas source for anti-D, which may be associated with risks such as infection.

## Specify how long the proposed medical service typically takes to perform:

The time to complete the test from sample receipt to report generation is 5 to 6 hours.19

## If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

MBS Pathology Table Category 6, Group P7 -Genetics

Proposed item descriptor: Non-invasive prenatal testing of blood from a Rhesus D negative pregnant woman for the detection of Rhesus D fetal DNA circulating in maternal blood.

Fee: $XXX

The economic analysis in an Australian setting compared the administration of Anti D to all pregnant women to those women who only received Anti D on the basis of the result of an NIPT test.
The number of pregancies per year was estimated at 365,732, with the number of RhD negative women estimated to be 54,860.
In the Universal group 41,693 woudl receive Anti D antenatally, 28,344 post-partum and 11,109 would receive Anti D for a sensitising event.
In the NIPT group, 27,755 women would receive Anti D antenatally, 28,622 post-partum and 11,121 would receive Anti D for a sensitising event.
Genetic testing was estimated to cost $2,231,783
Other costs considered were estimated costs to the National Blood Authority, which were $8,607,080 in the Universal group compared to $6,535,988 in teh NIPT group.
Estimated costs to the Blood Service were $2,569,394 and $1,953,116 in the Uiversal and NIPT groups, respectively.
Costs to public hospitals were estimated to be $314,297,739 and $314,593,626 in the Uiversal and NIPT groups, respectively.
Total annual costs were $325,474,214 in the Universal group compared to $325,314,513 in the NIPT group.

Figure 3 Summary of economic analysis of universal versus targeted anti-D prophylaxis (annual)10

# PART 9 – FEEDBACK

The Department is interested in your feedback.

## How long did it take to complete the Application Form?

Insert approximate duration here

## (a) Was the Application Form clear and easy to complete?

Yes

No

## If no, provide areas of concern:

Describe areas of concern here

## (a) Are the associated Guidelines to the Application Form useful?

Yes

No

## If no, what areas did you find not to be useful?

Insert feedback here

## (a) Is there any information that the Department should consider in the future relating to the questions within the Application Form that is not contained in the Application Form?

Yes

No

## If yes, please advise:

1. **The question numbers in the template do not align with the question numbers in the Guide**
2. **Question 41** **does not make sense – you are asking 2 questions here and yet require a Yes or No answer.**

## (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

Yes

No

The Questions needs to be

## (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

in addition to

instead of

Followed by

## If instead of, please outline the extent of which the current service/comparator is expected to be substituted:

1. **Question 8 in Template/ Question 9 in Guideline**

Question 8 in the template (2.4) does NOT have choice iv – which the Guideline DOES

vi. A service that tests for heritable mutations in clinically affected individuals to make a genetic diagnosis and thus estimate their variation in (predisposition for) future risk of further disease and, when also appropriate, cascade testing of family members of those individuals who test positive for one or more relevant mutations, to make a genetic diagnosis and thus estimate each family member’s variation in (predisposition for) future risk of developing the clinical disease.

References

1. Lyon, C. &English, A. (2018). 'PURL: A new protocol for RhD-negative pregnant women?'. *J Fam Pract*, 67 (5), 306;8;19.

2. RANZCOG (2015). Guidelines for the use of Rh(D) Immunoglobulin (Anti-D) in obstetrics in Australia. [Internet]. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Available from: <https://www.ranzcog.edu.au/Statements-Guidelines> [Accessed 1st August 2018].

3. Saramago, P., Yang, H.et al (2018). 'High-throughput non-invasive prenatal testing for fetal rhesus D status in RhD-negative women not known to be sensitised to the RhD antigen: a systematic review and economic evaluation'. *Health Technol Assess*, 22 (13), 1-172.

4. Sorensen, K., Kjeldsen-Kragh, J.et al (2018). 'Determination of fetal RHD type in plasma of RhD negative pregnant women'. *Scand J Clin Lab Invest*, 1-6.

5. Saramago, P., Yang, H.et al (2018). 'High-throughput, non-invasive prenatal testing for fetal Rhesus D genotype to guide antenatal prophylaxis with anti-D immunoglobulin: a cost-effectiveness analysis'. *BJOG*.

6. Manfroi, S., Calisesi, C.et al (2018). 'Prenatal non-invasive foetal RHD genotyping: diagnostic accuracy of a test as a guide for appropriate administration of antenatal anti-D immunoprophylaxis'. *Blood Transfus*, 1-11.

7. Clausen, F. B., Barrett, A. N.et al (2018). 'Non-invasive foetal RhD genotyping to guide anti-D prophylaxis: an external quality assurance workshop'. *Blood Transfus*, 16 (4), 359-62.

8. Mackie, F. L., Hemming, K.et al (2017). 'The accuracy of cell-free fetal DNA-based non-invasive prenatal testing in singleton pregnancies: a systematic review and bivariate meta-analysis'. *BJOG*, 124 (1), 32-46.

