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Final Decision  
Analytic Protocol  
(DAP) to guide the  
assessment of  
transthyretin (TTR)  
genetic testing to  
establish the  
diagnosis of  
transthyretin familial  
amyloid  
polyneuropathy (TTR-  
FAP) for access to  
tafamidis meglumine.

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September 2012

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## MSAC and PASC

The Medical Services Advisory Committee (MSAC) is an independent expert committee appointed by the Minister for Health and Ageing (the Minister) to strengthen the role of evidence in health financing decisions in Australia. MSAC advises the Minister on the evidence relating to the safety, effectiveness, and cost-effectiveness of new and existing medical technologies and procedures and under what circumstances public funding should be supported.

The Protocol Advisory Sub-Committee (PASC) is a standing sub-committee of MSAC. Its primary objective is the determination of protocols to guide clinical and economic assessments of medical interventions proposed for public funding.

### Purpose of this document

This document is intended to provide a draft decision analytic protocol that will be used to guide the assessment of an intervention for a particular population of patients. The draft protocol will be finalised after inviting relevant stakeholders to provide input to the protocol. The final protocol will provide the basis for the assessment of the intervention.

The protocol guiding the assessment of the health intervention has been developed using the widely accepted "PICO" approach. The PICO approach involves a clear articulation of the following aspects of the research question that the assessment is intended to answer:

- P**atients – specification of the characteristics of the patients in whom the intervention is to be considered for use
- I**ntervention – specification of the proposed intervention and how it is delivered
- C**omparator – specification of the therapy most likely to be replaced by the proposed intervention
- O**utcomes – specification of the health outcomes and the healthcare resources likely to be affected by the introduction of the proposed intervention

## Purpose of application

A proposal for an application requesting MBS listing of transthyretin (TTR) genetic testing to establish the diagnosis of transthyretin familial amyloid polyneuropathy (TTR-FAP) for access to tafamidis meglumine (hereafter, tafamidis) was received from Pfizer Australia Pty Limited by the Department of Health and Ageing in December 2011.

## Background

### Current arrangements for public reimbursement

Transthyretin (TTR) genetic testing is not currently available on the MBS. However, TTR genetic testing is presently accessible to Australian patients in commercial laboratories (via self-pay) or funded, in some cases (e.g. patients who physically attend the Westmead Amyloidosis Clinic). Laboratories that currently provide TTR testing service include: Applied Genetic Diagnostics (University of Melbourne) and Amyloid Clinic (Westmead Hospital, Sydney).

### Regulatory status

Under Therapeutic Goods Administration's (TGA) rules, human genetic tests are classified as Class 3 in-vitro diagnostic tests (IVDs) (TGA, 2011). TGA is currently in the process of developing a regulatory framework for in-vitro diagnostic devices. Under this framework, any IVDs that are currently listed, registered or exempt, will be required to undergo a review for inclusion on the Australian Register of Therapeutic Goods (ARTG) prior to 1 July 2014. Any new IVDs introduced in the Australian market after 1 July 2010 must be included on the ARTG prior to legal supply. As the TTR-FAP genetic test was first offered in Australia in 2008, it is therefore required to undergo a review for inclusion on the ARTG prior to 1 July 2014.

The Applicant proposes that access to tafamidis be contingent on the results of the genetic test. Tafamidis has been granted orphan drug status by the TGA<sup>1</sup>, and the Applicant advises that a submission is planned to the Pharmaceutical Benefits Advisory Committee for funding of tafamidis under the Life Saving Drugs Programme (LSDP) for adult patients with TTR-FAP.

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<sup>1</sup> See TGA's register of orphan drugs: <http://www.tga.gov.au/industry/pm-orphan-drugs.htm>

