TANDVÅRDS- OCH
LÄKEMEDELSFÖRMÅNSVERKET

How should we assess and pay?

Health-economic assessments and payment models for precision medicines and ATMPs

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Preface

‘Sweden is to be a leading Life Sciences Nation’ the government declared in its National Life Sciences Strategy. The implementation of precision medicines and ATMPs in Swedish health care is being emphasised as a vital component of this development.

For such implementation to be sustainable, a key piece of the puzzle is to have appropriate methods of assessment, pricing and payment in place. Consequently, the government’s 2020 appropriation directive assigned TLV to develop health-economic methods for precision medicines and investigate potential ATMP payment models. This report is a summary of the work that was conducted in the course of this government assignment.

In this report, TLV describes and analyses, from its perspective, the primary challenges associated with evaluating and paying for products within precision medicine and ATMPs. We also provide several proposals on solutions, as well as our opinion of what future efforts should focus on. One of our most important conclusions is that providing these new technologies to Swedish patients – at a reasonable cost for the public sector – is requisite on all parties concerned realising and assuming their responsibilities to find sustainable solutions. This pertains to companies that set the prices for their products, Sweden’s regions and health care providers that interact with patients, and government agencies that make decisions at a national level. TLV aims to assist with concrete solutions that proceed from the needs and conditions of our Swedish context. Our hope is that the analyses and conclusions presented in this report will contribute to this end, and in the long-term, become integral to the goals of the Life Sciences Strategy.

In the course of this work, TLV has maintained a continuous dialogue and cooperation with representatives from Sweden’s regions, industry, patient and consumer organisations, academia, other government agencies and stakeholder organisations. We would like to thank everyone who has contributed in various ways, to increasing our knowledge and understanding of the challenges and opportunities within this field. We look forward to continuing our collaboration!

Stockholm, April 2021

Agneta Karlsson
Director General, TLV

TLV (the Dental and Pharmaceutical Benefits Agency) is a government agency that works to achieve appropriate and cost-effective pharmaceutical utilisation and dental care, good access to pharmaceuticals in society and a well-functioning pharmaceuticals market. TLV makes pricing and subsidy decisions on pharmaceutical products and disposable products covered by benefits schemes, pharmaceutical market regulations and the trading margins of pharmacies, as well as high-cost protection schemes and reference prices for dental care. TLV's assignment includes providing supervision of the Act on Pharmaceutical Benefits (2002:160).

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Summary

Developments in precision medicine and advanced therapy medicinal products (ATMP) offer the hope of major health benefits for patients suffering from serious diseases. At the same time, the price for the treatments is often set to a very high level by the marketing pharmaceutical company, making the costs of use high. Not all new products provide sufficient health benefits to justify these high costs. As a result, health economic assessments to quantify what health benefits and costs can be expected are of key importance.

The essence of precision medicine is the ability to make more accurate diagnoses, risk assessments, and treatment choices. This means that patients can be given the correct diagnosis more quickly, which in turn means that a treatment can be implemented at an earlier stage. More precise information about an individual's disease also contributes to increased accuracy when choosing between treatment options – or when deciding that treatment should not be given at all, in cases where it would not be effective. Gene therapy, which is one type of ATMP, affects a gene sequence that cause disease or injury, and may have a potentially curative effect – sometimes for diseases that currently require lifelong treatment or for which no treatment currently exists. In brief, precision medicine and ATMP create opportunities for more effective healthcare, with increased health benefits for patients suffering from serious diseases.

At the same time, these treatments also challenge the existing system for health economic evaluations, payment, and financing. The evidence for the effect of these products often consists of data from trials with few patients, short follow-up, and no control group. How can TLV, as an HTA agency, assess the benefit of one treatment compared to an alternative treatment in these situations? How can TLV evaluate the value of diagnostic tests when they are just one building block of an entirely new testing and treatment strategy, and where the costs and health benefits of the subsequent treatments are decisive for the value of the test? When the payer (the healthcare provider) refrains from treating patients due to the risk of the treatment not meeting expectations – can we find ways in which the pharmaceutical companies and the payer can share the risks related to the effect of the treatment? In this report, TLV describes the challenges we consider to be most critical to health economic assessments of precision medicine and ATMP, and also provide suggestions for meeting some of these challenges. In addition, we outline our view of the opportunities for using new types of payment models for ATMP.

How do we separate the value of different products when the health benefits accrue from using them in combination?

One distinctive characteristic of precision medicine is the use of diagnostic, prognostic and treatment-predictive tests as an integral part of the treatment chain. This then raises questions about how to evaluate the costs and benefits of these medical devices. Among other things, TLV notes that if the introduction of a new

drug requires the use of a treatment-predictive test not normally carried out, the cost of this test must be included in the total treatment cost for the new drug in the health economic assessment. However, if the test is already being carried out on the patients in question, and the information from the test can be used for choosing between a range of subsequent treatments, then the cost of the test need not be added to the cost for the new drug.

We also reverse the perspective and ask ourselves the question: How should we assess the value of the treatment-predictive test that provides information about which drug to use? TLV concludes that the value of a treatment-predictive test is determined by the cost-effectiveness of the subsequent treatments. This makes it challenging to make full health economic evaluations, since they require a lot of information.

The emergence of precision medicine also means that targeted medicinal products are replacing a range of other "blunter", less effective, drugs. However, it is also common for precision treatments to be used as an addition to an existing treatment regime, which means TLV needs to assess an increasing number of combination treatments. A number of challenges arise if the drugs being used in combination are high-priced originator products. In this report, we discuss one of them: How should the total cost that can be accepted for the combination be allocated between the different products, i.e. what share of the total cost should each separate product be allowed to claim? TLV's view is that, as a starting point, at least one of the drugs must almost always be sold at a lower price than if it is used in monotherapy. Otherwise, the combination would be far too expensive.

TLV also suggests that the best way to resolve the issue of how the total acceptable cost for the combination should be allocated between the products is in negotiations between the companies selling the products in question. One reason is that the allocation must be made in such a way that the companies do not lose revenue when use of the combination is initiated, which may otherwise be the case. An agency such as TLV would have difficulty implementing such an allocation. Overall, TLV considers it important to address the challenges of pricing and payment that arise from the use of expensive drugs in combination. Part of the solution lies in more flexible pricing, i.e. that the price for a product in some circumstances should be allowed to vary between the different indications it is used for. TLV proposes collaboration with the regions and companies in order to continue to develop methods for this.

Additional value aspects of the treatment – what does the assessment include?

When it comes to patient values from precision medicine and ATMP, TLV considers it most important to include the two aspects that our preferred measure of health benefit, the Quality-Adjusted Life Year (QALY), intends to measure, namely the effect on health-related quality of life and life expectancy. These are also the type of values that precision medicine and ATMP are primarily expected to provide. But it is important to quantify them in precise enough a manner to accurately capture the benefits for the patient.

