Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1574 – Non-Invasive Prenatal Testing (NIPT) for Fetal Rhesus D Genotype

Applicant: The Royal College of Pathologists of Australasia (RCPA)

Date of MSAC consideration: MSAC 80th Meeting, 26-27 November 2020

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

An application requesting Medicare Benefits Schedule (MBS) listing of non-invasive prenatal testing (NIPT) for fetal rhesus (Rh) D genotype in RhD-negative pregnant patients, was received from the Royal College of Pathologists of Australasia (RCPA) by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for non-invasive prenatal testing (NIPT) for fetal rhesus D (*RHD*) genotype in both low-risk women who have not been isoimmunised and high-risk women who have been previously isoimmunised. MSAC considered that testing prevents over-treatment with anti-D immunoglobulin (anti-D Ig), but may be associated with a very small risk of isoimmunisation events in low-risk pregnancies in women with a false negative fetal genotype result.

Consumer summary
The Royal College of Pathologists of Australasia applied for public funding via the Medicare Benefits Schedule (MBS) of non-invasive prenatal testing (NIPT) to determine if a fetus is rhesus D antigen (RhD) positive or negative in pregnant women who are RhD-negative. The rhesus D antigen is a protein on the surface of most people's red blood cells. It partly determines whether the mother's blood and the fetus's blood are compatible. In general, people who have the *RHD* gene will have the RhD antigen, and are said to be RhD-positive ('rhesus positive'). NIPT can identify whether the fetus is RhD-positive or negative, by testing for *RHD* gene DNA in a sample of the mother's blood.

Consumer summary

If a RhD-negative woman is pregnant with a RhD-positive fetus, the mother may produce anti-RhD antibodies during pregnancy. If the mother later becomes pregnant with another RhD-positive fetus, these antibodies can cause a serious disease in the fetus called haemolytic disease of the fetus and newborn (HDFN). This cannot happen in RhD-positive women, so they do not need to be tested.

If a NIPT test for *RHD* is positive, then the mother will receive a treatment called anti-D immunoglobulin to help prevent her forming anti-RhD antibodies so that her future babies won't be harmed. If the NIPT test is negative, then the mother's future babies are not at risk of getting HDFN, so she does not need anti-D immunoglobulin.

Right now, almost all RhD-negative pregnant women receive anti-D immunoglobulin without knowing the babies' RhD status. This means that many women currently receive a treatment that they do not need. This is also a problem because anti-D immunoglobulin is produced by only a few donors in Australia, and the supply is getting lower.

The Medical Services Advisory Committee (MSAC) noted that *RHD*-NIPT was accurate and cost-effective, and is an important test for all RhD-negative pregnant women to have access to.

MSAC's advice to the Commonwealth Minister for Health

MSAC recommended that NIPT testing for RhD be publicly funded on the MBS. This is because MSAC believes this test is effective and cost-effective, and that it is important to keep the national supply of anti-D immunoglobulin for other people who need it.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that application 1574 was for MBS listing of NIPT to determine the fetal *RHD* genotype in RhD-negative pregnant women. This determines whether the mother is at risk for alloimmunisation following sensitising events during pregnancy, and directing management to prevent a subsequent RhD-positive fetus being at risk of developing haemolytic disease of the fetus and newborn (HDFN).

MSAC considered the proposed price to be appropriate. MSAC considered that transportation costs for the pathology sample should not be included in the proposed test fee, and noted that MBS items 73929 or 73939 should cover transportation.

MSAC noted that, currently, Australian Red Cross Lifeblood (Lifeblood) provides *RHD* NIPT across Australia within a temporary funding arrangement for high-risk pregnancies in women sensitised in a previous pregnancy (population 1). This application was for a separate population of women for whom Lifeblood is not funded to provide the testing because they are RhD-negative but not alloimmunised (population 2). Currently, population 2 is universally administered antenatal anti-D immunoglobulin (Ig) prophylaxis irrespective of fetal Rhesus genotype. MSAC noted that the Department-contracted assessment report (DCAR) did not initially include population 1 because the tests use different methods that have different laboratory costs, and the population of alloimmunised patients is quite small (approximately six per month nationally). However, MSAC agreed with PASC, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists and the Department, that a separate item for population 1 should be included for reimbursement on the MBS. MSAC noted that separate MBS items are necessary to enable quality assurance,

particularly for population 1, which should aim to evaluate the proportion of false negative results.

MSAC supported the Department's modification of the MBS descriptors for both item numbers.

MSAC noted the clinical need for fetal *RHD* genotyping as current anti-D Ig supply, which relies on approximately 120 altruistic and ageing blood donors, is diminishing. Fetal genotyping can direct a targeted reduction in unnecessary anti-D Ig prophylaxis to more than 20,000 women with *RHD*-negative fetuses in Australia each year.

MSAC noted the small risk of alloimmunisation due to a false negative NIPT result with women consequently not receiving routine antenatal anti-D Ig prophylaxis. This could have possible adverse effects on the current fetus or in subsequent pregnancies with a RhD-positive fetus. However, MSAC accepted that this risk is low (less than 6 additional alloimmunised pregnancies per 100,000 compared with universal anti-D Ig) due to the high:

- sensitivity – 95.4% [90.6%, 97.8%] (k = 37, n = 3,078) to 99.9% [99.5%, 100%] (k = 12; n = 60,396);
- specificity – 96.1% [94.2%, 97.5%] (k = 8; n = 49,291) to 99.2% [98.5%, 99.5%] (k = 12; n = 60,396);
- positive predictive value – 97.6% [96.2%, 98.5%] to 99.5% [99.1%, 99.7%]; and
- negative predictive value – 92.8% [86.0%, 96.4%] to 99.8% [99.2%, 100%].

MSAC noted the application presented a population-based analysis of costs and outcomes, and that using an NIPT-guided anti-D Ig strategy results in cost savings. In absolute terms, introducing *RHD* NIPT to current practice of universal anti-D Ig prophylaxis resulted in less than two additional alloimmunisations, an additional 0.03 cases per 100,000 of severe HDFN and 0.05 additional fetal deaths per 100,000 Australian RhD-negative women during their child-bearing years.

MSAC acknowledged that other accredited laboratories could establish NIPT using a variety of testing techniques, including quantitative reverse-transcription polymerase chain reaction (qRT-PCR), qRT digital PCR and array-based platforms, and that the service provider should not be limited to Lifeblood.

MSAC noted the pre-MSAC response from the applicant.

The MBS item descriptor proposed for low-risk non-alloimmunised patients is below. The item descriptor for high-risk alloimmunised patients is to be developed during implementation.

4. Background

MSAC has not previously considered non-invasive prenatal testing for fetal rhesus D genotype.

5. Prerequisites to implementation of any funding advice

The DCAR stated that as noted in the PICO, there are no Therapeutic Goods Administration (TGA) licensed tests currently available, therefore this would require laboratories to validate and register their test as an in-house in-vitro diagnostic (IVD). Platforms used in Australian

laboratories would likely vary across laboratories where a variety of techniques could be used including: qRT-PCR, qRT digital PCR, and array-based platforms.

The National Pathology Accreditation Advisory Council (NPAAC) stated that a quality framework would need to be established around this test as poor quality would pose a significant risk to a current and future fetus of HDFN, which can cause death. Currently, it is provided as an in-house test developed and performed by Lifeblood, and there is no existing Australian external quality assurance (EQA) program. While Lifeblood participates in the International Survey distributed by the Department of Clinical Immunology of Copenhagen University Hospital for EQA of non-invasive fetal *RHD* genotyping, an Australian EQA program would need to be established.

The NPAAC also commented that testing could be high volume (one in seven pregnancies is 40000/year) and could be set up by multiple providers, all of whom would need to validate their own in-house assays, which would require significant expertise. Inaccurate testing (sensitivity or specificity) poses a significant risk of HDFN to both a current and future fetus, as the opportunity to immunise the mother with anti-D Ig might be missed.

Lifeblood commented that they have been performing NIPT for *RHD* in alloimmunised women for many years, and have published their experience[1]. The test has now transitioned from research into the Lifeblood's reference laboratory and is NATA-accredited. Lifeblood recently received approval from governments (through the National Blood Authority and the Jurisdictional Blood Committee) to provide *RHD*-NIPT for women with high-risk pregnancies within existing Australia-wide funding arrangements. This testing includes the following clinical indications:

- RhD-negative pregnant women who are Rh(D) alloimmunised
- RhD-negative pregnant women with obstetric indications such as severe fetomaternal haemorrhage during pregnancy, or intrauterine fetal death
- Other scenarios in non-sensitised RhD-negative women with a relative contraindication to routine antenatal anti-D Ig prophylaxis, such that the fetal *RHD* genotype results in the risk-benefit assessment to guide anti-D Ig management decisions (for example prior allergic reaction to anti-D Ig, or cultural/religious beliefs).