## Intervention

### Description

#### Description of the medical condition

Transthyretin familial amyloid polyneuropathy (TTR-FAP) was first identified in 1952, in Portugal; cases were subsequently reported in Japan (1968), Sweden (1976), and worldwide (Plante-Bordeneuve & Said, 2011). The disease is extremely rare – the European Medicines Agency (EMA) estimates the overall population of TTR-FAP patients in Europe at 2,700-3,500, and the worldwide population of patients at 5,000-10,000 (European Medicines Agency, 2011). The prevalence in Australia is not presently known. The EMA numbers would suggest a patient population in Australia of between 81-105 persons, however, as Europe includes several populations with high mutation prevalence (e.g. Portugal, Sweden), this estimate is too high. The Applicant estimates that Australian patient population may consist of approximately 30 persons. This is in line with the opinions of the Clinical Experts, who estimate that the Australian patient population would be no more than 50, most likely somewhere between 30-50 persons. Penetrance rate of the disease is less than 100%, although the precise rate varies by mutation, geographic region and/or ethnic group. Pagon et al (2012), for example, note that penetrance rate in Sweden is 1.7% by age 30, 11% by 50, 36% by 70, and 69% by 90. Elsewhere, it has been reported that at 50 years of age, penetrance was 60% in Portuguese patients and 18% in French patients (Plante-Bordeneuve & Norgren, 2011).

TTR-FAP is transmitted in an autosomal dominant manner (i.e., first degree relatives have a 50% chance of inheriting the same mutation). The disease is caused by mutations in the transthyretin (TTR) gene – over a hundred disease-causing mutations have been identified in the TTR gene so far, with Val30Met and Ile84Ser being the most common mutations (Plante-Bordeneuve 2011; NHSC 2010). TTR protein is synthesised mainly by the liver; it is a transport protein that normally circulates in the plasma as a tetramer (i.e., a protein with four sub-units). In patients with the TTR gene mutation, however, this protein becomes structurally unstable, dissociating into monomers, and accumulating on nerves and in organs (Plante-Bordeneuve 2011; NHSC 2010).

Early-onset and late-onset versions of the disease have been identified. In early-onset patients, the first signs of the disease begin in the second or third decade of life, while late-onset patients begin to display symptoms past the age of 50 (Koike, 2004). Typically, death occurs within 10 years of onset (Plante-Bordeneuve & Said, 2011). The primary symptoms of TTR-FAP are the progressive loss of nerve functions (including sensory, autonomic and motor), however, differences exist in the clinical presentation of early-onset and late-onset patients. Early-onset clinical presentation is characterised by high penetrance rate, high autonomic dysfunction, sensory dissociation (e.g., loss of nociception, thermal sensation), cardiac involvement (requiring pacemaker implantation), and anticipation of age at onset. Sensory-motor deficit progresses rapidly. The late-onset presentation is characterised by low penetrance rate, relatively low autonomic dysfunction, loss of all sensory modalities (rather than a sensory dissociation), cardiomegaly (heart enlargement), extreme male preponderance, and absence of anticipation of age at onset. Polyneuropathy also progresses more slowly, with less autonomic dysfunction (Koike et al 2004; Plante-Bordeneuve & Said, 2011).

As liver is the site of TTR synthesis, liver transplantation has been utilised as treatment for TTR-FAP. Over 1900 transplants have taken place worldwide (FAP World Transplant Registry, 2010) and there is some evidence of improvement post-transplant (e.g. the Swedish survival rate is now reported to be 92%). However, the transplant does not prevent cardiac dysfunctions from developing, must be carried out early in the course of TTR-FAP, and requires patients to remain on immunosuppressants for the rest of their lives (Plante-Bordeneuve & Said, 2011). Other care currently provided to patients includes: treatment of pain with pharmaceuticals, surgical decompression for carpal tunnel syndrome, therapeutic measures for orthostatic hypotension, correction of hydration, and insertion of a pacemaker to correct cardiac dysfunction (Plante-Bordeneuve & Said, 2011; Bittencourt et al 2002).

### Description of the intervention

The Applicant proposes that the patient be typically referred for the test by a specialist physician. Blood samples would be collected and sent to a specialist testing laboratory. The analysis and interpretation of results would be performed by a specialist pathologist.

TTR genetic testing is not a trademarked technology. Testing is currently performed using Polymerase Chain Reaction (PCR) to amplify the sample, and DNA sequencing. The Applicant proposes that the method for determination of the TTR mutation need not be limited to this approach and requests that other appropriate methods be permitted. Other appropriate methods here could include tandem mass spectrometry analysis and restriction fragment polymorphism. However, the Clinical Experts advise that tandem mass spectrometry is typically confirmed by sequencing in practice, and fragment length polymorphism may not be able to detect less common mutations. The approach of using PCR and DNA sequencing is therefore the simplest and cheapest approach, and it is the one in routine use. However, PASC agreed not to specify the testing methodology in the MBS item descriptor, as the technology is rapidly evolving.

