Medicare Benefits Schedule Review Taskforce

Report from the Pathology Clinical Committee—Genetics

October 2017

Important note

The views and recommendations in this report from the Clinical Committee have been released for the purpose of seeking the views of stakeholders.

This report does not constitute the final position on these items, which is subject to:

- Stakeholder feedback.

Then

- Consideration by the MBS Review Taskforce.

Then, *if endorsed*, consideration by

- The Minister for Health.
- The Government.

Stakeholders should provide comment on the recommendations via mbsreviews@health.gov.au.

Confidentiality of comments:

If you would like your feedback to remain confidential, please mark it as such. It is important to be aware that confidential feedback may still be subject to access under freedom of information law.

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1. Executive summary

The Medicare Benefits Schedule (MBS) Review Taskforce (the Taskforce) is undertaking a program of work that considers how more than 5700 items on the MBS can be aligned with contemporary clinical evidence and practice and improves health outcomes for patients. The Taskforce will also seek to identify any services that may be unnecessary, outdated or potentially unsafe.

The Taskforce is committed to providing recommendations to the Minister for Health that will allow the MBS to deliver on each of these four key goals:

- Affordable and universal access
- Best-practice health services
- Value for the individual patient
- Value for the health system.

The Taskforce has endorsed a methodology whereby the necessary clinical review of MBS items is undertaken by clinical committees and working groups. The Taskforce has asked the clinical committees to undertake the following tasks:

1. Consider whether there are MBS items that are obsolete and should be removed from the MBS.
2. Consider identified priority reviews of selected MBS services.
3. Develop a program of work to consider the balance of MBS services within its remit and items assigned to the Committee.
4. Advise the Taskforce on relevant general MBS issues identified by the Committee in the course of its deliberations.

The recommendations from the clinical committees are released for stakeholder consultation. The clinical committees consider feedback from stakeholders then provide recommendations to the Taskforce in a Review Report. The Taskforce considers the Review Report from clinical committees and stakeholder feedback before making recommendations to the Minister for Health, for consideration by Government.

1.1 The Pathology Clinical Committee

The Pathology Clinical Committee (the Committee) was established in 2016 to make recommendations to the MBS Review Taskforce on the review of MBS items within its remit, based on rapid evidence review and clinical expertise.

The majority of recommendations relating to these items are included in this report for consultation. The Committee also provided recommendations on items that will be referred to other committees for consultation.

1.2 Key recommendations

The Committee has highlighted its most important recommendations below. The complete list of recommendations (and the accompanying rationales) for all items can be found in Section 4. Recommendations developed for referral to other committees are presented in Section 5.
A complete list of items, including the nature of the recommendations and the section number for each recommendation, can be found in Appendices A and B (in table summary form).

Recommendations for consultation

The Committee's provisional recommendations for stakeholder consultation are that:

- three items should be deleted from the MBS
- 15 items should be changed
- 17 items should remain unchanged.

These changes focus on encouraging best practice, modernising the MBS to reflect contemporary practice, and ensuring that MBS services provide value for the patient and the healthcare system.

The Committee has referred two items for extension of indications and one for review to the Medical Services Advisory Committee (MSAC).

Significant recommendations are summarised below.

Δ **Chromosome analysis by cytogenetic techniques (items 73287, 73289, 73290).** Exclude the use of whole genome sequencing as an appropriate technique covered by these items.

Δ **Chromosome analysis for specific constitutional abnormalities (item 73291).** Amend this test to include relatives only and define the resolution threshold for testing.

Δ **Chromosome analysis by genome-wide microarray (item 73292).** Amend the descriptor to define the resolution threshold for testing.

Δ **Detection of *FMR1* gene mutation (items 73300 and 73305).** Remove the older test method (Southern blot) and recommend a review of the cost of the contemporary test methods to diagnose fragile X syndrome.

Δ **In-situ hybridization (ISH) test for *HER2* for access to PBS listed trastuzumab for breast cancer (item 73332) and gastric cancer (item 73342).** Amend the descriptors to provide requestors and providers of the services with relevant information to improve test processes.

Δ **Analysis of gene mutations in the investigation of venous thromboembolism (items 73308, 73309, 73311, and 73312).** Limit these tests to include only the gene mutations and populations where there is sufficient evidence to support testing by only analysing for *factor V Leiden* (FVL) and *prothrombin 201210>A* (PT) gene mutations, by only analysing for these gene mutations in those persons who have an activated protein C resistance (APCR), and by no longer testing first degree relatives of persons proven to have abnormal genotypes.

Recommendations for referral to other committees

The Committee's recommendations for referral to MSAC for their consideration:

Δ **Extension of genome-wide microarray to include two additional populations and settings:**

- The prenatal setting, when invasive testing is undertaken in pregnancy to investigate a pregnancy where there are major fetal ultrasound abnormalities (in preference to karyotype testing).
- For two specific chronic haematological malignancies, chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM), often as an adjunct or alternative testing method to current investigations.

Δ **Extension of item 73325 to include an additional population and gene mutation in the diagnosis of myeloproliferative disorders:**

- the analysis of mutations in the calreticulin (*CALR*) gene, and

- a third myeloproliferative neoplasm population —patients with clinical and laboratory evidence of primary myelofibrosis (PMF).

Δ **Review of recently listed item 73342: ISH test for HER2 for PBS trastuzumab for gastric cancer**

The Committee's recommendations for referral to the Department:

Δ **Definition of tumour tissue relevant to items 73336 BRAF, 73337 EGFR and 73338 RAS.**

Δ **Discussion regarding use of items for 'screening' purposes.**

1.3 Consumer engagement and impact

The Committee includes experienced and committed health practitioners and consumer representatives. This section summarises the report's key recommendations from a consumer perspective. It aims to make it easier for health consumers and members of the general public to understand the report's recommendations.

A complete list of the recommendations can be found in Appendix C, including a description in plain English of the medical service and the Committee's recommendation, as well as an explanation of why the recommendation has been made.

Consumers rarely engage with MBS item numbers unless they are following up on out-of-pocket expenses. Nevertheless, item descriptions and restrictions are an important part of healthcare accountability. The Committee's recommendations encourage agreed best practice and reflect current clinical evidence.

Both consumers and clinicians are expected to benefit from these recommendations because they address concerns regarding consumer safety and quality of care, and take steps to simplify the MBS and make it easier to use and understand. Consumer access to services was considered for each recommendation. The Committee also considered the impact of each recommendation on requestor and provider groups to ensure that changes were reasonable and fair. However, if the Committee identified evidence of potential item misuse or safety concerns, recommendations were made to encourage best practice, in line with the overarching purpose of the MBS Review.

The Committee expects these recommendations to support better requesting, with the aim of ensuring that patients are provided with clinically indicated, high-quality care that reflects modern best practice.

The consumer representatives used the following framework to assess recommendations:

Safety: None of the recommendations negatively affects the safety of pathology services.

Quality: Many of the recommended changes are intended to improve quality, primarily by aligning the reimbursement system with evidence-based practice.

Access: The recommendations do not negatively affect appropriate access. However, some patient groups have been receiving services they do not need, which can result in either negative health impacts or unnecessary cost. Inappropriate access was restricted where possible.

Effectiveness: None of the recommendations reduces the effectiveness of pathology services.

Cost-effectiveness: The recommendations will have a positive effect on cost-effectiveness because they make it easier to determine which patient groups should have access to specific tests and treatments.

Accountability: Many of the changes include wording that facilitates future auditing for quality purposes.

Data collection: Data collection for research, monitoring and auditing presents a huge opportunity for a revised MBS, and the recommendations should improve the opportunities to use this data for targeted research in the future.

2. About the Medicare Benefits Schedule (MBS) Review

2.1 Medicare and the MBS

What is Medicare?

Medicare is Australia's universal health scheme which enables all citizens (and some overseas visitors) to have access to a wide range of health services and medicines at little or no cost.

Introduced in 1984, Medicare has three components:

- free public hospital services for public patients
- subsidised drugs covered by the Pharmaceutical Benefits Scheme
- subsidised health professional services listed on the MBS.

What is the MBS?

The MBS is a listing of the health professional services subsidised by the Australian Government. There are more than 5700 MBS items, which provide benefits to patients for a comprehensive range of services including consultations, diagnostic tests and operations.

2.2 The MBS Review Taskforce

What is the MBS Review Taskforce?

The Government established an MBS Review Taskforce (the Taskforce) to review all 5,700 MBS items to ensure that they align with contemporary clinical evidence and practice, and to improve health outcomes for patients. The Taskforce will also modernise the MBS by identifying any services that may be unnecessary, outdated or potentially unsafe. The Review is clinician-led, and there are no targets for savings attached to the Review.

What are the goals of the Taskforce?

The Taskforce is committed to providing recommendations to the Minister for Health that will allow the MBS to deliver on each of these four goals:

- **Affordable and universal access.** The evidence demonstrates that the MBS supports very good access to primary care services for most Australians, particularly in urban Australia. However, despite increases in the specialist workforce over the last decade, access to many specialist services remains problematic, with some rural patients particularly under-serviced.
- **Best-practice health services.** One of the core objectives of the Review is to modernise the MBS, ensuring that individual items and their descriptors are consistent with contemporary best practice and the evidence base, where possible. Although the MSAC plays a crucial role in thoroughly evaluating new services, the vast majority of existing MBS items pre-date this process and have never been reviewed.
- **Value for the individual patient.** Another core objective of the Review is to maintain an MBS that supports the delivery of services that are appropriate to the patient's needs, provide real clinical value and do not expose the patient to unnecessary risk or expense.
- **Value for the health system.** Achieving the above elements will go a long way towards achieving improved value for the health system overall. Reducing the volume of services that provide little or no clinical benefit will enable resources to be redirected to new and existing

services that have proven benefits but are underused, particularly for patients who cannot readily access these services.

2.3 The Taskforce's approach

The Taskforce is reviewing existing MBS items, with a primary focus on ensuring that individual items and usage meet the definition of best practice. Within the Taskforce's brief, there is considerable scope to review and provide advice on all aspects that would contribute to a modern, transparent and responsive system. This includes not only making recommendations about adding new items or services to the MBS, but also about an MBS structure that could better accommodate changing health service models.

The Taskforce has made a conscious decision to be ambitious in its approach, and to seize this unique opportunity to recommend changes to modernise the MBS at all levels, from the clinical detail of individual items, to administrative rules and mechanisms, to structural, whole-of-MBS issues. The Taskforce will also develop a mechanism for an ongoing review of the MBS once the current Review has concluded.

As the MBS Review is to be clinician-led, the Taskforce decided that clinical committees should conduct the detailed review of MBS items. The committees are broad-based in their membership, and members have been appointed in an individual capacity rather than as representatives of any organisation.