Number of service providers

Lifeblood further commented that it is well placed to provide this testing. Lifeblood reference laboratories already perform this testing on referred samples for high-risk pregnancies, and could rapidly accommodate the increased testing required for routine *RHD*-NIPT for all RhD-negative pregnant women. In addition, Lifeblood has extensive experience in RhD variants that may complicate the interpretation of NIPT for *RHD*, and has the facilities and expertise to perform additional RhD genotyping to further categorise these maternal or fetal RhD variants and determine the need for anti-D Ig. Furthermore, a single national provider (across multiple centres) of this testing provides efficiencies of scale, consistency of sample requirements and timing and an opportunity to avoid repeat or duplicate testing. It also enables assessment of the overall effectiveness of targeted antenatal anti-D Ig prophylaxis by aggregated reporting of testing error rates and sensitisations, which could not be monitored easily across multiple testing providers.

[1] Hyland CA, et al. Evaluation of non-invasive prenatal *RHD* genotyping of the fetus. Med J Aust 2009; 191: 21-25.

The RCPA responded to discussion at PASC's April 2019 meeting regarding Lifeblood potentially being the single provider of this test, that it would not be considered good medical practice to have a single provider perform pathology testing for an entire population. Their stated position on having a single provider performing the testing is that if something goes wrong with the methodology it may go undetected, or if something goes wrong and is detected there is no backup testing available. In addition, they state that development of expertise would be restricted thereby limiting the availability of suitable experts for second opinions regarding difficult cases. The applicant stated that other concerns with single-provider testing include a lack of current availability of regular external quality assurance, and no drive for competitive pricing.

6. Proposal for public funding

The DCAR proposed the following MBS item descriptor for *RHD*-NIPT. The DCAR statedthat the proposed MBS item descriptor in the PICO (Table 1, top row) did not specify whether the test was to be performed in RhD-negative women who were alloimmunised or not. Women with alloimmunised pregnancies are considered to be at high-risk, requiring testing with higher performance standards, therefore the MBS item descriptor has been modified by the HTA group (Table 1, bottom) to reflect that this test is to be performed only in Rhesus D-negative, non-alloimmunised pregnant patients.

Table 1: Proposed MBS item descriptor for NIPT

Category 6 – Pathology Services (Group P7 Genetics)
MBS item 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 to be determined
*MBS item (newly proposed)** *Non-invasive prenatal testing of blood from a Rhesus D negative* ***non-alloimmunised*** *pregnant patient for the detection of Rhesus D fetal DNA (in a singleton pregnancy only) circulating in maternal blood.* *Fee to be determined*

* Additional information included in the MBS item descriptor additional to that in the PICO
Source: DCAR, Table 1

The DCAR proposed that testing also be limited to singleton pregnancies due to the inability to ensure that DNA from all fetuses in a twin or higher order pregnancies can be satisfactorily identified.

MSAC considered that the fees being discussed for the two items ($56 and $550 respectively) were probably insufficient to cover the cost of testing and requested that the Department investigate what these fees should be. The agreed fees should then be factored into the estimated MBS costs.

7. Summary of public consultation feedback/consumer Issues

Targeted consultation feedback was received from Lifeblood, and also from a second clinical organisation.

Lifeblood stated that they strongly support the availability of NIPT for fetal *RHD* for all pregnant RhD-negative women.

Lifeblood commented that anti-D Ig is manufactured from the plasma of voluntary blood donors, and the donor pool has been shrinking in number over the past 3-4 years. While recruitment efforts continue, the trend is not favourable, suggesting there may be future challenges in providing adequate domestically sourced anti-D Ig for continued universal (un-targeted) antenatal prophylaxis. In the pre-ESC response the applicant agreed, noting that Australia's current anti-D Ig supply relies on approximately 120 altruistic donors. The donor pool is ageing, and it has been difficult to recruit new donors, who are required to be deliberately sensitised to RhD for the purpose of anti-D Ig plasma collections.
The clinical organisation commented that the proposed item would lead to major change in current clinical practice, with potential for large cost savings by avoiding unnecessary anti-D Ig administration to over 20,000 women with RhD-negative fetuses annually, and reducing exposure of pregnant women to a blood product. This approach has precedents in Europe (Denmark, the Netherlands, Finland, and some parts of Sweden, England and France).

The clinical organisation stated that false negative results would be the main risk with this approach (albeit a low risk), and suggested MSAC should consider the estimated rate of false negative results leading to RhD-negative women at risk of missing out on prophylactic anti-D Ig , as compared to the relatively higher current risk of sensitisation of 0.2% in RhD-negative women[2]. The Danish national experience was a false negative rate of 0.087% and false positive rate of 0.32% (1 in 300), which they considered acceptable[3]. Other studies observed rates of 0.1-0.2%. This is important to consider, as a recent cost-effectiveness decision-analytic modelling study concluded that fetal *RHD* genotyping is a cost-effective option for supporting targeted anti-D Ig prophylaxis in women with RhD-negative pregnancies, but that it "also appears less effective than current practice."

The clinical organisation commented that women who are RhD-negative and anti-D antibody positive (i.e. alloimmunised) should also have a clear pathway to *RHD* NIPT, as this will determine the risk status for that pregnancy and hence the degree of fetal surveillance required, without the increased risk of isoimmunisation with an invasive diagnostic procedure.

No consumer feedback/consumer comments were received for this application.

8. Proposed intervention's place in clinical management

The DCAR stated that the current clinical management of RhD-negative women (Figure 1, red arrows) is guided by their anti-D antibody status. Initially, clinical assessment includes an anti-D antibody screen. Non-alloimmunised RhD-negative patients are treated prophylactically with 625 International Units (IU) anti-D Igduring their pregnancy at weeks 28 and 34-36, alongside routine D-antibody screens to prevent the development of maternal anti-D. This regimen is currently recommended for all low-risk non-alloimmunised RhD-negative pregnant patients during their pregnancy as the Rh status of their fetus is unknown. At birth, a blood cord sample can be taken to determine the baby's RhD status, and if the baby is RhD-positive, the mother will receive an additional dose of 625 IU anti-D Ig. Additional doses of anti-D Ig are also recommended if a sensitising event occurs, such as miscarriage, termination, or chorionic villus sampling. Fetal blood escaping into the maternal system (fetomaternal haemorrhage) can cause the development of maternal anti-D antibodies. Testing to determine the extent of any fetomaternal haemorrhage is recommended to the appropriate dose of anti-D Ig can be given.

[2] DCAR Table 36, source: "Australian Red Blood (FAQ)"
[3] Clausen FB, et al. Routine noninvasive prenatal screening for fetal *RHD* in plasma of RhD-negative pregnant women-2 years of screening experience from Denmark. Prenatal diagnosis. 2014;34(10):1000-5.

The DCAR's proposed clinical management algorithm (Figure 1, green arrows) requires that all RhD-negative, antibody negative (non-alloimmunised) pregnant patients have a non-invasive prenatal test for fetal *RHD* genotype. If the test is positive (i.e. *RHD* cell-free fetal DNA [cffDNA] detected or inconclusive), then anti-D Ig is administered as prophylaxis similar to the current clinical pathway. Where the test is negative (i.e. *RHD* cffDNA not detected), then these patients do not receive treatment with anti-D Ig. In the pre-MSAC response, the applicant noted that where the cord RhD type is discrepant with the NIPT *RHD* genotyping, then this should be reported to the laboratory.