The patient population that would benefit from the TTR genetic test includes:

- (1) patients with symptoms of TTR-FAP, who have family history of TTR-FAP
- (2) patients with symptoms of TTR-FAP, and biopsy-proven amyloid, who lack family history of TTR-FAP

### **Prerequisites**

#### Professional restrictions on the request for and delivery of the intervention

The testing would typically be requested by specialist physicians, who would likely include: neurologists, haematologists, immunologists and/or cardiologists. The specialist physician would provide a referral for the genetic test, whilst a specialist pathologist would both perform the test and interpret its results. Restrictions around the provision of genetic tests are addressed through National Pathology Accreditation Advisory Council (NPAAC) standards<sup>2</sup> and the National Association of Testing Authorities (NATA) laboratory accreditation.<sup>3</sup>

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<sup>2</sup> See: <http://www.health.gov.au/internet/main/publishing.nsf/Content/health-npaac-publication.htm>

<sup>3</sup> See: <http://www.nata.com.au/>

### Geographic restrictions on the delivery of service

Two Australian laboratories currently provide TTR genetic testing services – one in Sydney (Westmead Hospital) and one in Melbourne (Applied Genetic Diagnostics, University of Melbourne). There are no known laboratories that provide this service in other areas of Australia. Therefore, samples need to be sent to one of those laboratories.

### **Co-administered and associated interventions**

#### Prerequisite interventions

The diagnosis of TTR-FAP has traditionally involved detection of protein deposits in tissues and on nerves (via biopsy), and the identification of the amyloid deposits by histology (Hund et al 2001). Immunohistochemistry (IHC) may be used to identify the responsible protein, although Clinical Experts advised that IHC is not carried out in all hospitals because it is both difficult to carry out and inaccurate.

The Clinical Experts consulted during the development of this protocol have advised that the interventions described above no longer represent routine clinical practice, particularly since the evolution of TTR-FAP genetic testing. The use of the genetic testing, although not presently funded through MBS, is now common in patients with symptoms suggestive of TTR-FAP disease (whether these patients have a family history or not). The costs of these genetic tests are met by the patients themselves, or, in some cases, are funded.

#### Co-dependent interventions

The Applicant proposes that TTR genetic testing be co-dependent with treatment with tafamidis.

Co-dependent technologies have been defined by the Department of Health and Ageing as those whose “use needs to be combined (either sequentially or simultaneously) to achieve or enhance the intended clinical effect of either technology. For example, a drug/test combination where a new medicine seeking listing on the PBS may have a related pathology test that helps to determine the population group for that medicine” (Dept. of Health and Ageing, undated).

A precise determination of patient population is highly desirable here, given the high cost of tafamidis, as well as the major consequences around undertaking of therapy (e.g. liver transplantation, palliation, etc). Insofar as the genetic test helps to determine the patient group for tafamidis, it is a co-dependent technology according to the Department's definition.

Tafamidis was developed as a stabiliser of the TTR tetramer. By binding to the tetrameric form of TTR (i.e. the 'normal' form, which consists of 4 monomers), tafamidis prevents TTR's dissociation into monomers (and its subsequent accumulation on nerves and organs) (European Medicines Agency, 2011). The Applicant intends to submit an application to PBAC for funding of tafamidis under the Life Saving Drugs Programme. Tafamidis would be available to symptomatic patients with all TTR mutations.

## Listing proposed and options for MSAC consideration

### Proposed MBS listing

The details of the proposed MBS listing for TTR genetic testing are shown in Table 1, below.

Table 1: Proposed MBS item descriptor for [item]

Category 6 – Pathology Services
Group P7 - Genetics
<p>MBS [item number]</p> <p>A test on behalf of a specialist or consultant physician to determine mutation in the transthyretin (TTR) gene for the following patient populations:</p> <p>(1) patients with symptoms of TTR-FAP, who have family history of TTR-FAP  (2) patients with symptoms of TTR-FAP, and biopsy-proven amyloid, who lack family history of TTR-FAP</p> <p>to determine if the requirements relating to TTR gene status for access to tafamidis under the Pharmaceutical Benefits Scheme (PBS) are fulfilled.</p> <p>Fee: \$350<sup>4</sup></p>

These tests are intended to serve patients identified by the Applicant as being eligible for access to tafamidis, for which it will be seeking approval under PBS arrangements within its planned submission.