The Taskforce asked all committees to review MBS items using a framework based on Appropriate Use Criteria accepted by the Taskforce. [1] The framework consists of seven steps:

1. Develop an initial fact base for all items under consideration, drawing on the relevant data and literature.
2. Identify items that are obsolete, are of questionable clinical value,[i] are misused[ii] and/or pose a risk to patient safety. This step includes prioritising items as 'priority 1,' 'priority 2' or 'priority 3,' using a prioritisation methodology (described in more detail below).
3. Identify any issues, develop hypotheses for recommendations and create a work plan (including establishing working groups, when required) to arrive at recommendations for each item.
4. Gather further data, clinical guidelines and relevant literature in order to make provisional recommendations and draft accompanying rationales, as per the work plan. This process begins with priority 1 items, continues with priority 2 items and concludes with priority 3 items. This step also involves consultation with relevant stakeholders within the committee, working groups, and relevant colleagues or colleges. For complex cases, full appropriate use criteria were developed for the item's explanatory notes.

[i] The use of an intervention that evidence suggests confers no or very little benefit on consumers; or where the risk of harm exceeds the likely benefit; or, more broadly, where the added costs of the intervention do not provide proportional added benefits.

[ii] The use of MBS services for purposes other than those intended. This includes a range of behaviours, from failing to adhere to particular item descriptors or rules through to deliberate fraud.

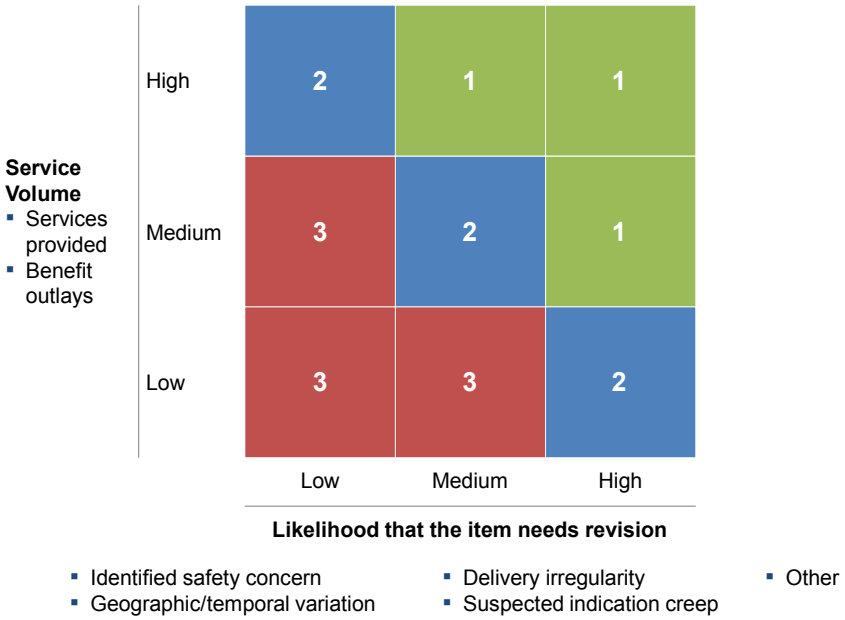
5. Review the provisional recommendations and the accompanying rationales, and gather further evidence as required.
6. Finalise the recommendations in preparation for broader stakeholder consultation.
7. Incorporate feedback gathered during stakeholder consultation and finalise the Review report, which provides recommendations for the Taskforce.

All MBS items will be reviewed during the course of the MBS Review. However, given the breadth of, and timeframe for, the Review, each clinical committee had to develop a work plan and assign priorities, keeping in mind the objectives of the Review. Committees used a robust prioritisation methodology to focus their attention and resources on the most important items requiring review. This was determined based on a combination of two standard metrics, derived from the appropriate use criteria: [1]

- Service volume.
- The likelihood that the item needed to be revised, determined by indicators such as identified safety concerns, geographic or temporal variation, delivery irregularity, the potential misuse of indications or other concerns raised by the committee (such as inappropriate co-claiming).

For each item, these two metrics were ranked high, medium or low. These rankings were then combined to generate a priority ranking ranging from 1 to 3 (where priority 1 items are the highest priority and priority 3 items are the lowest priority for review), using a prioritisation matrix (Figure 1.) The Committee used this priority ranking to organise its review of item numbers and apportion the amount of time spent on each item.

Figure 1. Prioritisation matrix.



3. About the Pathology Clinical Committee

The Pathology Clinical Committee (the Committee) was established in April 2016 to make recommendations to the Taskforce on MBS items within its remit, based on rapid evidence review and clinical expertise. The Taskforce asked the Committee to review genetics-related MBS items.

3.1 Committee members

The Committee consists of 19 members, whose names, positions/organisations and declared conflicts of interest are listed in Section 3.1. All members of the Taskforce, clinical committees and working groups were asked to declare any conflicts of interest at the start of their involvement and are reminded to update their declarations periodically.

Table 1.Pathology Clinical Committee members

Name	Position/organisation	Declared conflict of interest
Associate Professor Peter Stewart	Royal Prince Alfred Hospital (Public)	None
Professor Rita Horvath	South Eastern Area Laboratory Services (Public)	None
Dr Debra Norris	QML Pathology (Primary)	None
Dr Michael Harrison	Sullivan Nicolaides Pathology (Sonic)	None
Associate Professor Ken Sikaris	Melbourne Pathology (Sonic)	None
Dr Melody Caramins	Specialist Diagnostic Services (Primary)	None
Dr John Rowell	Pathology Queensland	None
Professor Dominic Mallon	PathWest	None
Dr Peter Roberts	Ryde Hospital (AESM)	None
Associate Professor Anthony Landgren	Australian Clinical Labs	None
Associate Professor Mary Jo Waters	St Vincent's Pathology (CHA)	None
Professor Richard MacIsaac	St Vincent's Hospital	None
Dr Emil Djakic	General practitioner	None
Dr Bev Rowbotham	MBS Taskforce	None
Dr Jill Thistlethwaite	General practitioner	None
Ms Valerie Hanrahan	Consumers Health Forum	None
Dr Robyn Lindner	NPS MedicineWise	None
Professor Hans Schneider	Alfred Pathology Service (Melbourne)	None
Associate Professor Adrienne Morey	ACT Pathology	None

It is noted that most committee and working group members share a common conflict of interest in reviewing items that are a source of revenue for them (i.e. committee members provide the services under review). This conflict is inherent in a clinician-led process and, having been acknowledged by the Committee and the Taskforce, it was agreed that this should not prevent a clinician from participating in the Review.

3.2 The Genetics Working Group

The Genetics Working Group is one of six clinical working groups supporting the work of the Pathology Clinical Committee. It was established to review genetics pathology items and make recommendations to the Pathology Clinical Committee based on rapid evidence review and clinical expertise.

The Genetics Working Group consists of seven members, whose names, positions/organisations and declared conflicts of interest are listed in Table 2 below.

Table 2. Genetics Working Group members

Name	Position/Organisation	Declared conflict of interest
Dr Melody Caramins	Specialist Diagnostic Services (Primary Healthcare Ltd.)	Noted below
Associate Professor Michael Buckley *	NSW Health Pathology	Noted below
Dr Christine Boyce *	General Practitioner	None
Dr Janice Fletcher	SA Pathology	None
Ms Eileen Jerga AM	Consumer	None
Associate Professor Julie McGaughran	Genetic Health Queensland	None
Professor Graeme Suthers	Sonic Healthcare	Noted below

* Attended one meeting

The following Genetics Working Group members declared these affiliations:

- Professor Suthers is employed by Sonic Healthcare, a private provider of MBS items under discussion.
- Dr Caramins is employed by Specialist Diagnostic Services (Primary Healthcare Ltd.), a private provider of MBS items under discussion.
- A/Prof Buckley is employed by NSW Health Pathology, and under private practice arrangements is a private provider of MBS items under discussion.

3.3 Areas of responsibility of the Committee

The Committee was assigned 35 MBS genetic test items to review. A complete list of these items can be found in Appendix A.

3.4 Summary of the Committee's review approach

The Committee completed a review of 35 genetic items across five meetings, during which it developed the recommendations and rationales outlined in Section 4. Recommendations were also developed for referral to other committees. These are outlined in Section 5.

The review drew on various types of MBS data, including data on:

- utilisation of items (services, benefits, patients, providers and growth rates)
- service provision (type of provider, geography of service provision)
- patients (demographics and services per patient)

- co-claiming or episodes of services (same-day claiming and claiming with specific items over time)
- additional provider and patient-level data, when required.

The review also drew on data presented in the relevant literature and clinical guidelines, all of which are referenced in the report.

The report will be released for public consultation, giving all Australians, including health professionals, an opportunity to have their say on the draft recommendations. Following this period of consultation, the Committee will consider stakeholder feedback before finalising the recommendations and presenting them to the Taskforce. The Taskforce will consider the report and stakeholder feedback before making recommendations to the Minister for Health for consideration by the Government.

4. Recommendations for consultation

Introduction

The Committee reviewed 35 genetics items and made recommendations based on evidence and clinical expertise, in consultation with relevant stakeholders. The item-level recommendations are described below. A summary list of recommendations can be found in Appendices A and B, and in the consumer summary table in Appendix C.

The Committee's recommendations for public consultation are that three items should be deleted (and their services no longer be provided under the MBS), 15 items should be changed and 17 items should remain unchanged. The Committee has also made general recommendations and referred two items to other committees.

The changes focus on encouraging best practice, modernising the MBS to reflect contemporary practice, and ensuring that MBS services provide value for the patient and the healthcare system. Some of this can be achieved by:

- deleting items that are not supported by evidence or are obsolete
- consolidating or splitting items to reflect contemporary practice
- modernising item descriptors to reflect best practice
- providing clinical guidance for appropriate use through explanatory notes.

4.1 Chromosome by cytogenetic or other technique (any tissue or fluid, except blood): item 73287

Table 3. Item introduction table for item 73287

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
73287	The study of the whole of every chromosome by cytogenetic or other techniques, performed on 1 or more of any tissue or fluid except blood (including a service mentioned in item 73293, if performed) – 1 or more tests	$394.55	13,292	$4,392,700	12,336	–12.6%

Recommendation 1

- Amend the descriptor to exclude whole genome sequencing, while allowing continued use of this item for cytogenetic techniques, including traditional karyotyping.
- Include an explanatory note indicating that the use of this item is not for screening purposes.
- Review again in three years (in 2020).