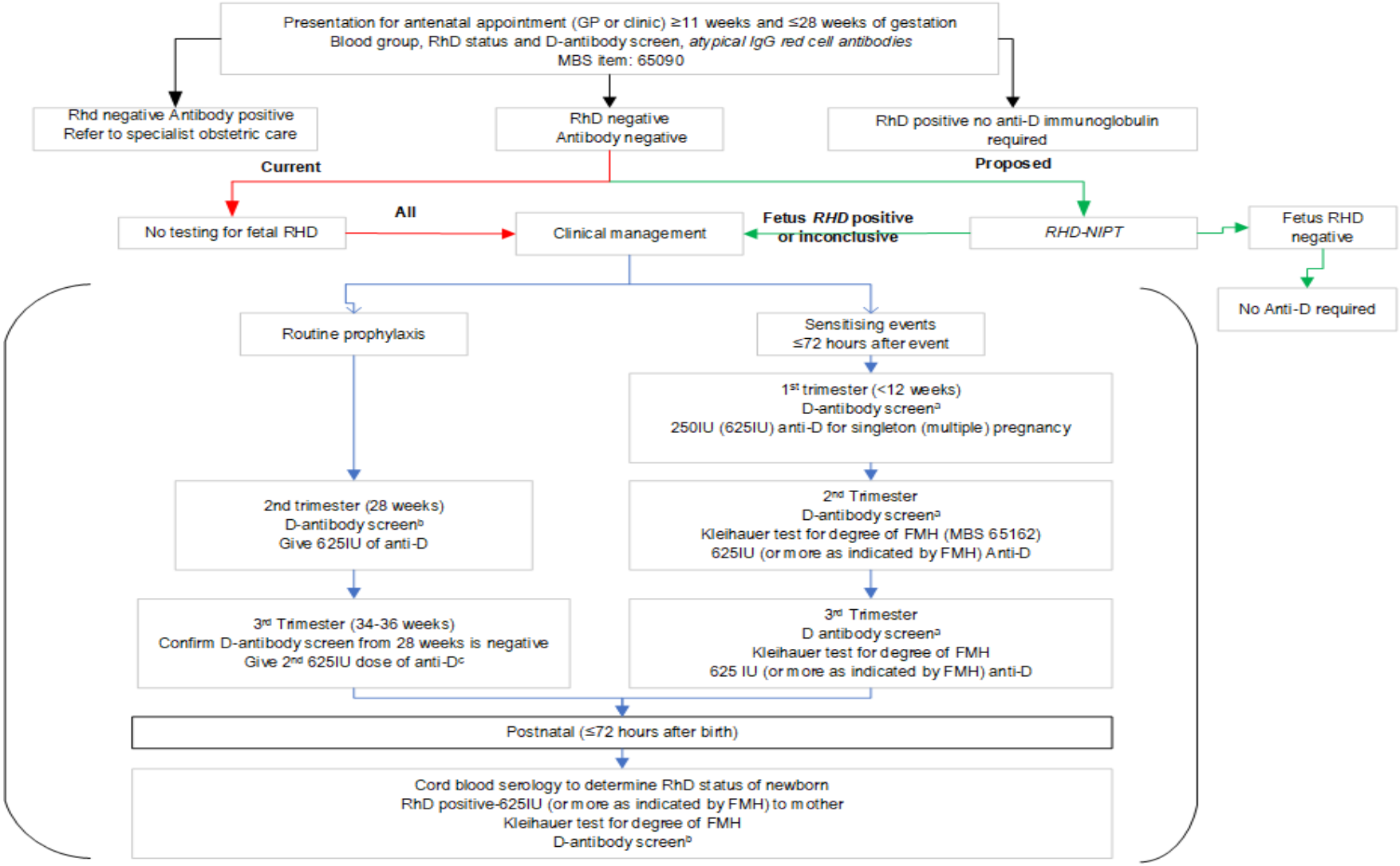

Figure 1 Current (red) and proposed (green) clinical management algorithm

[a] positive D-antibody screen leads to further investigation of red cell antibodies and possible referral to specialist

[b] it is not necessary to wait for the D-antibody screen result to give anti-D immunoglobulin

[c] new D-antibody screen test is not required prior to the second dose of anti-D immunoglobulin

Description of Proposed Intervention

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 an 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 reflects an RhD-positive fetus.

Description of Medical Condition(s)

Approximately one in seven women has an RhD-negative blood group. RhD-negative women carrying an RhD-positive fetus are at risk of becoming sensitised (alloimmunised), producing IgG antibodies against the RhD antigen if fetal cells enter the maternal circulation (fetomaternal haemorrhage). Alloimmunisation places future RhD-positive fetuses (and rarely the RhD-positive fetus of the pregnancy in which alloimmunisation occurs) at risk of HDFN. If undiagnosed and/or untreated, HDFN carries significant risk of perinatal morbidity and mortality[4]. Fetal *RHD* status can currently only be determined during pregnancy from chorionic villous sampling, amniocentesis to obtain fetal cells, or amniocentesis with fetal circulation sampling, each of which risks isoimmunisation and/or pregnancy loss and consequently are not performed in the setting of low risk, non-alloimmunised pregnancy, and universal anti-D Ig is administered to all RhD negative pregnant women.

In Australia, the current standard of care is the routine administration of anti-D Ig to all RhD-negative pregnant women at 28 and 34-36 weeks' gestation, and within 72 hours of delivery of an RhD-positive fetus, or following other obstetric events associated with a risk of fetomaternal haemorrhage. Determining the *RHD* genotype of the fetus using non-invasive testing will mean that declining stocks of anti-D Ig can be reserved for RhD-negative women found to be carrying an *RHD*-positive fetus.

Patient population

The DCAR proposed restricting testing to RhD-negative pregnant patients who are not alloimmunised, because the tests currently used by Lifeblood are different for alloimmunised pregnancies (Table 2). The DCAR noted that although PASC advised "that potential MBS funding should not exclude [alloimmunised patients], as equity must be considered, especially if current funding is time-limited", the DCAR only evaluated fetal *RHD*-NIPT testing for non-alloimmunised patients because the test is different, and the description of NIPT for alloimmunised patients (with multiple testing of different genes) is not the test as described in the PICO confirmation. In the pre-MSAC response, the applicant noted that if this application is supported, individual pathology providers may choose and validate different assays than those provided by Lifeblood.

Table 2: Difference between NIPT tests in non-alloimmunised compared to alloimmunised patients currently provided by Lifeblood

Test for non-alloimmunised patients	Alloimmunised patients
Redacted	Redacted

Source: DCAR, Table 15

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

9. Comparator

The comparator in RhD-negative pregnant patients who are non-alloimmunised, is no testing for the *RHD* genotype of the fetus.

10. Comparative safety

The DCAR stated that the test requires a simple venepuncture. Other safety-related outcomes arise from the change in clinical management conditional on the test result, so are discussed in the following section.

11. Comparative effectiveness

Clinical claim

The DCAR stated that the clinical claim is superiority of *RHD*-NIPT to determine fetal *RHD* status, over the comparator (no testing). A clinical claim of safety is not made in the PICO.

The DCAR added that the main safety issue would be consequences of false negatives (i.e., the fetus is actually *RHD*-positive but apparently *RHD* test negative), which would result in a small increase in the risk of alloimmunisation due to the lost opportunity to receive routine antenatal anti-D Ig prophylaxis and the possible adverse effects on the fetus or subsequent pregnancies carrying a *RHD*-positive fetus.

In the pre-ESC response, the applicant commented that the risk from false negatives is small for the current pregnancy: despite a false negative NIPT result, there is the opportunity to administer post-partum anti-D Ig based on cord blood RhD fetal serotyping. With current universal antenatal anti-D Ig administration the risk of maternal alloimmunisation in women at risk is reduced to approximately 0.2%, compared to approximately 2% of women at risk of sensitisation actually becoming sensitised without antenatal anti-D Ig administration. In addition, not all subsequent pregnancies will be RhD-positive: if the father is heterozygous, then each fetus has a 50% chance of being RhD-negative. The issue of women not receiving appropriate, clinically indicated, anti-D Ig represents an issue that is an order of magnitude greater than the risk of false-negative NIPT results. In the rejoinder, the HTA group responded that the probability of alloimmunisation with only post-partum anti-D Ig is estimated in the literature at 0.67% to 2%. The value of 1.5% as recommended by NHMRC was used in the base case and subjected to sensitivity analyses.

Clinical validity

The DCAR assessed the diagnostic accuracy of *RHD*-NIPT genotyping to be high, based on eight published meta-analyses (four at low risk of bias), each providing a comparison of *RHD*-NIPT to the reference standard (RhD antigen phenotype on fetal blood typing). The DCAR summarised the results of their systematic review (Table 3), noting that the highest estimates of sensitivity and specificity were both reported in the systematic review by Runkel *et al.* (2020)[5], which is the most recently published review, the study with the largest sample size (60,396 RhD-negative patients), and a study considered to have a low risk of bias.

[5] Runkel B, Bein G, Sieben W, Sow D, Polus S, Fleer D. Targeted antenatal anti-D prophylaxis for RhD-negative pregnant women: A systematic review. BMC Pregnancy and Childbirth. 2020;20(1).