### Clinical place for proposed intervention

#### Current diagnostic pathway

Under the current diagnostic pathway, tissue biopsy is typically obtained either from a clinically-affected organ (e.g. nerves, kidney) or from a non-specific site (e.g. rectal mucosa, abdominal fat). Collection from the non-specific sites is more common, as the procedure is less invasive. Amyloid deposits are identified by histology, and as noted above, in some hospitals immunohistochemistry is carried out to identify the responsible protein.

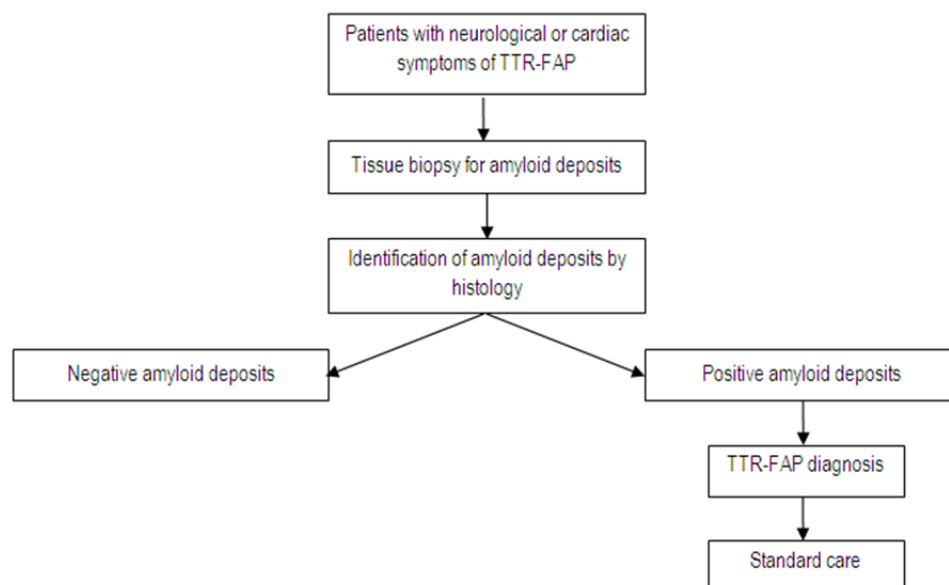
Patients who are diagnosed with TTR-FAP then go on to receive usual care, which includes some or all of the following: treatment of neuropathic pain with pharmaceuticals, alleviation of carpal tunnel syndrome with surgical decompression, therapeutic measures for orthostatic hypotension, correction of dehydration, insertion of a pacemaker to correct cardiac dysfunction. Eligible patients may also undergo liver transplantation, in order to prevent the formation of further amyloid deposits; those patients remain on lifelong immunosuppressants (Plante-Bordeneuve & Said, 2011; Bittencourt et al 2002).

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<sup>4</sup> PASC determined that this fee should reflect sequencing rather than point testing. The fee requires further confirmation.