9. Haimila, K., Sulin, K.et al (2017). 'Targeted antenatal anti-D prophylaxis program for RhD-negative pregnant women - outcome of the first two years of a national program in Finland'. *Acta Obstet Gynecol Scand*, 96 (10), 1228-33.

10. Gordon, L. G., Hyland, C. A.et al (2017). 'Noninvasive fetal RHD genotyping of RhD negative pregnant women for targeted anti-D therapy in Australia: A cost-effectiveness analysis'. *Prenat Diagn*, 37 (12), 1245-53.

11. Vivanti, A., Benachi, A.et al (2016). 'Diagnostic accuracy of fetal rhesus D genotyping using cell-free fetal DNA during the first trimester of pregnancy'. *Am J Obstet Gynecol*, 215 (5), 606 e1- e5.

12. Neovius, M., Tiblad, E.et al (2016). 'Cost-effectiveness of first trimester non-invasive fetal RHD screening for targeted antenatal anti-D prophylaxis in RhD-negative pregnant women: a model-based analysis'. *BJOG*, 123 (8), 1337-46.

13. de Haas, M., Thurik, F. F.et al (2016). 'Sensitivity of fetal RHD screening for safe guidance of targeted anti-D immunoglobulin prophylaxis: prospective cohort study of a nationwide programme in the Netherlands'. *BMJ*, 355, i5789.

14. Teitelbaum, L., Metcalfe, A.et al (2015). 'Costs and benefits of non-invasive fetal RhD determination'. *Ultrasound Obstet Gynecol*, 45 (1), 84-8.

15. Soothill, P. W., Finning, K.et al (2015). 'Use of cffDNA to avoid administration of anti-D to pregnant women when the fetus is RhD-negative: implementation in the NHS'. *BJOG*, 122 (12), 1682-6.

16. Gandhi, A. (2016). Haemolytic Disease of the Fetus and Newborn. [Internet]. Patient Platform Ltd. Available from: <https://patient.info/doctor/haemolytic-disease-of-the-fetus-and-newborn> [Accessed 1st August 2018].

17. Finning, K., Martin, P.et al (2008). 'Effect of high throughput RHD typing of fetal DNA in maternal plasma on use of anti-RhD immunoglobulin in RhD negative pregnant women: prospective feasibility study'. *BMJ*, 336 (7648), 816-8.

18. de Haas, M., Finning, K.et al (2014). 'Anti-D prophylaxis: past, present and future'. *Transfus Med*, 24 (1), 1-7.

19. NICE (2016). High-throughput non-inHigh-throughput non-invasive prenatal testing for fetal RHD genotype: Diagnostics guidance. [Internet]. National Institute for Health and Care Excellence. Available from: <https://www.nice.org.uk/guidance/dg25> [Accessed 22nd August 2018].

20. NSW Health (2015). *Guideline: Maternity - Rh (D) Immunoglobulin (Anti D)*, NSW Ministry of Health, Sydney <https://www1.health.nsw.gov.au/pds/ActivePDSDocuments/GL2015_011.pdf>.

21. Johnson, J. A., MacDonald, K.et al (2017). 'No. 343-Routine Non-invasive Prenatal Prediction of Fetal RHD Genotype in Canada: The Time is Here'. *J Obstet Gynaecol Can*, 39 (5), 366-73.

22. Kent, J., Farrell, A. M. &Soothill, P. (2014). 'Routine administration of Anti-D: the ethical case for offering pregnant women fetal RHD genotyping and a review of policy and practice'. *BMC Pregnancy Childbirth*, 14, 87.

23. NBA (2018). What Blood Products are Supplied - National Product List. [Internet]. National Blood Authority Australia. Available from: <https://www.blood.gov.au/national-product-list> [Accessed 21st August 2018].

1. See Australian Red Cross Blood Service <https://transfusion.com.au/blood_basics/blood_groups/abo_rh> [↑](#footnote-ref-1)
2. See Australian Red Cross Blood Service <https://www.donateblood.com.au/anti-d-program> [↑](#footnote-ref-2)
3. See Australian Bureau of Statistics <https://tinyurl.com/y884gkwj> [↑](#footnote-ref-3)
4. <http://www.abs.gov.au/ausstats/abs@.nsf/Latestproducts/3301.0Main%20Features32016?opendocument&tabname=Summary&prodno=3301.0&issue=2016&num=&view>= [↑](#footnote-ref-4)
5. See Australian Red Cross Blood Service <https://www.donateblood.com.au/anti-d-program> [↑](#footnote-ref-5)
6. See Australian Red Cross Blood Service <https://www.donateblood.com.au/anti-d-program> [↑](#footnote-ref-6)
7. See Australian Bureau of Statistics <https://tinyurl.com/y884gkwj> [↑](#footnote-ref-7)
8. See Australian Bureau of Statistics <http://www.abs.gov.au/ausstats/abs@.nsf/Latestproducts/3301.0Main%20Features42016?opendocument&tabname=Summary&prodno=3301.0&issue=2016&num=&view>= [↑](#footnote-ref-8)