Table 3: Summary statistics for RHD-NIPT from meta-analyses reported in the systematic reviews, against RhD blood typing

Accuracy	Index test
Sensitivity, % [95% CI]	95.4% [90.6%, 97.8%] (k=37, n=3,078) to 99.9% [99.5%, 100%] (k=12; n=60,396)
Specificity, % [95% CI]	96.1% [94.2%, 97.5%] (k=8; n=49,291) to 99.2% [98.5%, 99.5%] (k=12; n=60,396)
Positive predictive value, % [95% CI][a,b]	97.6% [96.2%, 98.5%] to 99.5% [99.1%, 99.7%]
Negative predictive value, % [95% CI][a,c]	92.8% [86.0%, 96.4%] to 99.8% [99.2%, 100%]

[a] based on a prevalence of 62% of fetuses in RhD-negative pregnancies being *RHD*-positive
[b] calculated as (sensitivity * prevalence) / ((sensitivity * prevalence) + ((1 - specificity) * (1 - prevalence)))
[c] calculated as (specificity * (1 – prevalence)) / (((1 - sensitivity) * prevalence) + (specificity * (1 – prevalence)))
Source: DCAR, Table 3

In the pre-MSAC response, the applicant noted that while the *RHD* genotype predicts the phenotype, there are more than a hundred *RHD* variants described, many of which result in a positive *RHD* genotype but with the phenotype being RhD-negative.

Clinical utility

The DCAR examined change in patient management as a result of test outcomes, in terms of avoidance of anti-D Ig administration for pregnancies with an RhD-negative fetus, and for all pregnancies (Table 4).

Table 4: Anti-D administration as a result of RHD-NIPT genotyping

Study	Anti-D immunoglobulin avoided with *RHD*-negative fetus	Anti-D immunoglobulin avoided in all pregnancies	Other
Damkjaer *et al.*, 2012[6]	68 of 69 *RHD*-negative (98.6%)	68 of 216 genotyped (31.5%)	1 of 69 (1.2%) received anti-D Ig before *RHD*-NIPT screening
Grande *et al.*, 2013[7]	90 of 95 *RHD*-negative (95%)	90 of 282 genotyped (30.8%)	5 of 95 (5%) with *RHD*-negative fetus requested anti-D Ig
Tiblad *et al.*, 2013[8]	100%	3,270 of 8,374 genotyped (39%)	-
Clausen *et al.*, 2014[9]	97.3%	4,706 of 12,668 genotyped (37.1%)	-
Soothill *et al.*, 2015[10]	Study: 185 of 185 *RHD*-negative (100%) Audit: 17 of 18 *RHD*-negative (94.4%)	Study: 185 of 529 genotyped (35.0%) Audit: 17 of 49 genotyped (34.7%)	Poisson regression 6% drop per month (95% CI: 4, 8%) in use of anti-D Ig; P <0.001. Audit: 1 of 18 (5.5%) *RHD*-negative received anti-D Ig (reason not provided) 5 of 49 (10%) inconclusive results received anti-D Ig
Papasavva *et al.*, 2016[11]	18 of 18 *RHD*-negative (100%)	18 of 71 genotyped (25.3%)	-
Haimila *et al.*, 2017[12]	3,626 of 3,641 *RHD*-negative (99.6%)	3,626 of 10,814 genotyped (33.7%)	39 of 10,814 genotyped (0.4%) received anti-D Ig primarily due to inconclusive results
Darlington *et al.*, 2018[13]	Using a second genotyping test to control an *RHD*-negative result Genotyping: 126 of 136 of *RHD*-negative (93%) Control: NR (27%)	Genotyping 126 of 515 genotyped (24.5%)	Treated appropriately: One test: 85% genotyped versus 62% control (P <0.0001) Two tests: 88% genotyped versus 63% control

DCAR's sources: Figure 1, p147 of Damkjaer 2012; p175 of Grande 2013; p3 of Tiblad 2013; p1002 of Clausen 2014; pp1684-1685 of Soothill 2015; p4 of Papasavva 2016; p1231 of Haimila 2017; p4, Table 2, p5 and p6 of Darlington 2018.
Source: DCAR, Table 4

The DCAR stated that there are harms associated with false negative results: withholding prophylactic antenatal anti-D Ig treatment in those patients whose fetus is determined to be *RHD*-negative when they are in fact *RHD*-positive, leading to a small increase in the risk of alloimmunisation (and the possibility of HDFN in each subsequent pregnancy carrying an

[6] Damkjaer MB, et al. Study of compliance with a new, targeted antenatal D immunization prevention programme in Denmark. Vox Sang. 2012;103(2):145-9.
[7] Grande M, et al. Clinical application of midtrimester non-invasive fetal *RHD* genotyping and identification of *RHD* variants in a mixed-ethnic population. Prenat Diagn. 2013;33(2): 173–8.
[8] Tiblad E, et al. Targeted routine antenatal anti-D prophylaxis in the prevention of RhD immunisation – outcome of a new antenatal screening and prevention program. PLOS ONE 2013;8:e70984.
[9] Clausen FB, et al. Routine noninvasive prenatal screening for fetal *RHD* in plasma of RhD-negative pregnant women-2 years of screening experience from Denmark. Prenatal diagnosis. 2014;34(10):1000-5.
[10] Soothill PW, et al. Use of cffDNA to avoid administration of anti-D to pregnant women when the fetus is RhD-negative: implementation in the NHS. BJOG: an international journal of obstetrics and gynaecology. 2015;122(12):1682-6.
[11] Papasavva T, et al. Prevalence of RhD status and clinical application of non-invasive prenatal determination of fetal *RHD* in maternal plasma: a 5 year experience in Cyprus. BMC research notes. 2016;9:198.
[12] Haimila K, et al. Targeted antenatal anti-D prophylaxis program for RhD-negative pregnant women – outcome of the first two years of a national program in Finland. Acta Obstetricia et Gynecologica Scandinavica. 2017;96(10):1228-33.
[13] Darlington M, et al. Effectiveness and costs of non-invasive foetal *RHD* genotyping in rhesus-D negative mothers: a French multicentric two-arm study of 850 women. BMC Pregnancy Childbirth. 2018;18(1):496.

RhD-positive fetus). One cost-effectiveness study (cited below in the Economic evaluation) estimated there would be three extra sensitisations per 100,000 women tested[14].

The DCAR stated that there are also harms associated with false positive results, arising from the unnecessary administration of anti-D Ig. However, in the pre-ESC response the applicant commented that universal antenatal administration of anti-D Ig is the comparator. The NIPT result enables the selective removal of unnecessary anti-D Ig administration in the approximately 37% of RhD-negative women who are carrying an RhD-negative fetus.

Translation issues

The DCAR stated that resource utilisation remains associated with a degree of uncertainty. Unit costs used in the modelled economic evaluation were obtained from Australian sources. However, in the alloimmunised population model, liberties were exercised in assembling specific MBS item costs to approximate the resources used in some of the procedures associated with monitoring and treatment of fetuses at risk of HDFN. The monetary value of the procedure was cross-validated with corresponding costs reported in the published literature whenever possible, ensuring that the unit cost estimates were at least of the same order of magnitude as reported in the international literature. This approach guaranteed a more nuanced representation of the current clinical pathway. It also limited costing based on the crude estimates of health care resources captured by the AR-DRG cost weights, although these could not be completely avoided.

12. Economic evaluation

Cost-effectiveness analyses were presented comparing NIPT-guided anti-D Ig administration with universal anti-D Ig prophylaxis, in non-alloimmunised and alloimmunised populations and in a population-based model (Table 5). The population-based model combined costs and the estimated incidence of alloimmunisation after the index pregnancy (the outcomes of the first model) with costs and the expected proportions of deaths and severe HDFN cases (the outcome of the second model) and applied these estimates to the cohort of primiparous individuals.

[14] Saramago P, 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).