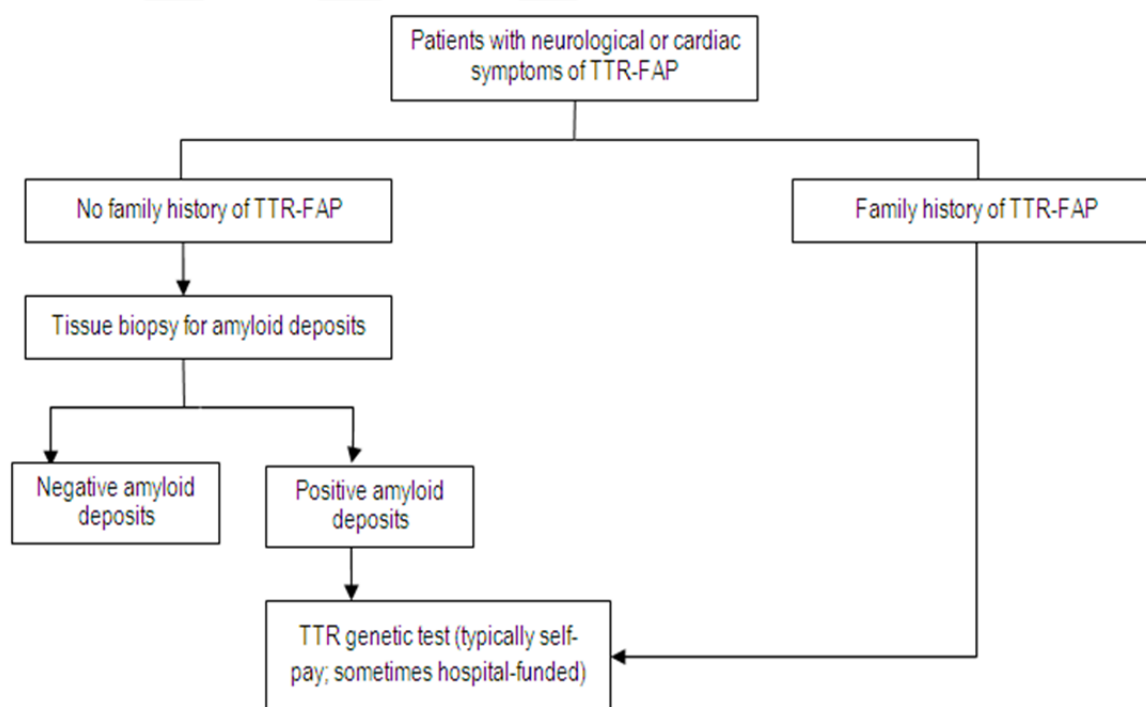
Figure 1: Traditional diagnostic pathway (funded by MBS)



NB: Clinical Experts advised that IHC is not carried out in all hospitals on account of its difficulty and inaccuracy. Consequently, it was omitted here.

Current diagnostic practice differs from the funded strategy (illustrated above), as a result of the advent of TTR-FAP genetic testing. The current clinical practice is depicted in Figure 2, below.

Figure 2: Current diagnostic pathway (in practice)



As illustrated above, in current practice, the symptomatic patients who have family history of TTR-FAP undergo genetic testing. Biopsy is bypassed, given the invasive nature of the test, the high likelihood that the symptoms are due to TTR-FAP, and the need for clinical certainty (in light of the clinical consequences of the diagnosis).

Symptomatic patients without family history of TTR-FAP, and whose biopsy results are negative, currently do not undergo further testing. Symptomatic patients without family history, and whose biopsy results are positive, undergo genetic testing.