TLV does not draw any firm conclusions in this report in terms of whether there are grounds for including new aspects in our health economic evaluation and decision-making, nor in terms of which aspects might be relevant in such a case. However, one conclusion we do draw is that if a value aspect is important and ethically reasonable to consider, it should be included regardless of technology – that is, regardless of whether it concerns a precision medical technology, ATMP or any other type of technology. Another conclusion is that the main obstacle to identifying the value of precision medicine and ATMP will be the lack of evidence for how large the health benefits will be from various treatments and tests – compared to the alternative and in the long term.

Precision medicine will not lead to higher precision in the health economic assessments

Precision medicine is currently very much a question of using molecular tests to identify which patients can be expected to benefit from a treatment. To some extent, this means that there will be more certainty about the effect of a treatment. It also means that money is not spent on treatments for patients in cases where it will not be effective. Despite this, TLV does not currently consider health economic assessment of precision medicine to be associated with less uncertainty than assessments of other types of drugs, as there is often less clinical evidence available for precision medicine technologies. TLV also suggests that there will not necessarily be an improvement in cost-effectiveness, despite the ability to identify patients who will not experience an effect in advance. This is because the pharmaceutical companies are likely to adjust the pricing of the drugs to reflect the effect in the targeted patient group.

Precision medicine also means that the treatment will become more adapted to the individual. For the health economic evaluations, it can create a conflict between the relevance of the decision, which requires a fine-grained analysis, and the level of detail in the available data. This balance is discussed with a starting point in an example of a so-called tumour agnostic cancer drug which is used for many different cancer indications. TLV argues that it will often be reasonable to make separate calculations for different subgroups where the aspects we know differ between groups are varied, for instance survival prognosis or which product is the relevant comparator. However, there will often be cases where effectiveness data is not available for different subgroups, which makes it harder to vary the effectiveness parameter in a well-informed manner in the simulations.

How can we manage the uncertainties?

When TLV conducts health economic evaluations, all available information about the long-term health benefits of a new drug is used. In addition to results from clinical trials, what is likely based on medical and biological considerations is also taken into consideration. For ATMP in particular, however, situations of genuine uncertainty will arise, i.e. when there is basically no knowledge of the likely outcome in the long term. If payment for these one-off treatments is made in full at the time of treatment and the actual long-term health benefit for the patient is not as large as

expected, the cost may be significantly higher than actual health gain can justify. ATMP therefore involves a greater risk for the payer than pharmaceutical treatment given continuously. The health economic evaluation must therefore reflect this higher uncertainty.

First, TLV wishes to emphasise the importance that the assumptions made do not mean that all uncertainty is unidirectional. By this, we mean that it is not reasonable to make assumptions in such way that all possible deviations in clinical practice from the assumptions will result in a higher cost per health benefit. Therefore, it is rarely reasonable to assume a lifelong effect: the duration cannot be longer than lifelong, so the uncertainty is unidirectional with this assumption. Secondly, it is important that the health economic evaluation reflects the possibility of different outcomes. In this report, TLV describes several methods for how this can be achieved. One of the methods we suggest is that the presented base case scenario consists of a probability-weighted average of different calculations of cost per health benefit (QALY), where each calculation reflects one possible outcome. For example, instead of having a base case scenario based on a fixed duration of the treatment effect, the base case can be calculated as a probability-weighted average of different ICERs, where the duration of treatment effect varies. These probabilities can then be standardised to a certain extent in order to create transparency and facilitate consistent assessments, i.e. that equals are treated equally. Using this method, the calculation better reflects the genuine uncertainty that exists as well as the possibility of different outcomes.

A higher discount rate is another method sometimes proposed in order to deal with situations of major uncertainty in cost-benefit calculations for publicly funded investments. However, TLV considers this method to be too crude for dealing with uncertainty, and is nothing that is proposed here.

One possibility for the paying party and/or decision-maker in the face of great uncertainty over for instance health benefits, is to wait for a number of years before subsidising or recommending a treatment until better evidence is available. However, the consequences of waiting for treatment differ between diseases. Consideration should therefore be given as to whether the long-term health effects to patients from postponing treatment should play a role in how much uncertainty is accepted, i.e. that more uncertainty is accepted if the condition is such that patient health would seriously and permanently deteriorate in an irreversible way if treatment were to be postponed. TLV therefore intends to continue the investigation into this idea, as well as to develop a measure to quantify patient health loss from waiting for treatment.

New types of payment models should be tested – outcome-based models in particular

In this report, a payment model refers to an agreement between companies and payers whereby the actual price paid deviates from the official list price. The purpose of a payment model is to facilitate the use of a product at a reasonable cost from the perspective of both the payer and the company. The agreement concluded

between the marketing company and the payer can be a simple percentage refund. The agreement can also stipulate that the payment is not a fixed amount per package, but varies depending on health outcomes, indication, volume purchased, or some other parameter.

Outcome-based payment models based on observed health benefits in clinical practice are, in theory, an effective way of reducing the risk to the payer. They may facilitate the use of the drug in situations where the parties (e.g. the drug company and the payer) have different views on the expected health gains at the time of the health economic evaluation, since payment takes place when the actual benefit has occurred. In addition, other types of outcomes than health benefits can be used, such as the patient's possible future use of other expensive pharmaceutical treatments. However, there are several challenges to making outcome-based models work in practice.

In this report, TLV outlines a number of different payment models, the risks they address, and the conditions required to facilitate their use. TLV's view is that outcome-based payment models with staggered payment and long follow-up have the potential to address several of the challenges associated with one-off treatments with great uncertainty, such as ATMP. We also outline some of the key challenges to facilitating the implementation of these models. One challenge lies in the current limitations to measuring relevant treatment outcomes. Currently most endpoints that are potentially useful in outcome based payment models, are not routinely registered in nationally available health data registers. For in-hospital products, it is not even registered which patient receives which drug. Another challenge lies in the practical and administrative restrictions for the public sector to sign agreements for payment models – even though it is not entirely clear exactly how extensive these restrictions are. However, TLV notes that one prerequisite is that the agreement is formulated in a way that minimises the risk of ambiguities and the parties making different interpretations. TLV argues that the best way to take this work forward is to try to develop payment models and agreements for the new ATMPs that will be launched in the future, and by this gain experience of what works.

TLV makes some further conclusions about the use of outcome-based agreement models for ATMP. One is that dividing the payment over a number of years does not reduce the budgetary problems of the regions to a significant extent. The reason is that, in the face of a continuous influx of patients, the annual expenses of the payer do not decrease more than during the first years. However, TLV finds that staggered payment, in combination with an outcome-based model, can serve a purpose; it makes sure payment takes place when and if the health benefit occurs.

Another conclusion is that if the number of years of patient follow-up under the agreement is significantly shorter than the number of years the new drug is expected to provide health benefits, it will be difficult – although not impossible – to account for a significant part of the uncertainty using a payment model. Therefore, with a limited follow-up period, several conditions need to be met in order for a payment model to be able to provide a significant risk reduction for the payer. One is that there must be a predictor to provide a clear indication of the

future effect of the drug on the patient. This predictor variable should be measured at the end of the follow-up period. Another condition is that a large proportion of the payment should be made at the end of the follow-up period, and only if the predictor indicates good and long-term future effect.