Table 4. Proposed change to item 73287

Item	Current item descriptor	Proposed new item descriptor
73287	The study of the whole of every chromosome by cytogenetic or other techniques, performed on 1 or more of any tissue or fluid except blood (including a service mentioned in item 73293, if performed) – 1 or more tests	The study of the whole of every chromosome by cytogenetic or other techniques, performed on 1 or more of any tissue or fluid except blood. This excludes genomic sequencing technologies, such as whole exome and whole genome sequencing (including a service mentioned in item 73293, if performed) – 1 or more tests. *Explanatory note: this item is only indicated in a person with specific risk indicated by personal or family history.*

Rationale 1

The recommendation focuses on modernising the MBS and ensuring best practice and is based on the following observations:

- The indications for this test commonly include, but are not limited to, diagnostic testing of cultured cells from amniotic fluid or chorionic villi during pregnancy for the detection of large fetal gene alterations, and the detection of large gene alterations in lymph nodes or other tissues in haematological malignancies.
- The Committee noted that there has been a predictable decrease in the use of item 73287 over the past few years due to the use of alternative non-invasive techniques for prenatal testing. It is anticipated that this decrease will continue for this indication but the test is still valuable for diagnostic confirmation in the prenatal setting, and for other indications.
- While there is no evidence of inappropriate use of this item, the Committee agreed that the current item descriptor is very broad and poses a risk that more advanced alternative techniques such as whole genome sequencing could be inappropriately claimed under this item. Whole genome sequencing is an expensive high-resolution test that is not currently funded via the MBS. The proposed change intends to limit the reporting to include lower-resolution cytogenetic or microscopy/microarray techniques, rather than whole genome sequencing. Using a higher-resolution technique than is clinically required raises ethical concerns due to collateral or incidental findings identified by higher-resolution methods. The test is intended to be a specific diagnostic test when there is a defined indication for testing based on personal or familial history, and is not intended to be used as a broader screening test.
- The Committee recommended including the words *'in a person with specific risk indicated by personal or family history'* to prevent this item being used for screening purposes.
- For patients, excluding whole genome sequencing (a test with high resolution) will ensure the most appropriate techniques (those with low to medium resolution) are used to provide the relevant amount of information for diagnosis.
- The Committee agreed that testing in this area is rapidly evolving and it would be appropriate to review the chromosome and microarray tests (i.e. items 73287, 73289, 73290, 73291 and 73292) again in three years (2020) in light of expected developments.

4.2 Chromosome by cytogenetic or other technique (blood): item 73289

Table 5. Item introduction table for item 73289

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
73289	The study of the whole of every chromosome by cytogenetic or other techniques, performed on blood (including a service mentioned in item 73293, if performed) – 1 or more tests	$358.95	42,651	$13,108,280	42,013	6.2%

Recommendation 2

- Δ Amend the descriptor of item 73289 to exclude whole genome sequencing, while allowing continued use of this item for cytogenetic techniques, including traditional karyotyping.
- Δ Include an explanatory note indicating that the use of this item is not for screening purposes.
- Δ Review again in three years (in 2020).

Table 6. Proposed change to item 73289

Item	Current item descriptor	Proposed new item descriptor
73289	The study of the whole of every chromosome by cytogenetic or other techniques, performed on blood (including a service mentioned in item 73293, if performed) – 1 or more tests	The study of the whole of every chromosome by cytogenetic or other techniques, performed on blood. This excludes genomic sequencing technologies, such as whole exome and whole genome sequencing (including a service mentioned in item 73293, if performed) – 1 or more tests. *Explanatory note: this item is only indicated in a person with specific risk indicated by personal or family history.*

Rationale 2

The recommendation focuses on modernising the MBS and ensuring best practice and is based on the following observations:

- Δ The potential indications for this test include, but are not limited to, the diagnosis of congenital or syndromic abnormalities or developmental delay, or in the investigation of infertility and/or pregnancy loss secondary to structural or numerical chromosome abnormalities. This test is the same as that described above (item 73287) but performed on blood rather than tissue or fluid. Traditional karyotyping is still the most appropriate test for patients with recurrent miscarriages, infertility, premature menopause, delayed puberty or other sexual development disorders.
- Δ The Committee noted that there has been growth in the use of this item over the past 5 years. Obstetrics and gynaecology specialists are the primary requesters and data confirm that IVF clinics are a driver of this growth. Requests from paediatricians have significantly decreased over the past few years, in line with best practice guidelines, which now recommend the use of

alternative microarray technology (item 73292) as the preferred method of testing for developmental delay. [3]

- The Committee agreed the current item descriptor is very broad and poses a risk that alternative advanced techniques such as whole genome sequencing could be inappropriately billed under this item. The recommendation aims to limit the methodology to cytogenetic techniques such as karotyping, that is, to exclude whole genome sequencing.
- As previously discussed for item 73287, using a higher-resolution technique than is clinically required raises ethical concerns due to collateral or incidental findings identified by higher-resolution methods. The test is intended to be a specific diagnostic test when there is a defined indication for testing based on personal or familial history, and is not intended to be used as a broader screening test. The proposed descriptor change is aimed at preventing future potential leakage to techniques such as whole genome sequencing.
- The Committee recommended including the words *'in a person with specific risk indicated by personal or family history'* to prevent this item being used for screening purposes.
- For patients, excluding whole genome sequencing (a test with high resolution) will ensure the most appropriate techniques (those with low to medium resolution) are used to provide the relevant amount of information for diagnosis.

4.3 Chromosome by cytogenetic or other technique on blood or bone marrow, for diagnosis and monitoring of haematological malignancy: item 73290

Table 7. Item introduction table for item 73290

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
73290	The study of the whole of each chromosome by cytogenetic or other techniques, performed on blood or bone marrow, in the diagnosis and monitoring of haematological malignancy (including a service in items 73287 or 73289, if performed). – 1 or more tests.	$394.55	8290	$2,649,095	7000	103.9%

Recommendation 3

- Amend the descriptor of item 73290 to exclude whole genome sequencing, while allowing continued use of this item for cytogenetic techniques, including traditional karyotyping.
- Review again in three years (in 2020).

Table 8. Proposed change to item 73290

Current item descriptor	Proposed new item descriptor
The study of the whole of each chromosome by cytogenetic or other techniques, performed on blood or bone marrow, in the diagnosis and monitoring of haematological malignancy (including a service in items 73287 or 73289, if performed). – 1 or more tests	The study of the whole of each chromosome by cytogenetic or other techniques, performed on blood or bone marrow, in the diagnosis and monitoring of haematological malignancy. This excludes genomic sequencing technologies, such as whole exome and whole genome sequencing (including a service in items 73287 or 73289, if performed). – 1 or more tests

Rationale 3

The recommendation focuses on modernising the MBS and ensuring best practice and is based on the following observations:

- This item was introduced onto the MBS in 2010 and, although the growth in services appears significant, it has slowed after the initial uptake to 6.1 per cent over the past three years. It has a defined indication for use in the diagnosis and monitoring of haematological malignancies and utilisation appears to be appropriate.
- For consistency within the MBS, the Committee recommended this item be reworded in keeping with the recommendations for other similar items (73287 and 73289) for which lower-resolution techniques such as karyotyping are appropriate. As previously mentioned, these tests are not intended to fund whole genome sequencing.
- For patients, excluding whole genome sequencing (a test with high resolution) will ensure the most appropriate techniques (those with low to medium resolution) are used to provide the relevant amount of information for diagnosis.

4.4 Chromosome specific constitutional abnormalities: item 73291

Table 9. Item introduction table for item 73291

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
73291	Analysis of one or more chromosome regions for specific constitutional genetic abnormalities of blood or fresh tissue in: (a) diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities, in whom cytogenetic studies (item 73287 or 73289) are either normal or have not been performed; or (b) studies of a relative for an abnormality previously identified in such an affected person. – 1 or more tests.	$230.95	1551	$304,082	1534	121.6%

Recommendation 4

- Amend the item descriptor to remove the patient test component of the item and only allow it in relatives of an affected person.
- Amend the descriptor to include an 'intermediate'-resolution threshold restriction of at least 100 kilobases (kb).
- Provide education and information for paediatricians about appropriate tests for investigating relevant childhood syndromes.

Table 10. Proposed changes to item 73291

Current item descriptor	Proposed new item descriptor
Analysis of one or more chromosome regions for specific constitutional genetic abnormalities of blood or fresh tissue in (a) diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities, in whom cytogenetic studies (item 73287 or 73289) are either normal or have not been performed; or (b) studies of a relative for an abnormality previously identified in such an affected person. – 1 or more tests.	Analysis for a specific constitutional genetic abnormality that is at least 100 kb in size in a relative of a person with that abnormality as described in item 73292.

Rationale 4

The recommendations focus on modernising the MBS and ensuring best practice and are based on the following observations.

- The indications for this test include investigations of childhood syndromes contributing to intellectual and developmental delay, autism and congenital abnormalities such as Williams syndrome or velocardiofacial syndrome.
- The current descriptor enables the use of this test in both child and parent, but higher-resolution techniques such as microarray are now recommended as first line for testing the child. [3] The age distribution of services processed in 2014–15 indicated the greatest use of this item is in adults rather than in children, indicating that the shift to microarray for children is occurring. The Committee considered that this item is still relevant in the relative population, as it is more targeted and therefore less expensive than microarray.
- From a patient perspective, microarray is the appropriate test for investigating the child, but this test is still appropriate for more targeted testing of relatives.
- This item was introduced in 2010 and there has been significant growth due to the initial uptake. However, this has slowed over the past 3 years to 5.6 per cent.

4.5 Chromosome by genome-wide microarray: item 73292

Table 11. Item introduction table for item 73292

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
73292	Analysis of chromosomes by genome-wide micro-array including targeted assessment of specific regions for constitutional genetic abnormalities in diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities (including a service in items 73287, 73289 or 73291, if performed) – 1 or more tests.	$589.90	14,189	$7,378,284	14,058	184.6%

Recommendation 5

- Amend the descriptor to remove the method and include an 'intermediate'-resolution threshold restriction instead.

Table 12. Proposed change to item 73292

Current item descriptor	Proposed new item descriptor
Analysis of chromosomes by genome-wide micro-array including targeted assessment of specific regions for constitutional genetic abnormalities in diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities (including a service in items 73287, 73289 or 73291, if performed) – 1 or more tests.	<u>The study of the whole of every chromosome to detect a constitutional genetic abnormality that is at least 100 kb in size,</u> in diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least 2 congenital abnormalities (including a service in items 73287, 73289 or 73291, if performed) – 1 or more tests.

Rationale 5

The recommendations focus on modernising the MBS and ensuring appropriate use and are based on the following observations:

- Growth in this item has been steady since its introduction in 2010. The Committee anticipates utilisation is likely to continue to increase in the future for other indications as awareness of the test increases and guideline recommendations are implemented. About 73 per cent of tests are requested by paediatricians, which is aligned with best practice guidelines. [3]
- Microarray is an intermediate-resolution technique, providing a higher diagnostic capacity compared with traditional karyotyping. The intent of this item, however, is not to fund high-resolution techniques such as whole genome sequencing. Restricting the resolution to at least 100 kb in size will discourage whole genome sequencing and avoid reporting of extra findings or collateral information.
- The Committee acknowledged that microarray is now recommended clinical practice for a number of other indications and populations, and specific recommendations to MSAC regarding these are included in section 5.1 of this report.

- From a patient perspective these changes would not make a difference. The change will, however, allow for potentially other medium-resolution techniques to be utilised.

4.6 *FMR1* gene mutation: items 73300 and 73305

Table 13. Item introduction table for items 73300 and 73305

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
73300	Detection of mutation of the *FMR1* gene where:(a) the patient exhibits intellectual disability, ataxia, neurodegeneration, or premature ovarian failure consistent with an *FMR1* mutation; or(b) the patient has a relative with a *FMR1* mutation 1 or more tests	$101.30	8688	$765,860	8563	10.9%
73305	Detection of mutation of the *FMR1* gene by Southern blot analysis where the results in item 73300 are inconclusive	$202.65	616	$113,023	611	10.0%

Recommendation 6

- Delete item 73305 (Southern blot) and, in the short term, reallocate the current funding to item 73300 to support the use of the appropriate methods in the diagnosis of fragile X syndrome.
- Conduct a cost analysis of the detection of a mutation of the *FMR1* gene, with a view to revising the schedule fee for item 73300 to reflect more realistic costs.