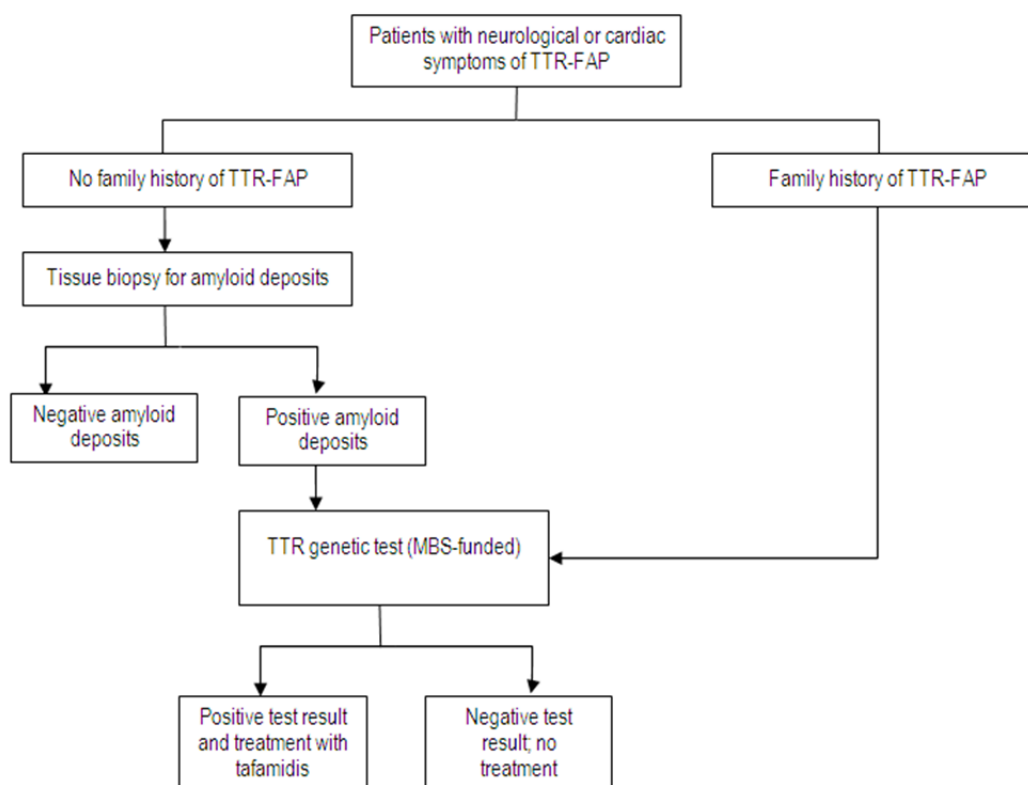
#### Proposed diagnostic pathway

The clinical diagnostic pathway with the proposed intervention is depicted in Figure 3, below. It is identical to the current actual management of symptomatic patients. However, in the proposed scenario, the TTR-FAP genetic test would be publicly funded and the patients would be treated with tafamidis.

Under the proposed pathway, symptomatic patients with family history would undergo genetic testing, bypassing the biopsy (as described above).

Symptomatic patients without family history of TTR-FAP would undergo biopsy. If the biopsy results are negative, these patients would not undergo further testing. If the biopsy results are positive, the patients would undergo further genetic testing, in order to confirm the results.

Figure 3: Proposed diagnostic pathway



## Comparator

TTR genetic testing is being proposed for access to tafamidis (the Applicant intends to submit an application to PBAC for the funding of tafamidis). Although TTR genetic testing is currently accessible in Australia through research laboratories, it is not listed on the MBS. Therefore, the appropriate comparators here are: genetic testing and treatment with tafamidis versus no genetic testing and standard care (that is, the proposed diagnosis and treatment vs. the diagnosis and treatment as they are currently funded by the MBS).

## Clinical claim

The clinical claim is that patients who test positive for TTR mutation via genetic testing and undergo subsequent treatment with tafamidis will have superior health outcomes and non-inferior safety outcomes in comparison to patients who do not undergo genetic testing and receive standard care.

Table 2: Classification of an intervention for determination of economic evaluation to be presented

		Comparative effectiveness versus comparator				
		Superior	Non-inferior	Inferior		
Comparative safety versus comparator	Superior	CEA/CUA	CEA/CUA	Net clinical benefit	CEA/CUA	
				Neutral benefit	CEA/CUA*	
				Net harms	None^	
	Non-inferior	CEA/CUA	CEA/CUA*	None^		
	Inferior	Net clinical benefit	CEA/CUA	None^	None^	
		Neutral benefit	CEA/CUA*			
Net harms		None^				

Abbreviations: CEA = cost-effectiveness analysis; CUA = cost-utility analysis

\* May be reduced to cost-minimisation analysis. Cost-minimisation analysis should only be presented when the proposed service has been indisputably demonstrated to be no worse than its main comparator(s) in terms of both effectiveness and safety, so the difference between the service and the appropriate comparator can be reduced to a comparison of costs. In most cases, there will be some uncertainty around such a conclusion (i.e., the conclusion is often not indisputable). Therefore, when an assessment concludes that an intervention was no worse than a comparator, an assessment of the uncertainty around this conclusion should be provided by presentation of cost-effectiveness and/or cost-utility analyses.