Table 5: Summary of the economic evaluation

	Non-alloimmunised population	Alloimmunised population	Population-based model
Perspective	Australian Health Care System	Australian Health Care System	Australian Health Care System
Comparator	Universal anti-D Ig prophylaxis offered to all pregnant persons not known to be alloimmunised	Universal intensive monitoring offered to all alloimmunised pregnant patients	Universal anti-D Ig prophylaxis offered to all pregnant patients not known to be alloimmunised
Type of economic evaluation	Cost-effectiveness analysis comparing anti-D Ig prophylaxis guided by results of the high-throughput NIPT with current practice	One arm model assessing costs and outcomes of intensive monitoring and treatment of HDFN in alloimmunised pregnancies	Cost-effectiveness analysis comparing anti-D Ig prophylaxis guided by results of the high-throughput NIPT with current practice
Sources of evidence	Systematic reviews of NIPT accuracy[15,16]	Literature search for the parameters to differentiate the degrees of HDFN severity by risks and resource use	Australian population statistics (AIHW, ABS)
Time horizon	From the 12 week gestation period to the resolution of pregnancy	From the first presentation to delivery (typically at 37 weeks)	17 years (up to 4 consecutive pregnancies)
Outcomes	Risk of alloimmunisation	Severe HDFN cases, mild HDFN cases, fetal and neonatal mortality, unaffected babies	Incremental risk of alloimmunisation, severe HDFN cases, fetal and neonatal mortality
Methods used to generate results	Decision tree model	Decision tree model	Arithmetic calculations
Discount rate	0%	0%	5%
Software packages used	TreeAge Pro 2019 R2.0	TreeAge Pro 2019 R2.0	EXCEL spreadsheet

Source: DCAR, Table 5

The DCAR stated that a key structural assumption in the model for the non-alloimmunised population, is the natural progression of the index pregnancy with the estimated risk of alloimmunisation associated with fetomaternal haemorrhage. No consequences of alloimmunisation are assumed in the index pregnancy where it occurs. The model for the alloimmunised population depicts the current clinical pathway of intensive monitoring in order to estimate risk of fetal/neonatal deaths, risk of severe and mild HDFN and the probability of having of unaffected baby. The costs were differentiated according to the severity of HDFN. Unit costs were taken from Australian sources but informed and cross-validated with international literature.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the *RHD* genotype testing strategy and the comparative testing strategy in the models, and using the base case assumptions, are shown in Table 6 and Table 7. Results of the population-based model are shown in Table 8.

[15] Saramago P, 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).

[16] Yang H, et al. High-throughput, non-invasive prenatal testing for fetal rhesus D status in RhD-negative women: A systematic review and meta-analysis. BMC Medicine. 2019;17(1).

Table 6: Results of the base case CEA in non-alloimmunised population

	Cost ($)	Incremental cost	Effectiveness Alloimmunisations*	Incremental effectiveness	ICER
NIPT-guided anti-D immunoglobulin	337.88	- 9.17	0.0017715	0.0000587	NIPT-guided anti-D immunoglobulin is less expensive and less effective
Universal anti-D immunoglobulin	347.06		0.0017129		

ICER = Incremental Cost Effectiveness Ratio
* used in the population-based model
Source: DCAR, Table 6

Table 7: Results of the base case analysis in alloimmunised population

	Cost ($)	Effectiveness (Deaths)*	Effectiveness (Mild HDFN)	Effectiveness (Severe HDFN)*	Effectiveness (Unaffected baby)
Universal intensive monitoring	11,726	0.05^	0.24	0.027	0.68

* used in the population-based model;
^ includes miscarriages and terminations
Source: DCAR, Table 8

Table 8: Results of the population-based analysis (no discounting)

Strategy	Alloimmunisations	Incremental alloimmunisations	Severe HDFN	Incremental severe HDFN	Deaths	Incremental Deaths
NIPT-guided anti-D Ig	56.35	1.87	0.86	0.03	1.59	0.05
Universal anti-D Ig	54.48		0.83		1.54	

Source: DCAR, Table 10

The DCAR noted that in the base-case analysis, NIPT-guided anti-D Ig prophylaxis is a cost-saving strategy, being less expensive than the comparator universal anti-D Ig prophylaxis, by $9.17 per pregnancy. The NIPT-guided strategy is also associated with a slightly higher risk of alloimmunisation (less than six additional alloimmunised pregnancies per 100,000). This is consistent with the published estimates where the NIPT-guided strategy resulted in about three extra sensitisations per 100,000 women, compared to the universal anti-D Ig prophylaxis strategy with a postnatal cord blood test and anti-D Ig, if required[17].

The DCAR commented that in absolute terms, the introduction of *RHD*-NIPT to the current practice of universal anti-D Ig prophylaxis resulted in less than two additional alloimmunisations, 0.03 additional severe HDFN cases and 0.05 additional deaths over the child-bearing period of an Australian RhD-negative woman. The modelled number of alloimmunisations was found to be consistent with real-world data on alloimmunisation rates in Australia provided by LifeBlood.

The DCAR stated that with respect to the size of the original cohort of primiparous RhD-negative patients with an *RHD*-positive fetus (N=13,280), results indicated that introduction of NIPT would be associated with 0.00013 additional alloimmunisations (1.3 per 10,000), 0.000002 (2 per 1,000,000) additional severe haemolytic disease of the fetus and newborn (HDFN) cases and 0.000004 (4 per 1,000,000) additional deaths. In the rejoinder, the HTA group clarified that while this means 'six additional severe HDFN cases, four of whom died', it would be confusing and suggest that all fetal and neonatal deaths occurred after the diagnosis of HDFN. This is inconsistent with some of the model inputs (DCAR, Table 42)

[17] Saramago P, 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).

where the probability of fetal loss included deaths due to HDFN, due to invasive procedures, but also miscarriages and terminations. Only late terminations might be associated with the pre-natal diagnosis of HDFN.

The DCAR calculated the incremental cost-savings under the assumption of a high-throughput NIPT being listed on MBS as below (Table 9), based on reducing the $9.17 NIPT-related savings per pregnancy (Table 6) to account for the larger number of alloimmunised pregnancies associated with introduction of *RHD*-NIPT. The mean cost of monitoring and treatment per alloimmunised pregnancy was $11,726 (Table 7), and the incremental cost of monitoring and treatment of alloimmunised pregnancies decreases to $1,521 in the third alloimmunised pregnancy. The aggregated incremental costs of monitoring and treatment of HDFN cases across the alloimmunised pregnancies was $14,699. Deducting this amount from the *RHD*-NIPT-related savings from the index pregnancy produced the final estimate of potential savings of $82,044 or $75,374 when 5% discounting was applied.

Table 9: Algorithm for calculation of incremental savings if a high-throughput NIPT were listed on MBS

Inputs	**Size of the original cohort (N) (A)**		**Incremental savings per pregnancy* ($) (B)**		**Total savings in the cohort ($) (A) * (B)**
Savings in non-alloimmunised population	10,550		9.17		96,743
Inputs	**Cost per alloimmunised pregnancy** ($) (C)**	**2nd pregnancy (n)/$ (D)**	**3rd pregnancy (n)/$ (E)**	**4th pregnancy (n)/$ (F)**	**Total incremental cost in the cohort ($) (G)**
Incremental alloimmunisations	11,726	0.85	0.28	0.13	14,699**
Incremental costs of managing alloimmunisations		9,937	3,241	1,521	
Balancing the results to estimate the overall incremental savings (A)*(B)-(G)					82,044

* relates to the first non-alloimmunised (index) pregnancy, where alloimmunisation occurs
** results are calculated either by applying the unit cost (C) to the alloimmunisation total (D+E+F) or by a simple cost aggregation (D+E+F)
Source: DCAR, Table 11

The DCAR's analysis included conditional probabilities of progressing to the next pregnancy of 91.4%, 40.5%, and 58.3% for progressing to the second, third and fourth pregnancies respectively given the previous pregnancy (DCAR, Table 33)[18]. In the pre-ESC response, the applicant queried these figures stating that the values seem high for the Australian context where few families have three or more children.

The DCAR stated that the reviewed economic literature did not unequivocally establish the cost-effectiveness of NIPT for fetal *RHD* genotyping to guide management of RhD-negative pregnancies. Conflicting results were reported across the identified economic studies. Six

[18] Saramago P, 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).

studies[19,20,21,22,23,24,25] reported *RHD*-NIPT not to be cost-effective in comparison to current practice of universal anti-D Ig prophylaxis. Two studies[26,27] reported that the main factor driving these results was the cost of the test itself (i.e. the clinical and economic benefits were not sufficient to offset the additional costs of the test). These and other earlier studies[28,29,30] found that the cost of *RHD*-NIPT would need to decrease by approximately three times for the targeted anti-D Ig prophylaxis in non-alloimmunised pregnancies to become cost neutral compared with universal prophylaxis.

Fee and test methodology

The DCAR stated that Lifeblood advised that the Tier 3 application to the National Blood Authority to provide a national screening service for all RhD-negative pregnant patients proposed a medium throughput assay using only two *RHD* markers (exons 5 and 10), and testing in triplicate with a single *CCR5* gene control and with no additional testing for markers of cffDNA in negative cases. LifeBlood's proposal costed this testing at $56.00 per test including staff time and consumables, which was the fee used in the DCAR's economic analyses (DCAR Table 37).