TLV considers that the special characteristics of ATMP, with a large up-front cost at the time of treatment as well as a potentially long-term health benefit, could justify the central government taking a role of co-financier for these products. One reason is that the central government is better able to manage a situation with large temporary expenses than individual regions are – a challenge which will be more pressing if and when ATMPs for more common diseases are launched. The government can also alleviate the budgetary problem a region may experience if there is a high concentration of patients afflicted with a particular disease in that particular region. A further reason is that if the government considers a rapid and broad use of ATMP in Sweden to be important for research or industrial policy reasons, co-financing could be a way to prioritise these issues.

The costs for the products need to be reasonable in relation to the benefits
Health economic evaluations are an important tool when deciding whether or not to use a specific medicinal product. Sweden has a system with value-based pricing: the price has to be reasonable in relation to the health benefit compared to the treatment that the patient would otherwise receive. The evaluations and decisions have to abide by the three basic principles of the ethical platform put into law by the Swedish parliament: that publicly funded healthcare provision should respect the equal value of all people; that people with the greatest medical needs should receive a larger share of the available resources available for healthcare than other patient groups; and cost-effectiveness – that the costs should be reasonable from a medical, humanitarian and socioeconomic perspective.

Based on the ethical platform, TLV's conclusion is that there should not be any favouring of precision medicine and ATMP compared to other healthcare technologies. These technologies are part of the overall healthcare landscape. They must therefore be considered part of the rest of the system and included in the overall priority setting. While emphasising the benefits of these technologies, we have a responsibility as public sector stakeholders to safeguard the common resources and ensure as far as possible that the price we pay for the products is reasonable in relation to the benefits we expect to receive. The aim is to achieve the maximum possible health for the taxpayers' money.

What do we suggest as next steps?

The work to develop health economic assessments for precision medicine and ATMP, and to investigate the possibilities for actual implementation of payment models, needs to continue. TLV proposes that this work take place in continued collaboration with other stakeholders with a focus on the following:

- Investigate how to carry out evaluations of precision medicine tests that are simplified yet informative.

- Investigate whether the cost per QALY presented by TLV in the base case scenario for ATMP should consist of a probability weighting of calculations with different outcomes, and, if we conclude this is a good idea, how this should be done.
- Continue the discussion of whether patients' long-term health loss from waiting for treatment should affect how much uncertainty is accepted for a new treatment, and develop a measure to quantify the health loss.
- Combination treatments: continue to investigate how we make it possible to set different prices for different uses in some situations.
- Continue to investigate the possibilities for the public sector to enter national agreements for payment models.
- Develop concrete drafts of outcome-based payment models and contractual arrangements for ATMP, and analyse lessons learned and experiences.

Terms and concepts

Opportunity cost – the alternative use of a resource that is lost by choosing a particular action option.

ATMP – advanced therapy medicinal products – advanced therapies or advanced pharmaceutical therapies/therapy products, including gene therapies, somatic cell therapies, tissue-engineered products.

Pharmaceutical formulation – various forms of a pharmaceutical for administration to the body, such as by tablet, injection fluids or patch.

Payment model – in this report, the term refers to a situation where the payment for a pharmaceutical deviates from the official list price, and is not a constant amount per package, but may vary depending on the patient, indication, purchased volume, health outcome or other parameter.

CAR-T – a type of ATMP that is based on the activation of the patient's own T cells for the treatment of cancer.

Single-arm trial – a study without a comparator arm, which is also known as an SAT or 'uncontrolled study'.

Approved indication – the medical condition that may be treated with a pharmaceutical product approved by the Medical Products Agency or the corresponding European Medicines Agency.

Incidence – the number of people who fall ill with a disease over a period of time, such as one year.

Cost per QALY – a parameter that sets the difference in cost between two treatment options in relation to the difference in health (measured in terms of QALY, or 'quality-adjusted life year'). The abbreviation for this parameter is *ICER,* for *incremental cost effectiveness ratio.*

Quality-adjusted life year (QALY) – a measure of health that captures both life expectancy and health-related quality of life.

Pharmaceutical benefit – a pharmaceutical that is encompassed by a pharmaceutical benefits scheme is subsidised and included in the high-cost protection scheme, which limits how much a customer needs to pay for their pharmaceutical product.

Precision medicine – is defined in this report as diagnostics, treatment and prevention based on the individual patient's molecular profile. With respect to

pharmaceuticals and other therapies, TLV refers to precision medicine as a treatment where a molecular test controls the choice of treatment.

Prevalence – indicates the proportion of individuals in a population who have a disease or a condition at a given point in time.

Original pharmaceutical – the first pharmaceutical on the market that contains a specific active ingredient. These pharmaceuticals are patent protected and are thus not exposed to competition from generic equivalents for several years.

Randomised controlled trial – study with a 'control arm' for comparison, where lots are drawn to randomly assign the study's participants to either one or the other treatment. This type of study design yields results of high evidential value. Also referred to as an 'RCT'.

Regions – what were referred to as County Councils until 2019.

Real world data (RWD) – data generated in clinical practice in connection with utilisation. 'Real world evidence' (RWE) are the conclusions that can be drawn by analysing RWD. RWD is described in more detail in TLV's forthcoming report, *Developed follow-up using the National Service Platform.*

Subsidy – the portion of the cost of a pharmaceutical, that is publicly funded.

Orphan medicinal products – pharmaceuticals used to treat rare conditions and has received orphan designation from the European Medicines Agency.

1 Background and description of the current situation

1.1 Government assignment to TLV

TLV was commissioned by the government to develop health-economic assessments for precision medicines and to investigate potential payment models for gene and cell therapies (ATMPs).[1]

Within the framework of the assignment, TLV is to analyse and submit proposals on how to formulate health-economic assessments of precision medicines. The entire treatment sequence must be factored in and a special focus placed on analysing how a health-economic assessment can be performed for, for example, diagnostic tests, genetic testing and software, such as through Bayesian analysis, simulations or other methods that TLV deems to be relevant.

TLV is also to investigate how payment models for gene and cell therapies (ATMPs) can be developed to manage the high treatment costs and uncertainties associated with, for example, the long-term effects of ATMPs.

The assignment is to be reported to the Government Offices of Sweden by no later than 1 May 2021.

1.2 TLV's objectives and interpretation of the assignment

The Swedish Government's Life Sciences Strategy highlights the field of precision medicines and ATMPs as being at the core of Sweden's ability to become a world-leading life sciences nation. (1) This strategy highlights, among other things, the importance of optimising the time between market authorisation and roll-out of these products. The need for improved knowledge of how to manage costs and uncertainties, and improved conditions for health-economic assessments are also emphasised.

TLV's overall objective in this assignment, has been to collaborate with other actors to advance knowledge about health-economic assessments and payment models for treatments within precision medicines and ATMPs. The knowledge must be translatable into practical utilisation and be useful and relevant in a Swedish context, for example in the development of TLV's health-economic assessments and in the analysis of what payment models could be useful and feasible and in which situation. The hope is that in the long run, this will strengthen the opportunities for

[1] Appropriation directions pertaining to the 2020 budget year for the Dental and Pharmaceutical Benefits Agency, https://www.esv.se/statsliggaren/appropriation directive/?RBID=20589

health care providers to offer patients access to the treatments – equal opportunities throughout the country – at a reasonable cost to the public sector.