^ No economic evaluation needs to be presented; MSAC is unlikely to recommend government subsidy of this intervention

## Outcomes and health care resources affected by introduction of proposed intervention

### Clinical outcomes

This assessment will consider the following outcomes:

Safety:

- Any adverse events arising from the genetic test

Analytic performance of TTR genetic test

- Specificity
- Sensitivity

- Positive predictive value
- Negative predictive value

#### Effectiveness (of Tafamidis)

- Neuropathy Impairment Score changes
- Norfolk Quality of Life changes
- Modified BMI changes
- Changes in composite endpoints, measuring small and large nerve fibre function

PASC also requests details on:

- The number of patients being tested per case of TTR-FAP detected
- The number of patients being tested per case of TTR-FAP treated
- The cost of testing per case of TTR-FAP detected
- The cost of testing per case of TTR-FAP treated

#### Health care resources

Should TTR genetic testing be listed on the MBS, the following resources would also be required in order to deliver the test: specialist physician consultation, genetic counselling, collection of the blood sample (patient episode initiation fee), sample transfer fee (P11), delivery of the test, and analysis and reporting of test results by a specialist pathologist.

The listing of TTR genetic testing on the MBS (and the availability of tafamadis treatment) would likely result in increased use of these healthcare resources.

The health care resources are listed in table 3, below.

Table 3: List of resources to be considered in the economic analysis

	Provider of resource	Setting in which resource is provided	Proportion of patients receiving resource	Number of units of resource per relevant time horizon per patient receiving resource	Disaggregated unit cost					
					MBS	Safety nets*	Other govt budget	Private health insurer	Patient	Total cost
<b>Resources provided to deliver proposed intervention</b>										
- Specialist consultations	Specialist physician	Outpatient								
- Genetic counselling	Genetic counsellor	Outpatient								
- Blood sample (and Patient Episode Initiation fee)	Technician	Outpatient								
- Sample Transfer Fee (P11)										
- Perform TTR genetic test	Specialist pathologist									
- Analysis and reporting of result	Specialist pathologist									
<b>If TTR positive, patient is eligible for treatment with tafamidis</b>										
- Specialist consultation	Specialist physician	Outpatient								
- Cost of tafamidis										
<b>Resources provided in association with the proposed intervention – TTR genetic testing and treatment with tafamidis</b>										
- Specialist consultation	Specialist physician	Outpatient								
- Tissue biopsy (and Patient Episode Initiation fee)	Specialist pathologist	Outpatient								
<b>Resources provided to deliver the comparator – diagnosis and treatment currently funded by the MBS</b>										
- Specialist consultation	Specialist physician	Outpatient								
- Tissue biopsy (and Patient Episode Initiation fee)	Specialist pathologist	Outpatient								
- Immunochemistry	Specialist pathologist	Outpatient								
<b>If TTR protein identified, patient receives usual care</b>										
- Specialist consultations	Specialist physician	Outpatient								
- Cost of usual care (a)										

\* Include costs relating to both the standard and extended safety net.

(a) Defined as symptomatic management and orthoptic liver transplant if eligible

NB: Genetic counselling is not currently MBS-listed (it may be partially or fully funded by the States, however).

## Proposed structure of economic evaluation (decision-analytic)

Table 4: Summary of extended PICO to define research question that assessment will investigate

Patients	Prior tests	Intervention	Comparator	Reference standard	Outcome claims
1. Patients without family history of TTR-FAP, who have neurological or cardiac symptoms of TTR-FAP, and biopsy-proven amyloid	Tissue biopsy	Genetic testing for TTR mutations and use of tafamidis in patients with confirmed TTR	No genetic testing and standard care*  *Standard care includes symptom management and orthoptic liver transplant with lifelong immunosuppressants (for eligible patients)	Not available	<p><i>Safety:</i> Any adverse events arising from the genetic test</p> <p><i>Analytic performance of the test</i></p> <ul style="list-style-type: none"> <li>- Specificity</li> <li>- Sensitivity</li> <li>- NPV</li> <li>- PPV</li> </ul>
2. Patients with family history of TTR-FAP, who have neurological or cardiac symptoms of TTR-FAP	N/A	Genetic testing for TTR mutations and use of tafamidis in patients with confirmed TTR mutation			<p><i>Effectiveness:</i></p> <ul style="list-style-type: none"> <li>- Neuropathy Impairment Score</li> <li>- Norfolk QoL (Diabetic neuropathy)</li> <li>- Modified BMI</li> <li>- Composite endpoints measuring small and large nerve fibre function</li> </ul> <p><i>PASC also requests details on:</i></p> <ul style="list-style-type: none"> <li>- # patients tested per TTR-FAP case detected</li> <li>- # patients tested per TTR-FAP case treated</li> <li>- cost of testing per case detected</li> <li>- cost of testing per case treated</li> </ul>

## Decision analytic tree

Decision analytic trees compare the clinical pathway without publicly-funded genetic test for TTR, to the clinical pathway with a publicly funded TTR test. Figure 4 reflects the clinical pathway for symptomatic patients with family history of TTR-FAP, and Figure 5 reflects the clinical pathway for symptomatic patients without family history of TTR-FAP.