Rationale 6

The recommendations focus on modernising the MBS and ensuring best practice and are based on the following observations:

- The fragile X syndrome (caused by a mutation of the *FMR1* gene) is the most common cause of hereditary intellectual disability. The clinical spectrum of features includes intellectual disability, premature ovarian failure and late-onset neurodegeneration. Although it is an X-chromosome-linked disorder, both men and women can be unaffected carriers or manifest aspects of the disorder.
- When genetic testing for the syndrome was added to the MBS in 2003, the test was done in two steps. An initial polymerase chain reaction (PCR) step (using item 73300) could resolve the genetic status for most patients, but a second analysis using Southern blot (item 73305) was necessary in a small subset (10-15%) of patients. Separate fees were listed for the two analyses, with the PCR assay being simpler and hence cheaper (currently $101.30) than the Southern blot assay (currently $202.65).
- Although current guidelines still make reference to Southern blot, the test is subjective, compared with more objective newer methods. The Southern blot assay is time-consuming and involves the use of hazardous materials, posing occupational health risks. Improved

(triplet-primed) PCR assays have reduced the need for Southern blot analyses but are more expensive than the PCR assay considered in 2003.

- The net effect of these changes has been a decline in the proportion of patients in whom Southern blot analyses are rebated, with laboratories bearing the increased cost of the improved PCR assay. The *Human Genetics Society of Australasia Guidelines* does not mandate use of Southern blot tests for patients, but refers to the use of '… Southern blot analysis using standard operating procedures or by another comparable method'. [4]
- The Genetics Working Group surveyed the eight Australian laboratories providing fragile X testing. Three responded, two reporting they no longer used a Southern blot analysis and one reporting only using it in four per cent of patients. Two of the laboratories provided cost data, reporting that the current PCR assay cost is 100 per cent to 200 per cent more per patient than the 2003 assay (CPI inclusive).
- The Committee recommended that item 73305 (Southern blot) be removed from the MBS and that if secondary testing is required it be included in the descriptor and fee for item 73300. The Committee also recommended that this should be coupled with an increase in the fee for item 73300, initially by shifting the current expenditure for Southern blot into the fee item 73300.
- The Committee agreed that the current fee for item 73300 significantly underestimates the cost of performing this test and recommended that a formal cost analysis be conducted to determine the cost of using contemporary methods to diagnose fragile X syndrome.

4.7 ISH test for *HER2* for PBS trastuzumab or Herceptin Program for breast cancer: item 73332

Table 14. Item introduction table for item 73332

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
73332	An in-situ hybridization (ISH) test of tumour tissue from a patient with breast cancer requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to human epidermal growth factor receptor 2 (HER2) gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme (PBS) or the Herceptin Program are fulfilled.	$315.40	12,882	$3,200,123	11,941	234.2%

Recommendation 7

- Amend the item descriptor for clarity around requesters and remove the reference to the redundant Herceptin Program.
- Include an explanatory note regarding the recommended *HER2* testing procedures when the proposed changes to testing guidelines are approved by the Royal College of Pathologists Australasia (RCPA).

- Ensure appropriate education is provided to support implementation of the proposed changes to the *HER2* testing guidelines and systems for effective communication between requesters and providers.
- Review the utilisation of this item in 12 months.

Table 15. Proposed changes to item 73332

Current item descriptor	Proposed new item descriptor
An in-situ hybridization (ISH) test of tumour tissue from a patient with breast cancer requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the `patient to determine if the requirements relating to human epidermal growth factor receptor 2 (HER2) gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme (PBS) or the Herceptin Program are fulfilled.	An in-situ hybridization (ISH) test of tumour tissue from a patient with breast cancer requested by a treating specialist or pathologist to determine if the requirements relating to human epidermal growth factor receptor 2 *(HER2)* gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled. *Explanatory note: To be included when tumour testing guideline changes have been implemented.*

Rationale 7

The recommendations are focused on modernising the MBS and encouraging best practice and are based on the following observations:

- The purpose of this test is to identify *HER2* gene amplification, required to meet specific criteria to access trastuzumab, a treatment available on the Pharmaceutical Benefits Scheme (PBS) for breast cancer. Gene amplification is an increase in the number of copies of a gene and is common in cancer cells. Some amplified genes may cause cancer cells to grow or become resistant to anticancer drugs. The Herceptin Program is no longer available and these words can be removed from the descriptor.
- This item was introduced to the MBS in 2012, and the growth in services over the past three years reflects the initial uptake of this test. The Committee acknowledged that repeat testing in some patients may be necessary to obtain a definitive clinical diagnosis. Clinically appropriate reasons for repeat testing include non-diagnostic or inconclusive results, bilateral or multiple tumours, and testing metastases when the status of the primary tumour is a concern. Repeat testing rates of up to 10 per cent would not be unreasonable. [5]
- The Committee is aware of proposed changes to guidelines on HER2 testing (via the Structured Reporting Committee of the RCPA) that will recommend a transition to testing on core biopsies rather than resected tissue. This is a significant deviation from current practice that may result in transiently higher utilisation of this item (due to duplicate testing) over the next 12 months until the changes are fully implemented.
- A note should be included with the recommendations to highlight the potential changes to guidelines around HER2 testing and to suggest utilisation of this item be monitored to detect an increase in repeat testing rate (resections vs core) greater than 10%, which may indicate unnecessary repeat testing. The Committee recommended that this item be reviewed again in 12 months.
- This item is a pathologist determinable item, and the Committee recommended clearly identifying this in the item descriptor. This also applies to the other pathologist determinable genetic items —73326 and 73337 (see Section 4.12), and potentially to other pathologist determinable items across the MBS.

Δ There would be no change for patients, but pathologists will have more information to assist them in performing the test appropriately.

4.8 ISH test for *HER2* for PBS trastuzumab for gastric cancer: item 73342

Table 16. Item introduction table for item 73342

Item	Long item descriptor	Schedule fee	Services FY2014–15	Benefits FY2014–15	Patient count 2014–15	5 year service change (CAGR)
73342	An in situ hybridisation (ISH) test of tumour tissue from a patient with metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, with documented evidence of human epidermal growth factor receptor 2 (*HER2*) overexpression by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+ on the same tumour tissue sample, requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to *HER2* gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme are fulfilled.	$315.40	—	—	—	—

Recommendation 8

Δ Include an explanatory note regarding the trastuzumab PBS criteria testing requirements for *HER2* in the MBS item descriptor.

Δ Refer to MSAC for a post-implementation review (see section 5.1.3).

Table 17. Proposed changes to item 73342

Current item descriptor	Proposed new item descriptor
An in situ hybridisation (ISH) test of tumour tissue from a patient with metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, with documented evidence of human epidermal growth factor receptor 2 (*HER2*) overexpression by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+ on the same tumour tissue sample, requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to *HER2* gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme are fulfilled.	An in situ hybridisation (ISH) test of tumour tissue from a patient with metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, with documented evidence of human epidermal growth factor receptor 2 (*HER2*) overexpression by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+ on the same tumour tissue sample, requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to *HER2* gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme are fulfilled. *Explanatory note to be added regarding trastuzumab test procedure related to PBS criteria.*

Rationale 8

- The purpose of this test is to identify *HER2* gene amplification, required to meet specific criteria to access trastuzumab, a treatment available on the PBS for gastric cancer.
- The Committee noted that the detail required to perform the test and report the results is only listed under the PBS criteria. The Committee recommended that the relevant PBS criteria for trastuzumab be included in full in the MBS descriptor for item 73342 in the context of metastatic adenocarcinoma of the stomach or gastro-oesophageal junction (gastric cancer).
- The PBS Authority requirements for testing are:

  The patient has, in the same tumour tissue sample, evidence of:

  a. *HER2* positivity as demonstrated by immunohistochemistry 2+ or more and
  b. *HER2* gene amplification as demonstrated by in situ hybridisation results based on more than 6 copies of *HER2*, and
  c. *HER2* gene amplification as demonstrated by in situ hybridisation results based on the ratio of *HER2* to chromosome 17 being more than 2.
- To adequately address the PBS criteria for gastric cancer, a dual-probe ISH test is required to perform the *HER2* ISH test, a consequence for the pathology laboratory that is not made explicit in the MBS item descriptor. As the fees for the two *HER2* ISH items (73332 and 73342) in the context of trastuzumab are the same, the cost for a dual-probe ISH assay for gastric cancer is currently not recognised within the MBS (given that only a cheaper single probe ISH assay is needed for breast cancer). At this stage, the numbers of *HER2* ISH tests for gastric cancer, which require a dual probe, are low, and laboratories are presumably absorbing the extra costs or billing patients, but this issue may require further consideration at a future review.
- The Committee noted this item is not listed as a pathologist-determinable service and have recommended this be reviewed by MSAC (see Section 5.1.3).
- There would be no change for patients, but pathologists will have more information to assist them in performing the test appropriately.

4.9 Genotype factor V Leiden or other gene mutations in investigation of venous thromboembolism: items 73308–73312

Table 18. Item introduction table for items 73308, 73309, 73311 and 73312

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
73308	Characterisation of the genotype of a patient for Factor V Leiden gene mutation, or detection of the other relevant mutations in the investigation of proven venous thrombosis or pulmonary embolism – 1 or more tests	$36.45	28 617	$888,209	27 710	12.2%
73309	A test described in item 73308, if rendered by a receiving APP – 1 or more	$36.45	1 627	$50,143	1 452	–3.7%

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
	tests (Item is subject to rule 18)					
73311	Characterisation of the genotype of a person who is a first degree relative of a person who has proven to have 1 or more abnormal genotypes under item 73308 – 1 or more tests	$36.45	6536	$204,095	6 511	4.6%
73312	A test described in item 73311, if rendered by a receiving APP – 1 or more tests (Item is subject to rule 18)	$36.45	56	$1,736	58	–14.8%

Recommendation 9

- Amend the descriptor for 73308 to limit the test to factor V Leiden (FVL) and prothrombin 20210G>A (PT) gene mutations only in persons who have an activated protein C resistance (APCR).
- No change to item 73309.
- Delete items 73311 and 73312 to remove funding for testing in first-degree relatives from the MBS.