TLV's assignment concerns two different types of technologies: precision medicines and ATMPs. Chapter 3 describes what the concepts refer to and how they relate to each other. In this government assignment, TLV has chosen an approach based on the challenges that arise in connection with the introduction and use of these products. The challenges for precision medicines and ATMPs are partly different and partly similar – both in terms of which health-economic principles and methods are to be applied, and how they can be paid for.

Consequently, to be able to delimit the scope of this assignment, it has proceeded from the basis of products within precision medicines and ATMPs. There are many other relevant issues concerning health-economic considerations and pricing and payment models for medication, which have not been analysed within the scope of this assignment. However, many of the conclusions we draw in the report also apply to pharmaceuticals and tests that are not strictly classified as precision medicines or ATMPs, but which are associated with the same challenges.

TLV's basic assignment includes conducting health-economic assessments of individual treatments, tests on the products for which companies have applied for subsidies, or products for which the regions have requested health-economic data. The approach of this assignment has therefore been to analyse the issues based on the situations that TLV is faced with when performing health-economic assessments of individual products within precision medicines and ATMPs. When investigating potential payment models, we adopted a more comprehensive perspective. Here too, however, the starting point has been to find solutions based on individual situations. Consequently, questions about how precision-medicine and ATMP products affect health care at the system level, whether it is cost-effective to adapt health care to the utilise the products and how the overall funding should be designed, were not the focus of this assignment. Neither has TLV performed a legal analysis of how payment models may be used within the framework of public procurement.

1.3 Various actors in the current system for approval, valuation and payment

1.3.1 Decisions on market approval are made by EU pharmaceutical agencies

The regulatory requirements for the approval of the sale of pharmaceuticals entail the applicant company demonstrating that the benefits of the treatment outweigh its risks, which mainly consist of side effects. The benefit-risk assessment does not involve a comparison of the pharmaceutical's effectiveness relative to other pharmaceuticals, nor is it an assessment of whether the cost in relation to the health gain is reasonable.

Currently, decisions on the approval of new pharmaceutical products are usually made at a centralised European level and are the result of collaboration between national pharmaceutical agencies and the European Medicines Agency, EMA (2). According to EU Regulation (EC) No 726/2004, certain types of medical products must be approved through a centralised procedure, which results in simultaneous EU-wide authorisation. The assessment is made by consensus or a majority decision by representatives of all EU member states at the EMA. The European Commission then confirms the approval. For other products, it is optional for the company to choose a centralised procedure or one of the national procedures.

Most precision medical products developed today, as well as all advanced therapies (ATMPs) fall into one of the categories where market approval can only be granted through a centralised procedure, namely:

- biotechnological pharmaceuticals, including ATMPs
- orphan medicinal products
- certain fields of therapy:
- HIV/AIDS
    - cancer
    - neurodegenerative diseases
    - diabetes
    - autoimmune diseases
    - viral diseases.

A common feature of most precision medicines is thus their centralised market approval.

For some pharmaceuticals, there is the possibility of obtaining conditional marketing authorisation. Such approval requires less clinical data than is normally acceptable. The assessment here is that the benefits of rapid introduction and early availability of the pharmaceutical outweigh the risks of limited knowledge about the pharmaceutical. In connection with a conditional approval, the regulatory authorities require that a certain set of additional data be reported to confirm that a positive benefit-risk balance exists. An assessment of current data is then performed annually until the product is granted full approval, when all of the conditions are met.

Many precision medical products are characterised by conditional market approval.

1.3.2 TLV decides on the prices and subsidies of prescription products

TLV decides which pharmaceuticals and disposable products are to be included under pharmaceutical benefits schemes. The products included in the benefits are subsidised for all patients who receive them by prescription. TLV is tasked with safeguarding shared resources to ensure that they are used wisely, in order to achieve the best possible health for our taxes.

TLV's decisions are based on the ethical platform's three fundamental principles. (3) These are:

- the human-value principle – that health care must respect everyone's equal value
- the needs and solidarity principle – that those with the greatest medical needs shall have access to more health care resources than other patient groups
- the cost-effectiveness principle – that the costs for utilising a pharmaceutical shall be reasonable from a medical, humanitarian and socioeconomic point of view.

To assess whether the cost is reasonable, TLV applies a value-based pricing model. The basis for this is Sect. 15 of the Act on Pharmaceutical Benefits (2002:160) (hereinafter referred to as the 'Benefits Act'). The Benefits Act states that a prescription pharmaceutical must be covered by a pharmaceutical benefits scheme and that the purchase price and sales price must be set for the pharmaceutical, provided that the costs of utilising the pharmaceutical appears reasonable from medical, humanitarian and socioeconomic point of view. The cost per health gain is assessed relative to the treatment that the patient would otherwise have received. A socio-economic perspective is applied, which means that costs and savings are included regardless of whether they arise for the individual, the municipality, the region or the state. However, TLV does not apply what can be called the 'exhaustive socio-economic perspective,' the reasons for which are explained in section 5.4. Within the scope of the Benefits Act, TLV may develop established practice and, if necessary, change this practice. One such change that has been made is that TLV no longer factors in the production-output value of gainful employment – whether a treatment results in an individual's ability to return to work. Another change is that TLV sometimes takes into account that a medical condition is very rare.

Pharmaceutical companies choose whether they want to apply to TLV for a price and subsidy for the product in question. TLV assesses the product's benefit in relation to cost, as well as the medical condition's degree of severity. The three principles of the ethical platform are then balanced. For example, a higher cost per health gain is generally acceptable when the degree of severity is high. Within 180 days, proposals for decisions are submitted to the Pharmaceutical Benefits Board for a decision.

1.3.3 Within the framework of the hospital pharmaceuticals and medical technology assignments, TLV prepares health-economic assessments for the New Therapy (NT) Council and Medical Device (MTP) Council

Sweden's regions then work together to achieve the equal, cost-effective and appropriate utilisation of the new pharmaceutical agent. (4) One example of such national-level cooperation is the orderly introduction of pharmaceuticals. The New Therapy (NT) Council, is an expert group with representatives from Sweden's regions. The NT Council designates the pharmaceuticals that are to be included in the national collaboration model, and provides recommendations on how these pharmaceuticals are to be used. Most of the pharmaceuticals covered by the collaboration model are primarily requisitioned by health care providers. As companies generally do not apply for a subsidy from TLV for these pharmaceuticals, they are not covered by any pharmaceutical benefits schemes.

At the request of the New Therapy (NT) Council, TLV produces health-economic data for certain hospital pharmaceuticals. (5) The assessments are performed within the scope TLV's hospital pharmaceuticals assignment. The initiative is part of the National Pharmaceutical Strategy to develop a pricing, prioritisation and financing model that is sustainable for all pharmaceuticals.