In contrast, the current *RHD*-NIPT performed by Lifeblood for high-risk pregnancies is not a high-throughput test – Lifeblood estimates approximately six tests per month are performed in the alloimmunised population, at a cost of $550 per test. Due to low test volumes, a significant part of the cost of this test is staff labour/salary. Also, because of the performance requirements for this test in these high risk pregnancies, the sample is tested for three *RHD* markers (exons 4, 5 and 10) and is run in quadruplicate, with a *CCR5* gene control and with additional testing for markers of cell free fetal DNA (*SRY* and *RASSF1A*) in negative samples.

The LifeBlood price of $56 per sample was very close to the break-even cost estimated in some of the published economic evaluations. For example, one base case analysis suggested that high throughput *RHD*-NIPT appeared to be cost saving when the overall test cost

[19] Szczepura A, et al. (2011) A new fetal *RHD* genotyping test: costs and benefits of mass testing to target antenatal anti-D prophylaxis in England and Wales. BMC Pregnancy Childbirth;11:5.
[20] Duplantie J, et al. (2013) Cost/effectiveness of Rh negative pregnant women management. Biochimica Clinica;37:S409.
[21] Hawk AF, et al. (2013) Costs and clinical outcomes of noninvasive fetal RhD typing for targeted prophylaxis. Obstet Gynecol;122(3):579-85.
[22] Neovius M, 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.
[23] Darlington M, et al. Effectiveness and costs of non-invasive foetal *RHD* genotyping in rhesus-D negative mothers: a French multicentric two-arm study of 850 women. BMC Pregnancy Childbirth. 2018;18(1):496.
[24] Demirel E, et al. (2018) Is the management of Rh-Rh incompatibility with noninvasive fetal Rh genotyping for targeted prophylaxis cost-effective in the Turkish population? Turkish Journal of Medical Sciences; 48: 1-4
[25] Moise KJ, et al. Cell free fetal DNA to triage antenatal rhesus immune globulin: is it really cost-effective in the United States? Prenatal Diagnosis. 2019.
[26] Hawk AF, et al. (2013) Costs and clinical outcomes of noninvasive fetal RhD typing for targeted prophylaxis. Obstet Gynecol;122(3):579-85.
[27] Szczepura A, et al. (2011) A new fetal *RHD* genotyping test: costs and benefits of mass testing to target antenatal anti-D prophylaxis in England and Wales. BMC Pregnancy Childbirth;11:5.
[28] Hawk AF, et al. (2013) Costs and clinical outcomes of noninvasive fetal RhD typing for targeted prophylaxis. Obstet Gynecol;122(3):579-85.
[29] Neovius M, 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.
[30] Duplantie J, et al. (2013) Cost/effectiveness of Rh negative pregnant women management. Biochimica Clinica;37:S409.

was ≤£26.60 (AU$48)[31]. A threshold analysis on the cost of NIPT found that, at a per-sample cost of CAD$88 (AU$91) the intervention strategy would be cost neutral[32].

The DCAR's literature review found that the reported cost of *RHD*-NIPT varied from as little as £17.97 (AU$32.52) for the in-house test including a royalty fee[33] to as high as US$450 (AU$649) for the commercial kit[34]. The cost depended on whether the test was developed in-house rather than relying on a commercial kit, whether the laboratory had a high annual throughput, and whether a royalty fee was included in the estimate. In Canada the test was not automated, which contributed to its high cost of CAD$471 (AU$499)[35], but in Germany the cost of the test after automation was estimated at €26 (AU$43)[36].

Sensitivity analyses

The DCAR stated that in the non-alloimmunised population, the overall conclusion of NIPT-guided strategy of anti-D Ig prophylaxis being both less expensive and less effective in comparison to the universal anti-D Ig prophylaxis was robust to most parameter variations (e.g. in prevalence of RhD-positive fetuses, and in probability of alloimmunisation due to incomplete prophylaxis). The modelled results were most sensitive to the proportion of inconclusive tests and the cost of high-throughput NIPT (Table 10). The current practice of universal anti-D Ig prophylaxis became a dominant strategy (marginally less expensive and more effective than NIPT-guided prophylaxis) when the proportion of inconclusive tests increased from 2.6% in the base case to 6.7%; the results became even more pronounced when the proportion of inconclusive tests increased to 11.7%.

Table 10: Key drivers of the model in the non-alloimmunised population (sensitivity analysis)

Description	Value	Impact
Assumption about the population prevalence of RhD-positive foetuses	Increased from 62% in the base case to 66%	Decreased the amount of savings per pregnancy by 2.3[a] to 6.5[a] times (*ceteris paribus*).
Proportion of inconclusive tests	Increased from 2.6% in the base case to 11.7%	Incremental risk of alloimmunisation increased by 2.7 times from 5.9 cases per 100,000 to 1.6 cases per 10,000
Cost of transportation per vial added to NIPT cost	Increased from $0 in the base case to $25	NIPT intervention was associated with an additional cost of $15.72 per pregnancy

[a] Series of three-way sensitivity analyses; the estimate vary with the NIPT diagnostic accuracy; proportion of inconclusive tests; and whether these are treated as positive

Source: DCAR, Table 7

In the pre-ESC response, the applicant queried how increasing the proportion of inconclusive results would increase the risk of alloimmunisation, as current practice dictates that all inconclusive NIPT results be managed as RhD-positive, followed by the administration of anti-D Ig. In the rejoinder, the HTA group responded that this is a difference between clinical

[31] Saramago P, 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).

[32] Ontario HTA Series (Draft). Noninvasive Fetal RhD Blood Group Genotyping: A Health Technology Assessment. 2020 https://www.hqontario.ca/Portals/0/Documents/evidence/open-comment/hta-noninvasive-fetal-rhd-blood-group-genotyping-2001.pdf [accessed 31 July 2020].

[33] Szczepura A, et al. (2011) A new fetal *RHD* genotyping test: costs and benefits of mass testing to target antenatal anti-D prophylaxis in England and Wales. BMC Pregnancy Childbirth;11:5.

[34] Hawk AF, et al. (2013) Costs and clinical outcomes of noninvasive fetal RhD typing for targeted prophylaxis. Obstet Gynecol;122(3):579-85.

[35] Duplantie J, et al. (2013) Cost/effectiveness of Rh negative pregnant women management. Biochimica Clinica;37:S409.

[36] Legler TJ, et al. Prenatal RhD Testing: A Review of Studies Published from 2006 to 2008. Transfus Med Hemother. 2009;36(3):189-198.

practice and how the clinical evidence is presented in the systematic reviews and utilised in mathematical calculations underpinning the decision analytic model.

In the pre-ESC response, the applicant also queried the cost of transportation of the NIPT sample in the sensitivity analysis increasing to $25, which is inordinately high. If MSAC allocates an MBS item number for NIPT, then the MBS item 73929 (fee $5.95) should cover the collection fee, including transportation. In the rejoinder, the HTA group responded that the descriptor for MBS item 73928 (fee $5.95) is silent about including the cost of transportation. The Australian study by Gordon *et al.* (2017)[37], which presumably also benefited from the Red Cross' advice, also used cost of transport as a separated parameter and found the results were sensitive to the cost of transport ($25 per test).

The DCAR stated that in the alloimmunised population, the mean cost per alloimmunised pregnancy was fairly robust to the probability of crossing the threshold (titre >1:16), the probability of having mild rather than severe HDFN, and variations in cost of intensive monitoring of low-risk alloimmunised pregnancies (Figure 2). The largest difference between the base case cost estimate and the cost associated with the lower probability of having mild HDFN (0.8) did not exceed 13% (Table 11). Risks of fetal/neonatal death and having severe HDFN were most sensitive to variation in probability of crossing the threshold (titre >1:16) and therefore developing HDFN (either mild or severe). Within the HDFN subgroup, risk of severe HDFN was quite naturally sensitive to the probability of having mild rather than severe HDFN.