Table 19. Proposed changes to items 73308, 73309, 73311 and 73312

Item	Current item descriptor	Proposed new item descriptor
73308	Characterisation of the genotype of a patient for factor V Leiden gene mutation, or detection of the other relevant mutations in the investigation of proven venous thrombosis or pulmonary embolism – 1 or more tests	Analysis of factor V Leiden and prothrombin 20210G>A (PT) gene mutations in a person who has an activated protein C resistance (APCR) – 1 or more tests.
73309	A test described in item 73308, if rendered by a receiving APP – 1 or more tests (Item is subject to rule 18)	No change
73311	Characterisation of the genotype of a person who is a first degree relative of a person who has proven to have 1 or more abnormal genotypes under item 73308 – 1 or more tests	Delete
73312	A test described in item 73311, if rendered by a receiving APP – 1 or more tests (Item is subject to rule 18)	Delete

Rationale 9

The recommendation is focused on ensuring appropriate use and value for the healthcare system. They are based on the following observations:

- Δ These items were introduced in 2006 but there has been considerable growth in service requests over the past few years. The purpose of this test is to identify the presence of gene mutations that predict the risk of recurrent venous thromboembolism (VTE) in patients who have previously had a VTE, or in first-degree relatives of patients identified as having a mutation.
- Δ A 'Rapid Review' of the literature was conducted to identify the current evidence regarding use of genetic testing for mutations in proven cases of VTE. [6] The review identified limited evidence associating mutations in factor V Leiden (FVL) and prothrombin 20210G>A (PT) with the risk of recurrent VTE and no evidence for mutations in methylene tetrahydrofolate reductase (MTHFR). Overall there was no evidence that genetic testing improved clinical outcomes or changed patient management. The review did not find sufficient evidence to recommend routine testing for these mutations in first-degree relatives.
- Δ The Committee acknowledged the input of the Haematology Working Group in the review of these items, and recommended limiting the test to FVL and PT genes only. They also recommended limiting the test to patients with the demonstrated risk factor of a positive activated protein C resistance (APCR). These changes will ensure that use of this test is sequential and only performed in the most relevant patients. Unnecessary testing wastes resources and exposes patients to irrelevant tests and results that can potentially cause undue anxiety.
- Δ The Committee agreed that this is a high-priority opportunity for provider and requester education and communication will be required for all stakeholders when recommendations are implemented.

4.10 Chromosome abnormalities products of conception: item 73293

Table 20. Item introduction table for item 73293

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
73293	Analysis of one or more regions on all chromosomes for specific constitutional genetic abnormalities of fresh tissue in diagnostic studies of the products of conception, including exclusion of maternal cell contamination. – 1 or more tests.	$230.95	447	$80,236	437	47.5%

Recommendation 10

- Δ Amend the descriptor to include, if performed, items 73287, 73289 and 73291.
- Δ Increase awareness of this item with general practitioners.

Table 21. Proposed change to item 73293

Item	Current item descriptor	Proposed new item descriptor
73293	Analysis of one or more regions on all chromosomes for specific constitutional genetic abnormalities of fresh tissue in diagnostic studies of the products of conception, including exclusion of maternal cell contamination. – 1 or more tests.	Analysis of one or more regions on all chromosomes for specific constitutional genetic abnormalities of fresh tissue in diagnostic studies of the products of conception, including exclusion of maternal cell contamination (including a service in items 73287, 73289 or 73291, if performed) – 1 or more tests.

Rationale 10

The recommendation focuses on ensuring appropriate use and is based on the following observations.

- Δ This item is used to identify genetic abnormalities in products of conception. The Committee agreed that the medical utility for this item is very low but it does provide support for parents, and is more cost effective than karyotyping. The low service volume may be because the test is being performed in public hospitals or possibly because private practice GPs are not offering the MBS service, in which education to raise awareness is warranted.
- Δ Appropriate use of this item should not include co-claiming a test using karyotyping techniques as described in items 73287, 73289 or 73291.

4.11 No changes

The Committee recommended that the MBS items listed in Table 22 do not require amendment, as they are clinically appropriate.

Table 22. MBS items that do not require amendment

Item	Item descriptor	Schedule fee	Services FY 2014–15
73294	Analysis of the *PMP22* gene for constitutional genetic abnormalities causing peripheral neuropathy, either as: (a) diagnostic studies of an affected person; or (b) studies of a relative for an abnormality previously identified in an affected person – 1 or more tests.	$230.95	292
73309	A test described in item 73308, if rendered by a receiving APP - 1 or more tests (Item is subject to rule 18)	$36.45	1 627
73314	Characterisation of gene rearrangement or the identification of mutations within a known gene rearrangement, in the diagnosis and monitoring of patients with laboratory evidence of:(a) acute myeloid leukaemia; or(b) acute promyelocytic leukaemia; or (c) acute lymphoid leukaemia; or (d) chronic myeloid leukaemia;	$230.95	10 000
73315	A test described in item 73314, if rendered by a receiving APP - 1 or more tests (Item is subject to rule 18)	$230.95	6 401
73320	Detection of *HLA-B27* by nucleic acid amplification includes a service described in 71147 unless the service in item 73320 is rendered as a pathologist determinable service. (Item is subject to rule 27)	$40.55	16 973
73321	A test described in item 73320, if rendered by a receiving APP - 1 or more test (Item is subject to rule 18 and 27)	$40.55	127
73323	Determination of *HLA-B5701* status by molecular techniques prior to the initiation of abacavir therapy including item 71203 if performed.	$40.55	905
73324	A test described in item 73323 if rendered by a receiving app1 or more tests (item is subject to rule 18)	$$40.95	77

Item	Item descriptor	Schedule fee	Services FY 2014–15
73326	Characterisation of the gene rearrangement *FIP1l1-PDGFRA* in the diagnostic work-up and management of a patient with laboratory evidence of: a) mast cell disease; or b) idiopathic hypereosinophilic syndrome; or c) chronic eosinophilic leukaemia; 1 or more tests	$230.95	163
73327	Detection of genetic polymorphisms in the thiopurine s-methyltransferase gene for the prevention of dose-related toxicity during treatment with thiopurine drugs; including (if performed) any service described in item 65075. 1 or more tests	$51.95	6767
73333	Detection of germline mutations of the von Hippel-Lindau (*VHL*) gene:in a patient who has a clinical diagnosis of VHL syndrome and:a family history of *VHL* syndrome and one of the following: haemangioblastoma (retinal or central nervous system); phaeochromocytoma; renal cell carcinoma; or2 or more haemangioblastomas; or one haemangioblastoma and a tumour or a cyst of: the adrenal gland; or the kidney; or the pancreas; or the epididymis; or a broad ligament (other than epididymal and single renal cysts, which are common in the general population); or in a patient presenting with one or more of the following clinical features suggestive of *VH*L syndrome: (i) haemangioblastomas of the brain, spinal cord, or retina; (ii) phaeochromocytoma; (iii) functional extra-adrenal paraganglioma	$600.00	4
73334	Detection of germline mutations of the von Hippel-Lindau (*VHL*) gene in biological relatives of a patient with a known mutation in the VHL gene	$340.00	14
73335	Detection of somatic mutations of the von Hippel-Lindau *(VHL)* gene in a patient with: 2 or more tumours comprising: 2 or more haemangioblastomas, or one haemangioblastoma and a tumour of:the adrenal gland; or the kidney; or the pancreas; or the epididymis; and no germline mutations of the VHL gene identified by genetic testing	$470.00	1
73338	A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV), requested by a specialist or consultant physician, to determine if the requirements relating to rat sarcoma oncogene (*RAS*) gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled, if:(a) the test is conducted for all clinically relevant mutations on *KRAS* exons 2, 3 and 4 and *NRAS* exons 2, 3, and 4; or (b) a *RAS* mutation is found.	$362.59	1462
73339	Detection of germline mutations in the *RET* gene in patients with a suspected clinical diagnosis of multiple endocrine neoplasia type 2 (MEN2) requested by a specialist or consultant physician who manages the treatment of the patient.one test. (Item is subject to rule 25)	$400.00	4
73340	Detection of a known mutation in the *RET* gene in an asymptomatic relative of a patient with a documented pathogenic germline *RET* mutation requested by a specialist or consultant physician who manages the treatment of the patient.one test. (Item is subject to rule 25)	$200.00	0
73341	Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (ALK) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score > 0, and with documented absence of activating mutations of the epidermal growth factor receptor *(EGFR)* gene, requested by a specialist or consultant physician to determine if requirements relating to ALK gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	$400.00	0

4.12 Minor changes

The Committee has made recommendations for minor changes to the items in the following table. The changes relate to removing redundant rules and clarifying descriptors as follows:

- Items 73317 and 73318— remove rule 20 (*elevated serum ferritin for a patient, means a level of ferritin above the normal reference range in respect of the particular method of assay used to determine the level*). This rule does not add any additional clinical value.
- Items 73336 and 73337 are pathologist-determinable services. Amending the item descriptors and/ or explanatory notes to clearly stipulate which items are pathologist-determinable will help avoid confusion and streamline pathology pathways to ensure efficient patient care.

Table 23. Minor changes recommended

Item	Item descriptor	Proposed amendment
73317	Detection of the *C282Y* genetic mutation of the HFE gene and, if performed, detection of other mutations for haemochromatosis where: (a) the patient has an elevated transferrin saturation or elevated serum ferritin on testing of repeated specimens; or (b) the patient has a first degree relative with haemochromatosis; or (c) the patient has a first degree relative with homozygosity for the *C282Y* genetic mutation, or with compound heterozygosity for recognised genetic mutations for haemochromatosis (Item is subject to rule 20)	Remove rule 20
73318	A test described in item 73317, if rendered by a receiving APP - 1 or more tests (Item is subject to rule 18 and 20)	Remove rule 20
73336	A test of tumour tissue from a patient with unresectable stage iii or stage iv metastatic cutaneous melanoma, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to *BRAF* V600 mutation status for access to dabrafenib under Pharmaceutical Benefits Scheme (PBS) are fulfilled.	A test of tumour tissue from a patient with unresectable stage iii or stage iv metastatic cutaneous melanoma, requested by a treating specialist or pathologist, to determine if the requirements relating to *BRAF V600* mutation status for access to dabrafenib under Pharmaceutical Benefits Scheme (PBS) are fulfilled.
73337	A test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to epidermal growth factor receptor *(EGFR)* gene status for access to erlotinib or gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	A test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by a treating specialist or pathologist, to determine if the requirements relating to epidermal growth factor receptor (*EGFR)* gene status for access to erlotinib or gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.

4.13 Items to be removed

The Committee recommended the MBS items listed in Table 24 be removed from the MBS.

- Item 73305 is redundant due to the availability of alternate methods (see section 4.6)
- Items 73311 and 73312 have been deleted due to lack of evidence supporting their use (see section 4.9).

Table 24. Items recommended for removal from the MBS

Item	Item descriptor	Schedule fee	Services (FY 2014–15)
73305	Detection of mutation of the *FMR1* gene by Southern blot analysis where the results in item 73300 are inconclusive	$202.65	616
73311	Characterisation of the genotype of a person who is a first degree relative of a person who has proven to have 1 or more abnormal genotypes under item 73308 - 1 or more tests	$36.45	6536
73312	A test described in item 73311, if rendered by a receiving APP - 1 or more tests (Item is subject to rule 18)	$36.45	56

5. Recommendations to other committees

Introduction

The Committee has also developed provisional recommendations for the consideration of other committees.

The item-level recommendations can be found below in Sections 5.1–5.2, and a summary recommendation table can be found in Appendix B.

5.1 Recommendations to Medical Services Advisory Committee

5.1.1 Extension of item 73292 microarray: include new populations

Recommendation 11

Δ The Committee seeks to brief the MSAC Executive and obtain its advice on the next steps for an application to MSAC to extend access to genome-wide microarray testing to additional populations beyond those currently specified in item 73292.