The regions have a corresponding structure for medical devices. (6) (7) The Medical Device Council, ('MTP Council'), is a national expert group with regional and external health care representatives. The MTP Council has the opportunity to order assessments from TLV within its medical technology assignment.

TLV performs health-economic assessments for hospital pharmaceuticals and medical devices based on the same principles that are applied to benefit decisions. TLV's health-economic knowledge bases then provide the foundation for, among other things, the NT Council's and MTP Council's negotiations and decisions on recommendations. TLV does not make any decisions for these products.

1.3.4 What prices do pharmaceuticals that are requisitioned by health care providers receive?

Pursuant to Sect. 10 of the Pharmaceutical Benefits Regulation (2002:687), etc., TLV is to publish a list of the pharmaceuticals covered by pharmaceutical benefits schemes, as well as information about the prices that may be charged for these products. The prices set by TLV are thus, as a general rule, public information and can only be classified if there is support for such in one of the provisions of the Public Access to Information and Secrecy Act (2009:400) (hereinafter referred to as the 'OSL') or any law to which the OSL refers.

Pharmaceuticals that are requisitioned for health care providers are instead procured by the regions in accordance with the Public Procurement Act (2016:1145) (hereinafter referred to as the 'LOU'). In these cases, the regions are the decisionmakers and the procedure is governed by Public Procurement Act regulations. In the procurement procedure, a dialogue about prices is held between pharmaceutical companies and the regions, involving a tender and evaluation, or negotiations. The pharmaceutical prices that are set through a procurement procedure are not encompassed by the Pharmaceutical Benefits Regulation's requirement on publication.

Within the framework of the national collaboration model, joint negotiations are sometimes held with the companies that market pharmaceuticals. (8) For hospital pharmaceuticals, these negotiations are initiated by the NT Council. On the part of the regions, the objective is to obtain a discount that allows for the treatment to be assessed as cost-effective, based on the health-economic assessment provided by TLV. The negotiation may result in an agreement on the contractual terms and conditions. All regions are then given the opportunity to sign agreements based on these terms and conditions.

1.3.5 The state pays the regions for pharmaceuticals covered by benefits schemes; whereas for hospital pharmaceuticals, the budget and financing responsibilities lie with the regions

In 2020, pharmaceuticals under benefits schemes ('benefit pharmaceuticals') accounted for sales of SEK 35.5 billion and hospital pharmaceuticals for SEK 10 billion. Of these costs, society pays SEK 28 billion for benefit pharmaceuticals and the entire sum (SEK 10 billion) for hospital pharmaceuticals.

The regions receive a targeted state subsidy for the costs of benefit pharmaceuticals. This means that the regions do not have a financing responsibility for pharmaceuticals prescribed under benefits schemes. The subsidies are based on the National Board of Health and Welfare's annual forecast of costs for benefit pharmaceuticals. Allocation between the regions follows a needs-based model that factors the population and composition of the regions. Consequently, each region does not receive a subsidy that corresponds precisely to the region's actual cost.

The regions finance hospital pharmaceuticals through county council taxes and the general state subsidy, and thus hold a financing responsibility for these pharmaceuticals.

1.3.6 The use of pharmaceuticals is largely governed by decisions and recommendations at a national level

The NT Council thus designates the pharmaceuticals that are to be included in the national collaboration model, and provides recommendations on how these pharmaceuticals are to be used. (9)

The regions conduct *horizon scanning* activities, to systematically map the new pharmaceuticals and indications that may be relevant for introduction in the next few years. Pharmaceuticals that, according to certain region-specific criteria, are deemed to have an impact on health care are described in an early assessment report that is communicated to the region. (9) Since 2009, these efforts have been undertaken by a working group within the four-county group: Region Stockholm, the Skåne Regional Council, Region Västra Götaland and Region Östergötland. Horizon scanning provides the regions and the NT Council with a basis for deciding whether a pharmaceutical should be managed through national collaboration in a joint process for its orderly introduction or whether it should be managed by each individual region.

To identify and select the pharmaceuticals where national collaboration is most crucial, there are a number of criteria as guidance. If a pharmaceutical product meets a criterion, it has been considered suitable for national collaboration. (9) The criteria are as follows:

- Large patient population.
- Significant morbidity associated with the health condition.
- Potential to add clinical benefits.
- Innovative method of treating the disease.
- Potential cost consequences.
- May lead to the need for reorganisation of care.

- Potential for influencing treatment guidelines and other recommendations.
- Potential safety aspects to consider.
- Potentially high media/patient interest.
- Introduction will be too fast or too slow following market authorisation.
- Potentially legal, ethical or political interest.

Consideration is also given to whether the substance/indication
- belongs to a growing group of pharmaceuticals or field of therapy
- is a new treatment method or is a new group of pharmaceuticals
- is relevant to Swedish conditions
- is in late Phase II or in Phase III of the clinical trial, or has been submitted to regulatory bodies for market authorisation.

ATMPs are a product group that meets the criteria for national collaboration.

Subsidy decisions from TLV and recommendations from the NT Council are of importance to how pharmaceuticals are assessed and utilised in health care. However, decisions about which patients should receive what pharmaceuticals, whether the patients should receive treatment and, if so, at what stage, are made by each region and thus not by TLV or the NT Council.

1.4 Cost effectiveness as a basis for decisions

Health-economic assessments provide important decision data for TLV when companies apply for a price and subsidy for a pharmaceutical product. Assessments must take into account numerous analytical considerations. These pertain to everything from relevantly defining the decision problem – which treatments should be compared and for which patient group –to making assumptions about the long-term effectiveness of treatments based on data from trials with short follow-up periods.

Modelling analysis has become the standard method for addressing all of the factors that impact costs and health gains. Depending on the nature of the assessed treatments and access to data, the end result of the analysis may be associated with a greater or lesser degree of uncertainty.

1.4.1 Decision problematisation, outcome parameters and relevant costs

The first step in a health-economic assessment is to problematise the decision, which must be clearly analysed. What treatments or preventive measures should be compared and which patient groups are impacted by the measures? Figure 1 shows a simple sketch of a decision problem, where a treatment is compared with an alternative treatment (which usually refers to the current standard treatment in routine clinical care) for a patient population. By estimating the costs and health gains of the assessed alternatives, the cost per QALY (ICER) can be calculated.

$$ICER = \frac{Cost\ (treatment) - Cost\ (control)}{Effect\ (treatment) - Effect\ (control)}$$

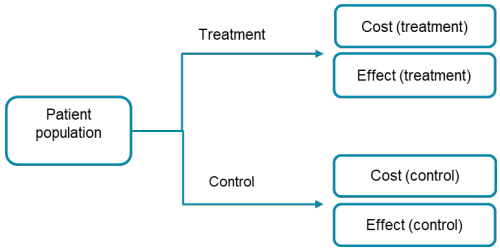


Figure 1. Illustration of decision-problem and cost-effectiveness analysis.