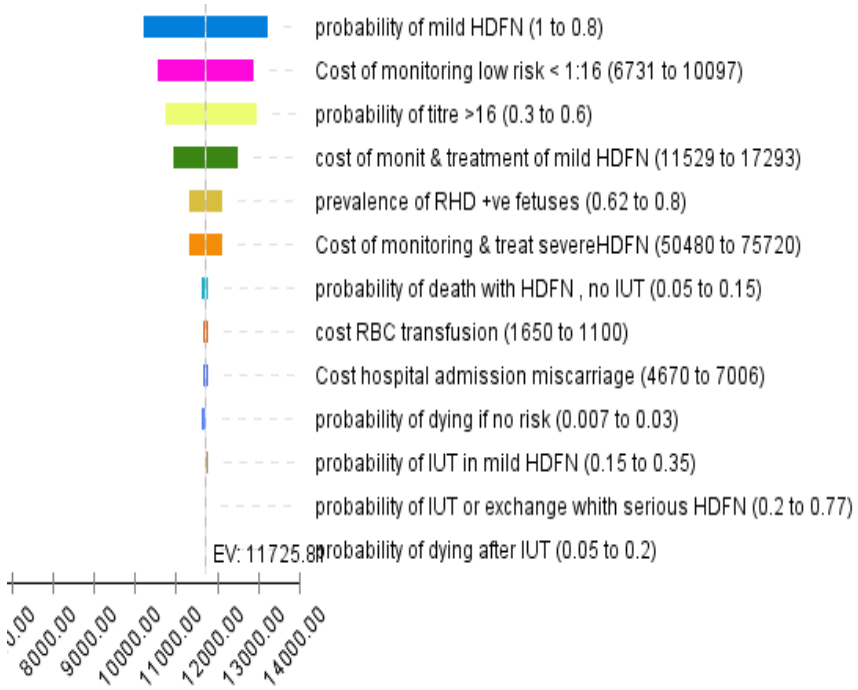

Figure 2: One-way sensitivity analyses of mean cost per alloimmunised pregnancy
Source: DCAR, Figure 6

[37] Gordon LG, 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.

Table 11: Key drivers of the model in the alloimmunised population (sensitivity analysis)

Description	Value	Impact
Probability of crossing the threshold (titre >1:16) and therefore developing HDFN (either mild or severe)	Decrease from 0.43 in the base case to 0.3 in a sensitivity analysis	Risk of death decreased from 0.05 to 0.04
		Risk of severe HDFN decreased from 0.027 to 0.019
	Increase from 0.43 in the base case to 0.6 in a sensitivity analysis	Risk of death increased from 0.05 to 0.06
		Risk of severe HDFN increased from 0.027 to 0.037

Source: Based on DCAR, Table 9

The DCAR stated that uncertainty remains around the mismatch between the high-throughput NIPT for which the MBS listing is sought, and the intended population that was expanded in the ratified PICO to include the alloimmunised population. This in turn raised uncertainty about the comparator and the outcome. Evidently, in this population the outcome is no longer the prevention of alloimmunisation, it is prevention of HDFN. The risk of HDFN is not exclusively related to anti-D antibodies, as the presence of other antibodies such as anti-K and anti-E is associated with 18.9% and 10.4% risk estimates respectively[38].

13. Financial/budgetary impacts

The DCAR used an epidemiological approach to estimate the financial implications of the introduction of *RHD*-NIPT, and a clinical utility approach to estimate the reduction in medically unnecessary use of anti-D Ig through the introduction of the NIPT test. The estimated changes in the numbers of medical services (Table 12) and financial implications to the MBS and the National Blood Authority (Table 13) resulting from the listing of *RHD*-NIPT are provided below. RhD immunoglobulin is supplied through NBA arrangements, hence funding is currently cost-shared between the Commonwealth and the States/Territories.

Table 12: Estimated changes in resource use from the introduction of the NIPT test

	2021* Yr1	2022* Yr2	2023* Yr3	2024* Yr4	2025* Yr5
Anti D immunoglobulin	18,865	18,910	18,954	18,998	19,043
MBS Screening Items	33,561	33,640	33,718	33,797	33,877
MBS Cord blood serology	581	583	584	586	587
MBS FMH quantification during pregnancy	889	892	894	896	898
MBS Post-partum FMH	516	517	518	519	520
NIPT	51,022	51,141	51,261	51,381	51,501

Red denotes a reduction of services with the introduction of the proposed intervention (savings), while black represents an increase in services.
FMH: fetomaternal haemorrhage
Source: DCAR, Table 12

[38] Sanchez-Duran MA, et al. Management and outcome of pregnancies in women with red cell isoimmunization: a 15-year observational study from a tertiary care university hospital. (2019) BMC Pregnancy and Childbirth (2019) 19:356.

Table 13: Total costs to the MBS and the National Blood Authority associated with NIPT introduction

-	2021 Yr1	2022 Yr2	2023 Yr3	2024 Yr4	2025 Yr5
NIPT					
Number of services	51,022	51,141	51,261	51,381	51,501
Sub-total cost	$2,857,205	$2,863,896	$2,870,603	$2,877,325	$2,884,063
MBS co-payment	$2,428,624	$2,434,312	$2,440,012	$2,445,726	$2,451,454
MBS services					
Number of services	33,354	33,432	33,510	33,588	33,667
Sub-total cost	($1,480,664)	($1,484,131)	($1,487,607)	($1,491,091)	($1,494,583)
MBS co-payments only for screening items	($1,264,733)	($1,267,694)	($1,270,663)	($1,273,639)	($1,276,622)
Co-administered services **Anti-D immunoglobulin**					
Number of services	18,865	18,910	18,954	18,998	19,043
Sub-total cost	$1,628,842	$1,632,657	$1,636,480	$1,640,312	$1,644,154
Total change					
Total services	1,197	1,200	1,203	1,206	1,209
Total cost	($252,301)	($252,892)	($253,484)	($254,078)	($254,673)
After co-pay	($457,694)	($458,766)	($459,840)	($460,917)	($461,996)

Red denotes a reduction of services/cost with the introduction of the proposed intervention (savings), while black represents an increase in services/cost.
Screening tests are associated with co-payment of 15%, fetomaternal haemorrhage quantification and cord blood serology assume co-payment of 0.25. For women who birth in the public hospital system they are unlikely to incur any MBS costs from being an inpatient. Therefore, the calculations only include co-payments for MBS screening item
* Savings to the MBS increase after co-payments because the proportion of the savings attributable to reduced anti-D Ig use (which does not attract a co-payment) is greater
Source: DCAR, Table 13

In the pre-ESC response, the applicant emphasised that it is recommended the current practice of performing cord blood serology on all babies born to RhD-negative women will continue even with the introduction of *RHD*-NIPT, therefore the number of cord blood serology services (Table 12) should remain the same. Whilst in the Netherlands cord blood serology typing was omitted as routine testing several years after the introduction of NIPT, this policy is not recommended in Australia at this point.

In the pre-ESC response, the applicant disputed the DCAR's proposal for co-payments (Table 13), stating that the Anti-D Ig expert reference group advised that for successful *RHD*-NIPT national screening that there should be no additional co-payment for individual women, either in the private or public sector. A co-payment would be associated with inequity of access to NIPT, and the associated management of their pregnancy based on its result, for socially disadvantaged individuals. In the rejoinder, the HTA group noted that budgetary impacts of any new intervention require the evaluators to present the calculation with and without co-payment. This does not reflect a recommendation by the evaluators.

The DCAR noted that the population in the population-based model differs between the economic and financial modelling, because the same patients would present up to four times for anti-D antibody screening, and if the fetus is RhD-positive, intensive monitoring and HDFN treatment would be required on more than one occasion.

Sensitivity analyses

The DCAR's sensitivity analysis (Table 14) showed that the financial estimates are most sensitive to the cost of the test. Increasing the cost of the NIPT by $10 per test will have financial implications for the MBS by incurring additional costs. The other sensitivity analyses indicate that the introduction of *RHD*-NIPT is likely to result in cost savings for the MBS.