Table 25. Item introduction table for item 73292

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
73292	Analysis of chromosomes by genome-wide micro-array including targeted assessment of specific regions for constitutional genetic abnormalities in diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities (including a service in items 73287, 73289 or 73291, if performed) – 1 or more tests.	$589.90	14,189	$7,378,284	14,058	184.6%

Rationale 11

Δ Item 73292 was added to the MBS approximately 10 years ago, after peer-reviewed and best-practice guidelines provided evidence of the clinical utility of genome-wide micro-array as a first line investigation, in diagnostic studies of a person with developmental delay, intellectual disability or autism. This item has been reviewed in section 4.5 of this report.

Δ The Committee concluded that there is sufficient clinical evidence of clinical utility to support an application or applications to MSAC to extend this intervention to include the use in two additional populations and settings:

– The prenatal setting, when invasive testing is undertaken in pregnancy to investigate a pregnancy in which there are major fetal ultrasound abnormalities (in preference to karyotype testing).

- For two specific chronic haematological malignancies, chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM), often as an adjunct or alternative testing method to current investigations.

Δ MSAC consideration of the use of this test in CLL and MM is also supported by the Haematology Working Group of the Committee.

Δ In the prenatal setting, the Committee proposed the population would be restricted to pregnancies with major fetal structural abnormalities detected on ultrasound, when chromosome microarray could be performed in lieu of karyotype. In this setting chromosome microarrays have been found to have a superior diagnostic yield over karyotyping, without increasing unexpected diagnoses. In this clinical population, karyotyping as a standalone test is no longer considered an appropriate diagnostic approach, with many clinical societies' recommendations incorporating guidelines on the use of chromosome microarrays. [8], [9], [10], [11], [12]

Δ In the setting of haematological malignancies, the Committee proposed the population would be restricted to chronic haematological malignancies – specifically chronic lymphocytic leukaemia, and multiple myeloma, for which strongest evidence for clinical utility exists. The evidence to incorporate the use of chromosome microarrays in these haematological malignancies has been emerging in the scientific literature in the last eight years (for CLL [13], [14], [15], [16] and for MM [17], [18], [19], [19], [21], [22]).

Δ The clinical utility of analysis of chromosomes by genome-wide microarray in this setting has been further recognised by the incorporation of this technique into current technical standards for cytogenetic studies in haematological malignancies. [7]

Δ The Committee proposed the MBS item descriptors (to either amend MBS item 73292 or create one or two new MBS items) as follows in Table 26:

Table 26. Proposed descriptors for new items for microarray

Item	Proposed changes to item 73292 descriptor	Proposed new item descriptors
73292	The study of the whole of every chromosome to detect a constitutional genetic abnormality that is at least 100 kb in size, in diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least 2 congenital abnormalities (including a service in items 73287, 73289 or 73291, if performed) – 1 or more tests. (refer to Section 4.5)	Population 1: prenatal Analysis of chromosomes by genome-wide micro-array in diagnostic studies of a pregnancy where one or more major fetal structural abnormalities have been detected on ultrasound (including a service in item 73287, if performed) - 1 or more tests Population 2: CLL and MM Analysis of chromosomes by genome-wide micro-array in diagnostic studies of a patient with chronic lymphocytic leukaemia or multiple myeloma (including a service in item 73290, if performed) - 1 or more tests

5.1.2 Extension of item 73325: include an additional population and a new mutation

Recommendation 12

Δ The Committee seeks to brief the MSAC Executive and obtain its advice on the next steps for an application to MSAC to extensively review item 73325 to include additional populations and mutations beyond those currently specified, as well as undertake a costing review of this item.

Table 27. Item introduction table for item 73325

Item	Long item descriptor	Schedule fee	Services FY 2014–15	Benefits paid FY 2014–15	Patient count 2014–15	5-year service change (CAGR)
73325	Characterisation of mutations in:(a) the *JAK2* gene; or (b) the *MPL* gene; or (c) both genes; in the diagnostic work-up, by, or on behalf of, the specialist or consultant physician, of a patient with clinical and laboratory evidence of: a) polycythaemia vera; or b) essential thrombocythaemia;1 or more tests	$74.50	9170	$580,129	8685	—

Rationale 12

- Δ Item 73325 was added to the MBS in 2011 after the emergence of peer-reviewed evidence for prognostic and therapeutic clinical utility of specific mutation testing (in *JAK2* and *MPL* genes) in the clinical stratification of two specific (non-CML) myeloproliferative neoplasms — polycythaemia vera (PV), and essential thrombocythaemia (ET).
- Δ The Committee concluded that there is sufficient evidence of clinical utility to support an application to MSAC to extend this intervention to include:
  - the characterisation of mutations in the calreticulin (*CALR*) gene, and
  - a third myeloproliferative neoplasm population—patients with clinical and laboratory evidence of primary myelofibrosis (PMF).
- Δ This additional population would extend appropriate testing to include all appropriate populations as per current clinical guidelines.
- Δ The diagnostic workup for myeloproliferative disorders can include testing for a combination of one, two or possibly three genes and multiple mutations, depending on the clinical circumstances. The addition of *CALR* mutations to the test is recommended clinical practice; however, identification of *CALR* requires a different and more costly method than those used for the other genes and will thus increase the cost of performing the test. Therefore, a cost review for this item is also proposed. This application is also supported by the Haematology Working Group of the Pathology Clinical Committee.
- Δ Primary myelofibrosis (PMF), like PV and ET, is a non-CML myeloproliferative neoplasm and shares with these clinical entities driver mutations in *JAK2, CALR*, and *MPL*. These mutations help to stratify likelihoods for patient survival, outcomes, and potential complications such as the development of anaemia and thrombocytopenia.
- Δ Extensive evidence is available to support the clinical utility of testing for *CALR, JAK2* and *MPL* in the diagnosis of myeloprolific neoplasms PV, ET and PMF. [23], [24], [25], [26], [27], [28], [29], [30]

Table 28. Proposed changes to item 73325

Item	Item descriptor	Proposed new item descriptor
73325	Characterisation of mutations in:(a) the *JAK2* gene; or (b) the *MPL* gene; or (c) both genes; in the diagnostic work-up, by, or on behalf of, the specialist or consultant physician, of a patient with clinical and laboratory evidence of: a) polycythaemia vera; or b) essential thrombocythaemia;1 or more tests	Characterisation of mutations in: (a) the *JAK2* gene; or (b) the *MPL* gene; or (c) the *CALR* gene or (d) up to all three genes; in the diagnostic work-up of a patient with clinical and laboratory evidence of: a) polycythaemia vera; or b) essential thrombocythaemia; or c) primary myelofibrosis, requested by a treating specialist - 1 or more tests

- The annual incidence of primary myelofibrosis is 1 per 100,000 population (Leukaemia Foundation). This would therefore increase the rate of current testing by about 250 tests annually.

5.1.3 Review of recently listed item 73342: ISH test for HER2 for PBS trastuzumab for gastric cancer

In reviewing this item (see section 4.8), the Committee noted that it was not a pathologist-determinable service as had been advised by MSAC. [31], [32] The Committee noted that MSAC's rationale was that:

- the proposed MBS item descriptor should require that *HER2* ISH testing in the context of metastatic gastric cancer be performed on the same specimen in the same laboratory and only when prerequisite immunohistochemistry (IHC) testing for *HER2* overexpression is scored at 2+ or 3+ using scoring guidelines reflecting the approach which was standardised for the Trastuzumab for Gastric Cancer trial of trastuzumab.
- the proposed MBS item should therefore be made a pathologist-determinable service to allow HER2 ISH testing to be guided by the 'hot spots' revealed by the prerequisite IHC test result (the heterogeneity of IHC staining across a sample of tumour and the difficulty of scanning a slide for positive cells using ISH alone), rather than the pathologist being interrupted to get a referral from a clinician to do so.

Given the importance assigned by MSAC to ensuring optimal testing performance, the Committee recommended that this implementation of the MBS listing be drawn to the attention of MSAC through the MSAC Executive. The low uptake of laboratories billing Medicare for this item to date suggests that those rendering this service are likely to be aware of the importance of adopting the optimal approach to testing in the context of this item. However, this may not be sustained if uptake extends beyond MSAC's preference for a centralised approach to testing in the context of this item.

The Committee suggested that the Department provide MSAC with the rationale for why this aspect of MSAC advice had not been implemented and check with those rendering the service whether the current situation is an impediment to this aspect of optimal testing in practice. The Committee noted that it was possibly relevant that the MBS item for immunohistochemistry (IHC) testing of HER2 (72848) makes no reference to the staging of the cancer of the patient from whom the biopsy was taken, and so the first time that the pathology laboratory would need confirmation of this staging (which could not be determined by the pathologist) would be when proceeding to the ISH test if so justified by the IHC test.

5.2 Referral to the Department

5.2.1 Definition of tumour tissue relevant to items 73336 BRAF, 73337 EGFR and 73338 RAS

- The Committee is aware that there is a current practical issue affecting patients requiring testing for *BRAF, EGFR* and *RAS* gene mutations. The Anatomical and Cytology Working Group (ACWG) proposes there is a lack of clarity around the definition of 'tissue' used in the MBS, and this excludes the ability for pathologists to be able to retrieve and use existing cytology slides as a tissue of last resort. They suggested that this is particularly relevant for testing for *EGFR* in patients with non-small cell lung cancer. Feedback from the ACWG indicated that, while this is a rare event, enabling the use of existing cytology slides would prevent these patients having to have another invasive procedure.
- The Committee supported the proposal from the ACWG to define a tumour tissue as 'tumour tissue that has been assessed by a pathologist to contain sufficient intact tumour cells for testing' or words similar. The Committee proposed that the addition of an explanatory note to the relevant items, such as 'this does not include cell free DNA' would help define these rare situations.
- The Committee recommended that there should be further consultation with relevant clinical experts on the definitional terminology, and consideration within the Department regarding the application of the definition in practice in terms of the MBS.

5.2.2 Discussion regarding use of genetics items for 'screening' purposes

- To prevent genetics items being used for screening purposes, the Committee has recommended to include the words *'in a person with specific risk indicated by personal or family history'* to items where this is a risk. Within the current genetics table, this applies to items 73287 and 73289 (see section 4.1 and 4.2). The Committee noted that this may be a broader consideration relevant to other items across the MBS where tests may be at risk of being inappropriately used for screening.