Usually, the treatment in the simplified sketch is a new treatment, for example a new pharmaceutical agent that is the object of a price and subsidy application to TLV, while the comparison alternative can be another active treatment or only the best subsidiary treatment. Problematising the decision is not always as simple as illustrated in the above sketch, and several challenges emerge when assessing precision medicines.

An example of such a challenge is that the treatment alternative is not necessarily a distinctive therapy, but may include a sequence of interventions comprising diagnostic tests and customised treatment. Furthermore, precision medicine by definition entails a narrowing, often a substantially, of the patient group that is to be treated, which can lead to challenges, both in defining the relevant patient population and in estimating costs and health gains, since decreases in the size of patient groups decrease the available data.

In addition to well-defined decision problematisation, it is necessary to decide what is a relevant effectiveness parameter and what costs are to be included in the analysis. The effectiveness parameter generally used in health-economic assessments is the Quality-Adjusted Life Year (QALY). One reason for its frequent use is that it enables comparisons between different medical conditions.

In terms of costs, the basic principle is that all consequences, regardless of where in society they may occur, should be taken into account. Costs for hospital admissions, visits to outpatient and primary care and pharmaceuticals are generally charged to the regions' budgets and are usually referred to as health care costs. Social care and rehabilitation costs can also reasonably be regarded as health care costs and are essentially charged to municipality budgets with the current organisational set up. Costs may also be borne by the individuals themselves, or by relatives or other parts of society due to an impact on functional and work capacity. Note that due to legislation and other circumstances, various decisionmakers may not always factor all the costs when making decisions.

1.4.2 Time horizon

The effectiveness of treatments may impact health well into the future, either directly, through long-term treatment effectiveness, or indirectly, when a treatment prevents a negative health outcome such as a stroke from occurring today, which could impact expected survival and quality of life in the future. Therefore, the costs and QALY of different treatment alternatives often need to be calculated across a

relatively long period of time. Consequently, many health-economic assessments utilise a lifetime perspective.

With a longer time horizon for the analysis, it follows that both costs and effects will arise in different time periods. To manage this, costs and effects need to be discounted to a common reference year. The basic principle of discounting is that costs and health effects that occur in the future are valued lower than if they occur in the present(10). Although the arguments for discounting are not explored in detail here, it is relatively uncontroversial that future consequences are generally discounted in assessments, not just within the health sector(11). A frequent subject of discussion is how high a discount rate should be applied, whether it should be constant over time and whether the same discount rate should be applied to costs and health effects.

1.4.3 The analytical method

Data from clinical trials often forms the basis for cost-effectiveness analyses. Modelling analyses are usually applied to amalgamate clinical trial data with data from other sources, to enable the extrapolation of costs and effects over time, as well as to extrapolate intermediate disease-specific outcome parameters to more general health outcomes such as QALY. Since all relevant evidence for problematising a decision is rarely found in a trial with a sufficiently long follow-up period, modelling analyses have become the key approach. Although this does not contradict the fact that controlled experiments (Randomised clinical trials) are an important study design for investigating, above all, relative treatment effectiveness, modelling analyses often require more information than what is available from randomised control trials.

In order to estimate relevant costs and QALY, a number of analytical choices must be made. We have already mentioned the time horizon for the analysis. The structure of the model also needs to be determined. This includes deciding which clinical events and health conditions must be included in the model to describe and simulate the natural course of the disease, and the impact of treatments on the disease's natural sequence, in accordance with up-to-date information about the disease. It is often a question of how detailed the modelling of disease's progression needs to be, in order to generate relevant and credible results.

Health-economic concepts
In a *health-economic assessment* of a medical intervention, health gains and costs are quantified. Health gains are often expressed in units of QALY *(Quality-Adjusted Life Year)*, a measure that captures both life expectancy and health-related quality of life. The result of the assessment is expressed as *cost per gained QALY*, abbreviated *ICER (Incremental Cost Effectiveness Ratio)*. It shows the additional costs required to achieve an additional unit of health, 1 QALY, if the treatment is administered, instead of the comparison alternative.

The estimated ICER is used to assess whether a treatment is *cost-effective*. If the ICER is below the decisionmaker's acceptance threshold, the treatment is said to be cost-effective,

where the accepted level relates to how much benefit the funds would provide if they had been used for something else – known as the *opportunity cost*. If the cost of the treatment is lower than the opportunity cost, it is thus said to be cost-effective.

Consequently, a health-economic assessment is often referred to as a cost-effectiveness analysis, despite a certain difference in meaning. If we are to interpret the term strictly, cost-effectiveness should be used dichotomously: either a treatment is cost-effective or it is not. However, treatments are often expressed as being more or less cost-effective, in which case the cost per QALY is regarded as low or high. In this report, we sometimes use the term in this manner.

Pursuant to the Pharmaceutical Benefits Act, TLV must approve an application for a price and subsidy for a pharmaceutical product, if the *cost is reasonable* from a medical, humanitarian and socio-economic point of view, and taking into account the ethical platform of health care.

TLV uses estimated cost per QALY as a basis for assessing whether the cost is reasonable. However, reasonable cost is not synonymous with cost-effectiveness– even if TLV occasionally uses the term in this manner. Reasonable cost also includes considerations other than economic efficiency. For example, TLV accepts that treatments of serious conditions cost more per QALY than treatments of mild conditions, which reduces the overall cost-effectiveness of health care resources, compared with if the same level were to be applied regardless of the severity of illness. However, this would still be acceptable for other reasons, and it is consistent with the ethical platform that prioritisation must take into account the severity of the disease.

1.5 Several precision medicines and ATMP products are expected to be introduced in the next few years

1.5.1 Horizon scanning initiatives can provide the health care system with the prerequisites to prepare for future cost challenges

Horizon scanning involves the collection, documentation and assessment of information about new pharmaceuticals and indications prior to their approval. This enables the party responsible for providing and paying for care to gain better foresight into the work of preparing care providers for the introduction of new pharmaceutical products. Advance planning creates better conditions for managing future cost challenges and preparing for resource redistributions. This in turn, can ensure good and equal access to new pharmaceuticals. Horizon scanning provides the regions and the NT Council with a basis for deciding whether a pharmaceutical should be managed through national-level collaboration, in the joint process for orderly introduction (refer to section 1.3.6).

1.5.2 According to industry estimates, ATMPs for a dozen disease areas are expected to be introduced over the next five years

The Pharmaceutical Industry Association (LIF) has scanned the horizon within the field of ATMPs to help clarify and predict specific therapy areas and individual

products that are in the development phase. In addition, on behalf of the pharmaceutical company Pfizer, Re-Think has performed an analysis to identify products that are presumed to be on the verge of market introduction, and their expected sales volumes (12). This was rendered as a function of the expected number of patients and a rough assumption was made about the product's future price.

The results from these two horizon scanning initiatives provide similar answers as to which disease therapies and products can be expected reach the market in about the next five years. Below is a list of the disease groups that are expected to result in the largest cost volume (i.e. number of patients multiplied by assumptions about price) in Odmark's report. (12)

Disease groups (number of products in the pipe-line):
- Parkinson's (6)
- cystic fibrosis (2)
- haemophilia (11)
- Huntington's (1)
- ALS (1)
- frontal lobe dementia (2)
- AMD (6)
- cardiac insufficiency (1).