Table 14: Sensitivity analyses for the financial estimates

	2021 Yr1	2022 Yr2	2023 Yr3	2024 Yr4	2025 Yr5
NIPT					
Phlebotomy charge added ($3.33)					
Change in total cost	($82,400)	($82,593)	($82,786)	($82,980)	($83,174)
Increase in cost of test (from $56 to $66)	$257,914	$258,518	$259,123	$259,730	$260,338
Reduced prevalence of RhD-negative pregnancies $ (based on ethnicity estimates)	($203,325)	($203,801)	($204,279)	($204,757)	($205,237)
Reduced prevalence of RhD-negative pregnancies services (based on ethnicity estimates)	965	967	969	971	974
Removal of cord blood serology test after two years (as occurred in the Netherlands)	($262,156)	($262,770)	($263,385)	($264,002)	($264,621)
Dose of post-partum anti-D Ig (increase from 61% to 74%)	($624,290)	($625,752)	($627,218)	($628,687)	($630,159)

Red denotes a reduction of services/cost with the introduction of the proposed intervention (savings), while black represents an increase in services/cost.
Source: DCAR, Table 62

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Test provider	Ensure an external quality assurance program and robust evaluation program to monitor false negatives are in place.
Clinical population	Consider whether women with previously sensitised to the anti-D antigen (population 1) should be included in the application.
Safety	ESC considered NIPT testing to be safe
Effectiveness	To note the inferior effectiveness due to false negative results from *RHD*-NIPT, leading to a potential increase in the proportion of patients who become alloimmunised. ESC considered the very high sensitivity of NIPT (reported to be 99.7%[39] and 99.9%[40]) and the high clinical utility.
Economic modelling	Ensure the economic modelling (i.e. health states/events included) reflect the current NBA guidelines.
Threshold analysis to identify an acceptable fee, given other values of inconclusive reports and probability of mild HDFN (reduced fee)	Overseas interannual cost of NIPT varied from as little as £17.97 (AU$32.52) to as high as US$450 (AU$649) for the commercial kit. Consider whether the cost of transporting the samples should be included in the MBS fee.

ESC discussion

ESC noted that this application from the Royal College of Pathologists of Australasia (RCPA) was for Medicare Benefits Schedule (MBS) listing of high-throughput non-invasive prenatal testing (NIPT) to determine fetal rhesus (Rh) D genotype. NIPT for fetal RhD genotype is used to predict the RhD phenotype of the fetus in pregnancies where the mother is RhD-negative. This determines whether the mother is at risk of alloimmunisation in that pregnancy, and whether in a subsequent pregnancy a RhD-positive fetus is at risk of developing haemolytic disease of the fetus and newborn (HDFN).

ESC noted the lack of consumer feedback for this application.

ESC noted that the submission contained two populations:

- Population 1 (currently eligible for testing with Lifeblood though limited funding), which includes pregnant women who are known to be RhD-negative and are alloimmunised; these women require intensive monitoring during their current and subsequent pregnancies
- Population 2 (currently, Lifeblood does not have Government approval to provide testing to this group), which includes pregnant women who are RhD-negative and who are not alloimmunised; these women are currently universally administered antenatal anti-D Ig prophylaxis (prenatal and postnatal prophylaxis, and after sensitising events).

ESC noted that the Department-contracted assessment report (DCAR) did not include population 1 because the tests used a different (manual vs high throughput) process with different costs. The population of RhD-alloimmunised pregnant patients in Australia is small (Lifeblood estimates 6 per month nationally). The applicant supported the decision to not

[39] Yang H, et al. High-throughput, non-invasive prenatal testing for fetal rhesus D status in RhD-negative women: A systematic review and meta-analysis. BMC Medicine. 2019;17(1).
[40] Runkel B, et al. Targeted antenatal anti-D prophylaxis for RhD-negative pregnant women: A systematic review. BMC Pregnancy and Childbirth. 2020;20(1).

include this population in the DCAR. The PICO Advisory Sub-Committee (PASC) recommended including both populations to ensure equity of access; this was supported by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZOG). The Department suggested considering a separate MBS item for each of the two populations.

ESC noted that the test would be used as a triage to identify women who definitely require prophylaxis, so that anti-D Ig treatment is targeted to only those at risk of sensitisation. ESC noted the advantages of a more targeted anti-D Ig treatment to reduce overall demand for anti-D Ig, due to future reduction in anti-D Ig availability, and noted that the pre-ESC response highlighted this issue.

ESC considered NIPT testing to be safe due to the low risk of adverse events arising from a simple venepuncture required for the blood sample, and from women appropriately not receiving anti-D Ig administration as they are not at risk of sensitising events.

ESC noted the inferior effectiveness due to false negative results from *RHD*-NIPT, leading to a potential increase in the proportion of patients who become alloimmunised (currently approximately 0.2% of all RhD-negative women, despite the availability of universal anti-D Ig). However, ESC noted the very high sensitivity of NIPT (reported to be 99.7%[41] and 99.9%[42]), and considered this and the high clinical utility to be acceptable.

ESC noted the economic evaluation considered:

1. the cost-effectiveness of NIPT (versus no testing and universal prophylaxis) estimating costs and outcomes (risk of alloimmunisation) of the interventions
2. a one-arm model reflecting current practice (e.g. intensive monitoring and blood transfusion), predicting costs and consequences of alloimmunisation (including HDFN)
3. a population-based analysis of costs and outcomes informed by (1) and (2).

ESC accepted the economic model and evaluation, but queried the rates of failed tests and invalid tests used in the base case and how these may impact the sensitivity analyses. The Department confirmed that the real-world proportion of failed tests in Australia is 2.3% (source: Lifeblood), and that all women with a failed test would receive anti-D Ig regardless. The Department also confirmed that invalid tests are repeated, which is funded through alternative arrangements for high-risk women. In addition, Lifeblood confirmed that equivocal test results are considered positive for RHD and the woman would proceed to anti-D Ig prophylaxis. ESC accepted the base case and sensitivity analyses presented.

ESC noted that the sensitivity analysis used a probability of 0.9 for a baby acquiring mild HDFN, sourced from Daniels 2004, but that the details of this publication were not included in the DCAR's reference list. ESC recommended these details be provided.

ESC noted the cost of $59.33 in the base case analysis. This cost included $56 for the test (advice from Lifeblood, including staff time and consumables) and $3.33 for blood collection (weighted average of relevant MBS items). ESC noted the National Institute for Health and Care Excellence 2016 recommendation that *RHD*-NIPT for non-alloimmunised women is a cost-effective option, provided that the overall cost of testing is ≤£24 (AU$43.31). ESC noted

[41] Yang H, et al. High-throughput, non-invasive prenatal testing for fetal rhesus D status in RhD-negative women: A systematic review and meta-analysis. BMC Medicine. 2019;17(1).
[42] Runkel B, et al. Targeted antenatal anti-D prophylaxis for RhD-negative pregnant women: A systematic review. BMC Pregnancy and Childbirth. 2020;20(1).

that the fee used in the base case does not include the cost of transportation of the sample. ESC also noted the varying prices for commercial kits used overseas (AU$32.52 in the UK to AU$649 in the US). ESC noted that the threshold pricing needs to be considered carefully, to ensure the testing remains cost-effective. ESC considered the transport cost of $25 (Gordon 2017) used in the sensitivity analysis to be excessive, and that an upper threshold cost of $10 is needed to ensure that *RHD*-NIPT remains cost-effective if transport was covered in the MBS fee.

ESC noted that the financial impact did not account for the costs of managing the potential increase in patients becoming alloimmunised, but noted the number of patients would likely be small. ESC noted that the Department estimated the additional financial impact of including population 1 (i.e. testing an additional 102–103 alloimmunised women each year), which resulted in an additional $57,000 to the MBS each year using a fee of $550. This fee is substantially higher than the $56 proposed for testing non-alloimmunised women because it is a low-throughput test, and includes salary and labour for the pathology laboratories.

Consumer issues noted by ESC included the need for clear and consistent language and definitions of abbreviations across test settings (e.g. NIPT (implying testing requiring a further confirmatory test) vs. NIPD (implying a diagnosis is made, not requiring further confirmation)), and whether external quality assurance (EQA) results should be shared in the public domain to allow more informed decision-making.

ESC noted that Lifeblood developed and performs the current in-house test. The testing is not subjected to an Australian external quality assurance program, which would need to be established. ESC considered that establishing a central haemovigilance reporting system to collate reported cases of false negatives could be necessary.

ESC noted the RCPA view that testing for an entire population should not be restricted to one laboratory, and summarised this as “poor medical practice”. However, ESC noted that, although Lifeblood was the sole provider of the current testing, the testing was performed in multiple laboratories around the country, which should alleviate some concerns about risk of failure if a single laboratory was responsible for all of the testing.

ESC queried whether the updated National Blood Authority (NBA) guidelines may potentially impact the base case and subsequent sensitivity analyses, but the Department confirmed that the draft NBA guidelines are very similar to the base case that was constructed in the assessment.

15. Other significant factors

Nil.

16. Applicant comments on MSAC’s Public Summary Document

The Royal College of Pathologists of Australasia (the College) would like to take this opportunity to thank the Department and the MSAC for their assistance in moving this application forward to a successful outcome, which will deliver great benefits to pregnant Australian women and their babies.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: visit the MSAC website