Figure 4: Decision analytic tree for symptomatic patients with family history of TTR-FAP

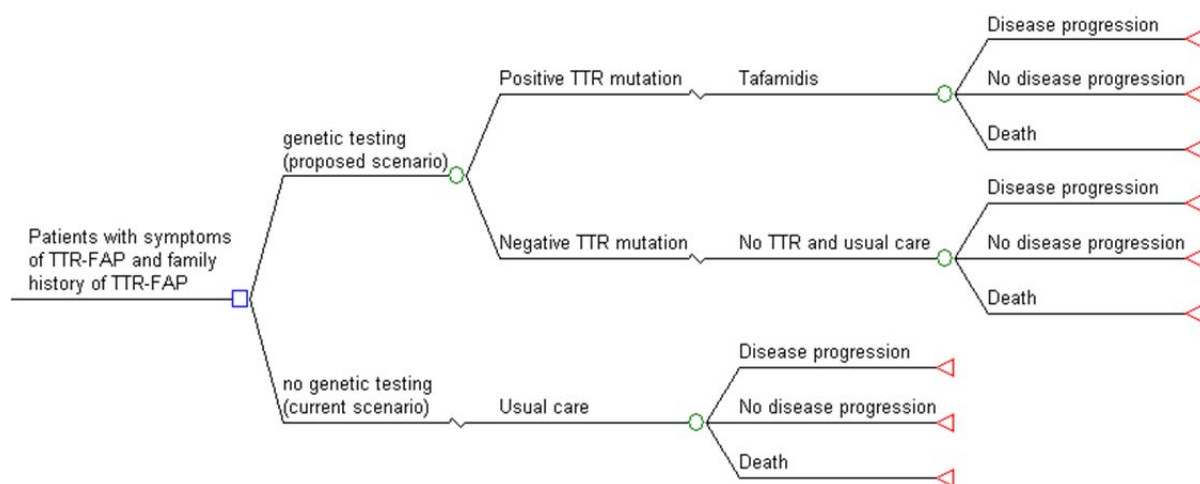
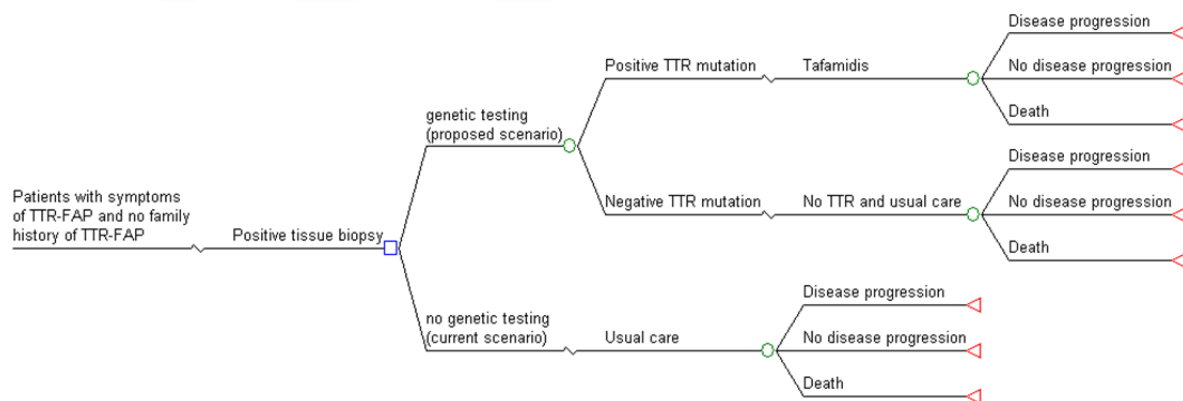


Figure 5: Decision analytic tree for symptomatic patients without family history of TTR-FAP



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