For several disease areas, there are also products in later research phases, but which have a slightly less expected total cost volume. Examples of these are treatments that are linked to skin, blood, muscles, eyes, ears, neurology and metabolism. In addition, there is a large group of products under the heading, 'other diseases'.

1.5.3 How widespread are ATMPs expected to be used in the next few years?

The Odmark report contains several sections that are relevant to TLV's government assignment, and the reasoning below is largely based on the information presented by Odmark. The report uses the term gene therapies (which is included under the term, ATMP), and Odmark has estimated the extent of the costs for treating Swedish patients if and when the products that are currently in the research phase are approved. The study emphasises that all cost estimates are highly uncertain and that they were based on assumptions made about the number of patients with a specific disease, and the percentage of these patients who will actually benefit from a pharmaceutical treatment. An assumption about the future price of pharmaceuticals factors in the severity of the disease, the availability of other treatments and the form of gene therapy in question. The pharmaceuticals are then placed in either of two categories: the lower price level, approximately SEK 7 million per patient, or the higher price level, approximately SEK 20 million per patient.

Based on horizon scanning and assumptions about patient sample sizes and price levels, the author estimates that the total (accumulated) cost of new gene therapies – i.e. a subset of all ATMPs – will be a little over SEK 20 billion in total over the next ten years. The author's insertion of a complementary assumption of a 50 per

cent probability that each product will succeed in obtaining market approval, brings the cost to approximately SEK 11 billion. As mentioned, these assumptions are associated with several material uncertainties, the most material being: which specific indications will each product actually be approved for, and the prevalence and incidence of these indications. It is worth noting that the cost estimate does not include the two disease groups that comprise the largest number of patients (Parkinson's disease and heart failure), as the author deemed that estimates of treatable subgroups will be too complex for these areas of study.

Based on the assumptions and analyses in Odmark's report, it appears that several factors will impact the utilisation of various pharmaceuticals. Assumptions about the degree of incidence and prevalence will be decisive for the number of patients and total costs. An assumption of high costs may need to be qualified, and two different scenarios can be used to predict how the costs will arise over time. Scenario 1: a high prevalence (the number of patients who currently have the disease) and a low incidence (the number of newly diagnosed cases each year) indicates that there will initially be a larger group in society that requires treatment, but that few will subsequently fall ill within each time period. This leads to a significant initial cost hump, followed by lower costs in the longer term. Scenario 2: a high incidence but low prevalence indicates that a larger group falls ill within each time period, which then results in the same (higher) costs in the longer term.

According to the Odmark report, another factor that will be important is whether the disease is curative or disease-modifying. Some diseases are monogenic, that is, they are caused by mutations in *one* gene, which increases the chance of finding a cure. Other diseases are due to mutations to *several* genes. For a third group of diseases, we are unfamiliar with the mechanisms that cause them. In the latter cases, the treatments are often symptom-relieving, and in some cases they will mainly work by enhancing the effectiveness of an existing treatment. For a monogenic disease without good existing treatment, it can be assumed that the treatable patient group will be larger and the value of the treatment higher.

The report also emphasises that there are uncertainties about how many patients will receive treatment and generate costs without obtaining the desired or expected medical effect. One reason for this may be what is known as 'vector immunity', which refers to a patient acquiring immunity against the current carrier of the gene treatment (the vector). Much more experience and knowledge is needed about the risks of indication shifting, the utilisation of the new therapies in addition to existing ones (and sometimes very costly therapies), etc.

TLV welcomes the attempts made to estimate the extent of the utilisation of the products moving forward. At the same time, we see a need for continued horizon scanning in the field, including refined computations of the prevalence of various diseases. There are additional aspects that can reasonably impact both the costs of the pharmaceuticals and the number of patients who receive the treatments, and which TLV deems to be missing in the reasoning of the Odmark report. One such aspect is the extent to which these treatments will cause side effects and adverse effects. This will potentially affect both how the costs develop and how willing

patients will be to commence treatments. Another aspect is whether competition arises. In some disease areas, there are several pharmaceutical candidates that have come a relatively long way in their development. One example is the ‘bleeding disorder’, haemophilia. How the launch of several competing products may affect price levels and costs in this area is very difficult to assess at present.

2 How the assignment was implemented

2.1 The assignment was implemented based on TLV's perspective of the challenges

Sweden currently has a system for pharmaceutical pricing and subsidies that works well in many respects, but with the rapid pace of development, new therapies such as ATMPs and precision medicines are challenging the system.

In this government assignment, TLV has proceeded from some of the typical characteristics of precision medicines and ATMPs, and formulated questions based on the challenges that arise. The framework in Figure 2 provides an overview of the four themes we have divided the issues into, and the following sections provide an introduction to these themes and list the respective issues.

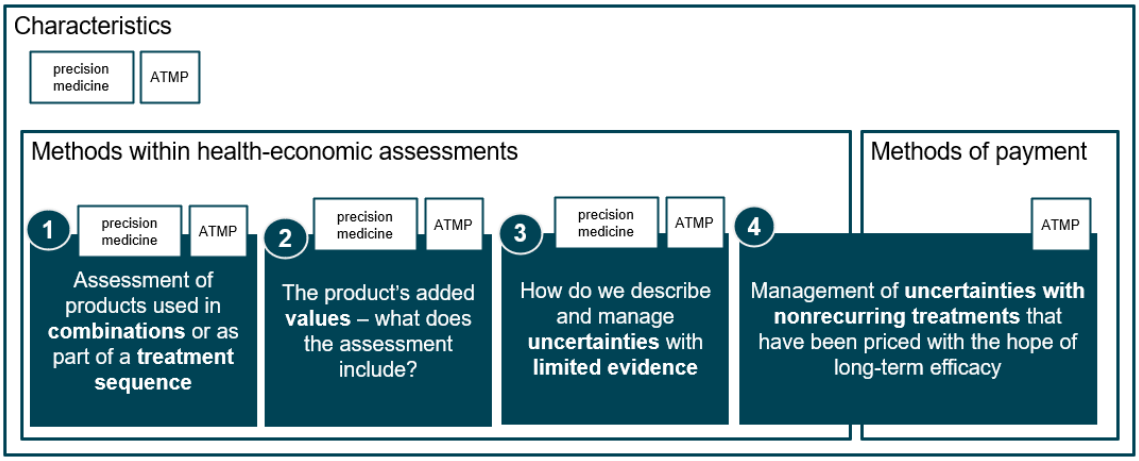


Figure 2. Theme for the assignment's formulated questions

The terms precision medicine and ATMP overlap in some aspects and many products can be categorised under both definitions. Precision medicine is a broader concept and encompasses much more than just ATMPs. Furthermore, some ATMPs are utilised without being preceded by a genetic test or other molecular profiling and should therefore not be described as precision medicine.