6. References

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Appendix A: Assigned items recommendations list

Item	Current descriptor	Recommendation	Section reference
73287	The study of the whole of every chromosome by cytogenetic or other techniques, performed on 1 or more of any tissue or fluid except blood (including a service mentioned in item 73293, if performed) - 1 or more tests	Change	4.1 & 5.2.2
73289	The study of the whole of every chromosome by cytogenetic or other techniques, performed on blood (including a service mentioned in item 73293, if performed) - 1 or more tests	Change	4.2 & 5.2.2
73290	The study of the whole of each chromosome by cytogenetic or other techniques, performed on blood or bone marrow, in the diagnosis and monitoring of haematological malignancy (including a service in items 73287 or 73289, if performed). - 1 or more tests.	Change	4.3
73291	Analysis of one or more chromosome regions for specific constitutional genetic abnormalities of blood or fresh tissue in a) diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities, in whom cytogenetic studies (item 73287 or 73289) are either normal or have not been performed; or b) studies of a relative for an abnormality previously identified in such an affected person - 1 or more tests.	Change	4.4
73292	Analysis of chromosomes by genome-wide micro-array including targeted assessment of specific regions for constitutional genetic abnormalities in diagnostic studies of a person with developmental delay, intellectual disability, autism, or at least two congenital abnormalities (including a service in items 73287, 73289 or 73291, if performed) - 1 or more tests.	Change	4.5 & 5.1.1
73293	Analysis of one or more regions on all chromosomes for specific constitutional genetic abnormalities of fresh tissue in diagnostic studies of the products of conception, including exclusion of maternal cell contamination. - 1 or more tests.	Change	4.10
73294	Analysis of the *PMP22* gene for constitutional genetic abnormalities causing peripheral neuropathy, either as: a) diagnostic studies of an affected person; or b) studies of a relative for an abnormality previously identified in an affected person - 1 or more tests.	No change	4.11
73300	Detection of mutation of the *FMR1* gene where: (a) the patient exhibits intellectual disability, ataxia, neurodegeneration, or premature ovarian failure consistent with an *FMR1* mutation; or (b) the patient has a relative with a *FMR1* mutation 1 or more tests	Change	4.6
73305	Detection of mutation of the *FMR1* gene by Southern blot analysis where the results in item 73300 are inconclusive	Delete	4.6 & 4.13
73308	Characterisation of the genotype of a patient for *factor V Leiden* gene mutation, or detection of the other relevant mutations in the investigation of proven venous thrombosis or pulmonary embolism - 1 or more tests	Change	4.9
73309	A test described in item 73308, if rendered by a receiving APP - 1 or more tests (Item is subject to rule 18)	No change	4.9 & 4.11

Item	Current descriptor	Recommendation	Section reference
73311	Characterisation of the genotype of a person who is a first degree relative of a person who has proven to have 1 or more abnormal genotypes under item 73308 - 1 or more tests	Delete	4.9 & 4.13
73312	A test described in item 73311, if rendered by a receiving APP - 1 or more tests (Item is subject to rule 18)	Delete	4.9 & 4.13
73314	Characterisation of gene rearrangement or the identification of mutations within a known gene rearrangement, in the diagnosis and monitoring of patients with laboratory evidence of: (a) acute myeloid leukaemia; or (b) acute promyelocytic leukaemia; or (c) acute lymphoid leukaemia; or (d) chronic myeloid leukaemia;	No change	4.11
73315	A test described in item 73314, if rendered by a receiving APP - 1 or more tests (Item is subject to rule 18)	No change	4.11
73317	Detection of the *C282Y* genetic mutation of the HFE gene and, if performed, detection of other mutations for haemochromatosis where: (a) the patient has an elevated transferrin saturation or elevated serum ferritin on testing of repeated specimens; or (b) the patient has a first degree relative with haemochromatosis; or (c) the patient has a first degree relative with homozygosity for the *C282Y* genetic mutation, or with compound heterozygosity for recognised genetic mutations for haemochromatosis (Item is subject to rule 20)	Change	4.12
73318	A test described in item 73317, if rendered by a receiving APP - 1 or more tests (Item is subject to rule 18 and 20)	Change	4.12
73320	Detection of *HLA-B27* by nucleic acid amplification includes a service described in 71147 unless the service in item 73320 is rendered as a pathologist determinable service. (Item is subject to rule 27)	No change	4.11
73321	A test described in item 73320, if rendered by a receiving APP - 1 or more tests. (Item is subject to rule 18 and 27)	No change	4.11
73323	Determination of *HLA-B5701* status by molecular techniques prior to the initiation of abacavir therapy including item 71203 if performed.	No change	4.11
73324	A test described in item 73323 if rendered by a receiving app1 or more tests (item is subject to rule 18)	No change	4.11
73325	Characterisation of mutations in:(a) the *JAK2* gene; or (b) the *MPL* gene; or(c) both genes; in the diagnostic work-up, by, or on behalf of, the specialist or consultant physician, of a patient with clinical and laboratory evidence of: a) polycythaemia vera; or b) essential thrombocythaemia;1 or more tests	Change	5.1.2
73326	Characterisation of the gene rearrangement *FIP1l1-PDGFRA* in the diagnostic work-up and management of a patient with laboratory evidence of: a) mast cell disease; or b) idiopathic hypereosinophilic syndrome; or c) chronic eosinophilic leukaemia; 1 or more tests	No change	4.11
73327	Detection of genetic polymorphisms in the thiopurine s-methyltransferase gene for the prevention of dose-related toxicity during treatment with thiopurine drugs; including (if performed) any service described in item	No change	4.11

Item	Current descriptor	Recommendation	Section reference
	65075. 1 or more tests		
73332	An in-situ hybridization (ISH) test of tumour tissue from a patient with breast cancer requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to human epidermal growth factor receptor 2 *(HER2)* gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme (PBS) or the Herceptin program are fulfilled.	Change	4.7
73333	Detection of germline mutations of the von Hippel-Lindau *(VHL)* gene: in a patient who has a clinical diagnosis of *VHL* syndrome and: a family history of *VHL* syndrome and one of the following: haemangioblastoma (retinal or central nervous system); phaeochromocytoma; renal cell carcinoma; or 2 or more haemangioblastomas; or one haemangioblastoma and a tumour or a cyst of: the adrenal gland; or the kidney; or the pancreas; or the epididymis; or a broad ligament (other than epididymal and single renal cysts, which are common in the general population); or in a patient presenting with one or more of the following clinical features suggestive of *VHL* syndrome: (i) haemangioblastomas of the brain, spinal cord, or retina; (ii) phaeochromocytoma; (iii) functional extra-adrenal paraganglioma	No change	4.11
73334	Detection of germline mutations of the von Hippel-Lindau *(VHL)* gene in biological relatives of a patient with a known mutation in the VHL gene	No change	4.11
73335	Detection of somatic mutations of the von Hippel-Lindau *(VHL)* gene in a patient with: 2 or more tumours comprising: 2 or more haemangioblastomas, or one haemangioblastoma and a tumour of: the adrenal gland; or the kidney; or the pancreas; or the epididymis; and no germline mutations of the VHL gene identified by genetic testing	No change	4.11
73336	A test of tumour tissue from a patient with unresectable stage iii or stage iv metastatic cutaneous melanoma, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to *BRAF v600* mutation status for access to dabrafenib under Pharmaceutical Benefits Scheme (PBS) are fulfilled.	Change	4.12 & 5.2.1
73337	A test of tumour tissue from a patient diagnosed with non-small cell lung cancer, shown to have non-squamous histology or histology not otherwise specified, requested by, or on behalf of, a specialist or consultant physician, to determine if the requirements relating to epidermal growth factor receptor *(EGFR)* gene status for access to erlotinib or gefitinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	Change	4.1.2 & 5.2.1
73338	A test of tumour tissue from a patient with metastatic colorectal cancer (stage IV), requested by a specialist or consultant physician, to determine if the requirements relating to rat sarcoma oncogene *(RAS)* gene mutation status for access to cetuximab or panitumumab under the Pharmaceutical Benefits Scheme (PBS) are fulfilled, if:(a) the test is conducted for all clinically relevant mutations on *KRAS* exons 2, 3 and 4 and *NRAS* exons 2, 3, and 4; or (b) a RAS mutation is found.	No change	4.11 & 5.2.1

Item	Current descriptor	Recommendation	Section reference
73339	Detection of germline mutations in the *RET* gene in patients with a suspected clinical diagnosis of multiple endocrine neoplasia type 2 (MEN2) requested by a specialist or consultant physician who manages the treatment of the patient.one test. (Item is subject to rule 25)	No change	4.11
73340	Detection of a known mutation in the *RET* gene in an asymptomatic relative of a patient with a documented pathogenic germline *RET* mutation requested by a specialist or consultant physician who manages the treatment of the patient.one test. (Item is subject to rule 25)	No change	4.11
73341	Fluorescence in situ hybridisation (FISH) test of tumour tissue from a patient with locally advanced or metastatic non-small cell lung cancer, which is of non-squamous histology or histology not otherwise specified, with documented evidence of anaplastic lymphoma kinase (ALK) immunoreactivity by immunohistochemical (IHC) examination giving a staining intensity score > 0, and with documented absence of activating mutations of the epidermal growth factor receptor *(EGFR)* gene, requested by a specialist or consultant physician to determine if requirements relating to ALK gene rearrangement status for access to crizotinib under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.	No change	4.11
73342	An in situ hybridisation (ISH) test of tumour tissue from a patient with metastatic adenocarcinoma of the stomach or gastro-oesophageal junction, with documented evidence of human epidermal growth factor receptor 2 *(HER2)* overexpression by immunohistochemical (IHC) examination giving a staining intensity score of 2+ or 3+ on the same tumour tissue sample, requested by, or on the advice of, a specialist or consultant physician who manages the treatment of the patient to determine if the requirements relating to *HER2* gene amplification for access to trastuzumab under the Pharmaceutical Benefits Scheme are fulfilled.	Change	4.8 & 5.1.3

Appendix B: Additional items recommendations list

Item	Descriptor	Recommendation	Section reference
New/amend 73292	Analysis of chromosomes by genome-wide micro-array of a pregnancy where major fetal structural abnormalities have been detected on ultrasound	The Committee seeks to brief the MSAC Executive and obtain its advice on the next steps for an application to MSAC to extend access to genome-wide microarray testing to the prenatal setting, when invasive testing is undertaken in pregnancy to investigate a pregnancy where there are major fetal ultrasound abnormalities (in preference to karyotype testing).	5.1.1
New/amend 73292	Analysis of chromosomes by genome-wide micro-array of a patient with chronic lymphocytic leukaemia or multiple myeloma	The Committee seeks to brief the MSAC Executive and obtain its advice on the next steps for an application to MSAC to extend access to genome-wide microarray testing to two specific chronic haematological malignancies, chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM), often as an adjunct or alternative testing method to current investigations.	5.1.1
New/amend 73325	Characterisation of mutations in: (a) the JAK2 gene; or (b) the MPL gene; or (c) the CALR gene or (d) all three genes; in the diagnostic work-up of a patient with clinical and laboratory evidence of: a) polycythaemia vera; or b) essential thrombocythaemia; or c) primary myelofibrosis, requested by a treating specialist or pathologist - 1 or more tests	The Committee seeks to brief the MSAC Executive and obtain its advice on the next steps for an application to MSAC to extensively review item 73325 to include additional populations and mutations beyond those currently specified, as well as undertake a costing review of this item. (see section 5.1.2)	5.1.2

Appendix C: Summary for consumers

This summary describes the medical service, the recommendations of the clinical experts and why the recommendation(s) has been made.

Recommendation 1: Chromosome by cytogenetic or other technique (on tissue or fluid): item 73287

Item	What it does	Committee recommendation	What would be different	Why
73287	This is a genetic test to identify and evaluate the size, shape and number of chromosomes in a sample of tissue or fluid. Extra or missing chromosomes, or abnormal positions of chromosomes, can cause problems with growth, development and body functions.	Exclude the use of whole genome sequencing as an appropriate technique covered by this item.	Excluding whole genome sequencing (a test with high resolution) will ensure the most appropriate techniques (those with low to medium resolution) are used to provide the relevant amount of information for diagnosis.	Using a high-resolution technique that provides more information than is required for a specific investigation is unnecessary and not appropriate. A low- to medium-resolution technique is appropriate for the investigations covered by this item.

Recommendation 2: Chromosome by cytogenetic or other technique (on tissue or fluid): item 73289

Item	What it does	Committee recommendation	What would be different	Why
73289	This is a genetic test to identify and evaluate the size, shape and number of chromosomes in a sample of blood. Extra or missing chromosomes, or abnormal positions of chromosomes, can cause problems with growth, development and body functions.	Exclude the use of whole genome sequencing as an appropriate technique covered by this item.	Excluding whole genome sequencing (a test with high resolution) will ensure the most appropriate techniques (those with low to medium resolution) are used to provide the relevant amount of information for diagnosis.	Using a high-resolution technique that provides more information than is required for a specific investigation is unnecessary and not appropriate. A low- to medium-resolution technique is appropriate for the investigations covered by this item.

Recommendation 3: Chromosome by cytogenetic or other technique on blood or bone marrow, for diagnosis and monitoring of haematological malignancy: item 73290

Item	What it does	Committee recommendation	What would be different	Why
73290	This is a genetic test to identify and evaluate the size, shape and number of chromosomes in a sample of blood or bone marrow. Extra or missing chromosomes, or abnormal positions of chromosomes, can cause some blood disorders. This test is used to diagnose and to monitor certain blood disorders.	Exclude the use of whole genome sequencing as an appropriate technique covered by this item.	Excluding whole genome sequencing (a test with high resolution) will ensure the most appropriate techniques (those with low to medium resolution) are used to provide the relevant amount of information for diagnosis.	Using a high-resolution technique that provides more information than is required for a specific investigation is unnecessary and not appropriate. A low- to medium-resolution technique is appropriate for the investigations covered by this item.

Recommendation 4: Chromosome for specific constitutional abnormalities: item 73291

Item	What it does	Committee recommendation	What would be different	Why
73291	This genetic test is used to investigate the cause of intellectual and developmental delay in children. It is also used to test the relatives of the children.	Remove the specification of the test technique from the descriptor. Remove the testing of the child from this item, and just keep it for testing the relatives. Extend the resolution techniques to enable low- to medium-resolution techniques to be used.	The current item covers testing both child and relatives, but there are better techniques on the MBS (microarray) which are now recommended as first line for testing children. This item is still relevant to test the relatives, as it is more targeted and therefore less expensive than microarray.	Microarray is the appropriate test for investigating the child, but this test is still appropriate for more targeted testing of relatives.

Recommendation 5: Chromosome by genome-wide microarray: item 73292

Item	What it does	Committee recommendation	What would be different	Why
73292	Microarray is a medium-resolution technique used to investigate the cause of intellectual and developmental delay.	Remove the specification of the technique (microarray) from the descriptor and include a medium-resolution threshold descriptor instead.	There would be no difference for patients. The change will allow for potentially other medium-resolution techniques to be utilised.	Specifying the test method i.e. microarray, limits the test. Defining the level of detail expected from this test will help ensure that only the appropriate level of testing is done.

Recommendation 6: *FMR1* gene mutations: item 73300 and 73305

Item	What it does	Committee recommendation	What would be different	Why
73300 and 73305	These tests are used to detect a gene mutation *(FMR1)* that causes fragile X syndrome, a hereditary intellectual disability.	Delete item 73305 (Southern blot method) and revise the costing of the preferred method covered by 73300.	The method covered by 73305 is not as reliable and no longer routinely used. Removing it will ensure that the more appropriate method covered by 73300 are used instead.	The Southern blot method has been superseded by the more modern PCR method covered by 73300. Since its introduction to the MBS in 2003, the costs of modern PCR have increased and the schedule fee needs to be reviewed.

Recommendation 7: ISH test for *HER2* for PBS trastuzumab for breast cancer: item 73332

Item	What it does	Committee recommendation	What would be different	Why
73332	This test is used to identify the increase in the *HER2* gene in breast cancer, in order to meet specific criteria to access a treatment available on the Pharmaceutical Benefits Scheme (PBS).	Update the wording to modernise the descriptor and provide more information to pathologists.	There would be no change for patients. Pathologists will have more information to assist them in performing the test appropriately.	Having any additional information that assists in obtaining the tissue for the test is practical.

Recommendation 8: ISH test for *HER2* for PBS trastuzumab for gastric cancer: item 73342

Item	What it does	Committee recommendation	What would be different	Why
73342	This test is used to identify the increase in the *HER2* gene in gastric cancer, in order to meet specific criteria to access a treatment available on the Pharmaceutical Benefits Scheme (PBS).	Update the wording to modernise the descriptor and provide more information to pathologists.	There would be no change for patients. Pathologists will have more information to assist them in performing the test appropriately.	Having the criteria required for the testing in the MBS descriptor is practical.

Recommendation 9: Genotype factor V Leiden or other gene mutations in investigation of venous thromboembolism: items 73308—73312

Item	What it does	Committee recommendation	What would be different	Why
73308—73312	These tests are used to identify the presence of gene mutations that predict the risk of recurrent blood clots called venous thromboembolism (VTE) in patients who have previously had a VTE. They are also used to test first-degree relatives of patients who have the mutation.	Restrict the test to only two gene mutations (factor V Leiden and prothrombin) in patients who have had a positive activated protein C resistance (APCR) test.	Only the most appropriate tests will be performed. At the moment unnecessary tests may be performed when there is no evidence of them adding any value.	Evidence does not support the test for other gene mutations and does not support use in testing any of these gene mutations in relatives. These changes support best clinical practice and prevent unnecessary tests being performed and inappropriate costs. There is no evidence they add any value to patient care or change the way patients are managed.

Recommendation 10: Chromosome abnormalities products of conception: item 73293

Item	What it does	Committee recommendation	What would be different	Why
73293	This test is used to identify abnormal genes in placental or fetal tissue after, for example, a miscarriage.	Add restrictors to ensure that this test is not unnecessarily repeated.	There would be no difference to patients.	This will prevent inadvertent claiming of similar tests.

Recommendation 11: Extension of microarray populations

Item	What it does	Committee recommendation	What would be different	Why
73292- new or amended.	Microarray is a medium-resolution technique used to investigate the cause of major fetal abnormalities and some specific blood diseases.	Extend the approved indications for this test to include: - investigation of major fetal ultrasound abnormalities and, - investigation of chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM).	This test would be able to be used in more people and enable more accurate and timely diagnosis of either fetal abnormalities or blood diseases.	There is strong evidence to support using this test in these new populations. Using the most effective test will enable more accurate and timely diagnosis in these patient groups.

Recommendation 12: Extension of the population and a new gene mutation: item 73325

Item	What it does	Committee recommendation	What would be different	Why
73325 extended	These tests are used to diagnose a group of diseases in which the bone marrow makes too many red blood cells, white blood cells, or platelets.	Add a new gene mutation *(CALR)* to the list currently covered by this item, and add a new disease to the list that can be detected (primary myelofibrosis).	More patients would be able to be tested, and all patients would be tested for an additional gene mutation. This will improve the diagnosis of these diseases.	Extending the testing to include the new gene mutation and the additional disease is supported by the biomedical literature and will support best clinical practice and enable better diagnosis.

Appendix D: Glossary

Term	Description
APCR	Activated protein C resistance – a test used in the investigation of tendency to venous thromboembolism
CAGR	Compound annual growth rate, or the average annual growth rate over a specified time period.
Change	When referring to an item, describes when the item and/or its services will be affected by the recommendations. This could result from a range of recommendations, such as: (i) specific recommendations that affect the services provided by changing item descriptors or explanatory notes, (ii) the consolidation of item numbers, and (iii) splitting item numbers (e.g., splitting the current services provided across two or more items).
CLL	Chronic lymphocytic leukaemia
Department, The	Australian Government Department of Health
Delete	Describes when an item is recommended for removal from the MBS and its services will no longer be provided under the MBS.
ET	Essential thrombocythaemia
FISH	Fluorescence in situ hybridization
FVL	Factor V Leiden
FY	Financial year
GP	General practitioner
GPPCCC	General Practice and Primary Care Clinical Committee
High-value care	Services of proven efficacy reflecting current best medical practice, or for which the potential benefit to consumers exceeds the risk and costs.
IHC	immunohistochemistry
Inappropriate use / misuse	The use of MBS services for purposes other than those intended. This includes a range of behaviours, from failing to adhere to particular item descriptors or rules through to deliberate fraud.
ISH	In Situ Hybridization
Karyotyping	Identifying and evaluating the size, shape, and number of chromosomes in a sample of body cells.
kb	kilobase: a measurement of the size of a piece of DNA/RNA (1000 contiguous nucleotide bases in a strand of DNA or RNA).
Low-value care	Services that evidence suggests confer no or very little benefit to consumers; or for which the risk of harm exceeds the likely benefit; or, more broadly, where the added costs of services do not provide proportional added benefits.
MBS	Medicare Benefits Schedule
MBS item	An administrative object listed in the MBS and used for the purposes of claiming and paying Medicare benefits, consisting of an item number, service descriptor and supporting information, schedule fee and Medicare benefits.
MBS service	The actual medical consultation, procedure or test to which the relevant MBS item refers.
Microarray, Chromosome microarray (CMA)	A chromosome microarray is a test which detects extra or missing segments of DNA in a person's genome. Chromosome microarrays can detect much more subtle copy number variants than conventional chromosome analysis (also known as karyotype analysis) and so are more effective at finding the cause of developmental or other health problems.
MM	Multiple myeloma

Term	Description
MSAC	Medical Services Advisory Committee
No change or unchanged	Describes when the services provided under these items will not be changed or affected by the recommendations. This does not rule out small changes in item descriptors (e.g., references to other items, which may have changed as a result of the MBS Review or prior reviews).
Obsolete services	Services that should no longer be provided as they do not represent current clinical best practice and have been superseded by superior tests or procedures.
Pathologist determinable	Certain tests on the MBS are 'pathologist determinable', meaning that a pathologist can add them on to a request without a written request from the clinician ordering the test if the pathologist, on the basis of requested test outcomes, determines they are necessary.
PBS	Pharmaceutical Benefits Scheme
PCR	Polymerase chain reaction: a method for amplifying (producing multiple copies of) a gene for identification/testing
PMF	Primary myelofibrosis
PT	Prothrombin
PV	Polycythemia vera
RACGP	Royal Australian College of General Practitioners
RCPA	Royal College of Pathologists Australasia
Services average annual growth	The average growth per year, over 5 years to 2014/15, in utilisation of services. Also known as the compound annual growth rate (CAGR).
The Committee	The Pathology Clinical Committee
The Taskforce	The MBS Review Taskforce
Total benefits	Total benefits paid in 2014/15 unless otherwise specified.
VTE	Venous thromboembolism