Although most of the challenges identified through this assignment (which are based on the characteristics of the products) are important for both precision medicines and ATMPs, some apply specifically to either one or the other. The challenges surrounding health-economic assessments apply broadly to both precision medicines and ATMPs. However, in the discussion about the opportunities offered by new types of payment models, we focus on nonrecurring treatments that are priced with the hope of a long-term effect, which mainly applies to ATMPs.

TLV would like to point out that many of the challenges addressed in this assignment are not new. For example, TLV's day-to-day activities include performing health-economic assessments based on limited evidence of a pharmaceutical's effectiveness, and there has been an ongoing discussion for many years about whether the QALY parameter captures the relevant aspects of a treatment's health gains. However, the fact that the challenges are particularly pronounced and that several of them coincide with these treatments warrants that we address them in this report.

2.1.1 Theme 1: Assessment of products used in combinations or as part of a treatment sequence

By definition, precision medicine entails that treatment sequences are tailored to the individual patient, both in terms of what pharmaceuticals are combined and the order in which they are administered. Many of the pharmaceuticals also require the use of a medical device, which also contributes to the overall health gain.

In a health-economic assessment, the health gain is calculated based on a product's utilisation, which is then set in relation to the cost. However, if two different products are needed to create the health gain, or if an intervention is one of several components in a treatment sequence, how do we measure the value of each intervention separately? Or, in other words, how do we estimate the contribution of an individual product to the total health gain?

The formulated questions discussed in this area include the following:

- How and when should the cost of treatment-predictive tests be included in a health-economic assessment of the subsequent treatment?
- What are the basic factors that determine the value of treatment-predictive tests that provide information about what pharmaceutical to use?
- Should TLV develop guidelines for how the total health gain of combination therapies should be distributed between the individual pharmaceuticals?

2.1.2 Theme 2: The treatment's added values – what does the assessment include?

There is an ongoing discussion that precision medicines and ATMPs generate new types of parameters that should be included in health-economic assessments. For example, precision medicine entails that patients receive the right treatment more quickly or that the treatment is more targeted. ATMPs may also entail the patient being potentially cured of their disease.

Some formulated questions discussed in this area are as follows:

- What patient benefit is particularly clear for precision medicines and ATMPs?
- What is important to consider before new value aspects are included in the health-economic assessment and factored into decisions and recommendations?

2.1.3 Theme 3: How do we describe and manage uncertainties?

Today, market approval of new therapies is often granted based on limited information about the pharmaceutical's clinical effectiveness. This is especially true for pharmaceuticals aimed at rare and serious diseases, with no previously existing efficacious treatments.

Clinical trials are primarily designed to provide evidence of the pharmaceutical's safety relative to its effect, which is required for regulatory market approval. However, to perform a useful health-economic assessment, more information is needed about its long-term effect, compared with the treatment that the patient would otherwise have received. Consequently, a health-economic assessment must often be based on qualified assumptions about the long-term clinical effectiveness of the pharmaceutical product, which for natural reasons, will be characterised by uncertainty.

The issues discussed in this area are as follows:

- What do we mean by uncertainties and what types of uncertainties are important to distinguish?
- What should be the basis for choosing the level of subgroup analyses when performing assessments? What evidence is there for the different subgroups?
- How can the estimated cost per QALY reflect genuine uncertainty, i.e. factors on which no evidence-based assumptions can be made, such as the duration of effect for ATMPs?
- Is there reason to accept greater uncertainty in some situations than others? Is there therefore reason to estimate the consequences for patients of holding off on a treatment? If so, how can this be done?

2.1.4 Theme 4: Management of nonrecurring treatments that have been priced with the hope of long-term effectiveness

ATMPs are often a one-time treatment with the potential for long-term health gains and, sometimes, to be a cure. A risk arises for the payer (Sweden's regions), because the pharmaceutical agent is administered on a single occasion and is priced at a level that assumes that the patient will experience high effectiveness for a long period of time, while no guarantees are provided for the effectiveness of the treatment. If the full price is paid for everyone who receives the treatment, there is a risk that the pharmaceutical's utilisation will not be cost-effective – that the health care system will pay too much for patients who do not gain solid long-term effectiveness. This risk could entail the health care system opting not to utilise the therapies, despite the potential of some patients achieving significant health gains.

Payment models where the amount paid reflects the actual realised health gain could in theory fix the problem. However, this presupposes that the pharmaceutical company and payer succeed in agreeing on a contract based on such a payment model. The challenge is to make such a contractual solution work in practice.

The issues discussed in this area are as follows:

- What are the main challenges for the cost-effective use of ATMPs? What could lead to underuse and overuse?

- What risks could different types of payment models manage?
- What are the experiences of other countries from using performance-based payment models?
- What payment models could potentially be useful for ATMPs?
- What prerequisites must be in place for the payment models to be applicable in Sweden?
- How should performance-linked payment models be designed to effectively reduce the payer's risk?

2.2 Various methods have been used to answer the questions of this assignment

2.2.1 Most analyses have been based on literature, modelling and internal and external collaborations

In many respects, the starting point for the investigation has been the issues and situations that TLV is faced with on a daily basis. An important part of the work has thus been to involve health-economic and medical expertise at TLV, in order to utilise the available knowledge and experience. To conduct the investigation, TLV examined relevant health-economic literature, which was discussed and analysed. We performed some of our own theoretical analyses and received external assistance in conducting certain health-economic simulations.

TLV has collaborated with two groups of economic researchers. The first group consisted of Martin Henriksson and Lina Gruneau at Linköping University's Centre for Medical Technology Assessment. Their work is reported in a separate background report that describes the basics of health-economic assessments in detail, with a focus on precision medicines. The second group comprised Mats Bergman, Jonas Björnerstedt, both at the School of Social Sciences, Södertörn University, and Johan Stennek at the Department of Economics, University of Gothenburg. This group has analysed questions about how ATMPs should be evaluated and paid for from a theoretical national-economic perspective, and reflected on how similar problems are solved in other markets. Their work is presented in two separate background reports. All background reports are independent of TLV's report and each author is fully responsible for their conclusions and content. A database from the University of Washington was used to provide an international outlook on payment models in Chapter 9.

2.2.2 An important part of the investigation of relevant payment models has consisted of a collaborative project with the regions

In November 2019, the Swedish Association of Local Authorities and Regions (SKR) commissioned its central office to initiate development work on new payment models for innovative medicines (13). Region Stockholm's politicians tasked their officials with a corresponding assignment. Since these assignments have a clear connection to TLV's government assignment and, in order to reduce the risk of a duplication of efforts, TLV took the initiative to work collaboratively in the spring of 2020.

The collaboration has primarily consisted of a pilot project with the aim of testing the opportunities for new contract structures and payment models for ATMPs and corresponding innovative treatments. The regions' work was undertaken within the scope of the regions' collaboration model for pharmaceuticals. Although TLV's and the regions' assignments largely coincide, given the basic assignments of the different actors, we have assumed different roles and responsibilities in the assignment. Refer to Figure 3 for a description of the specific parts of the project that TLV and the regions' representatives are responsible for. The pilot project has had a steering group with representation from SKR, Region Stockholm and TLV.

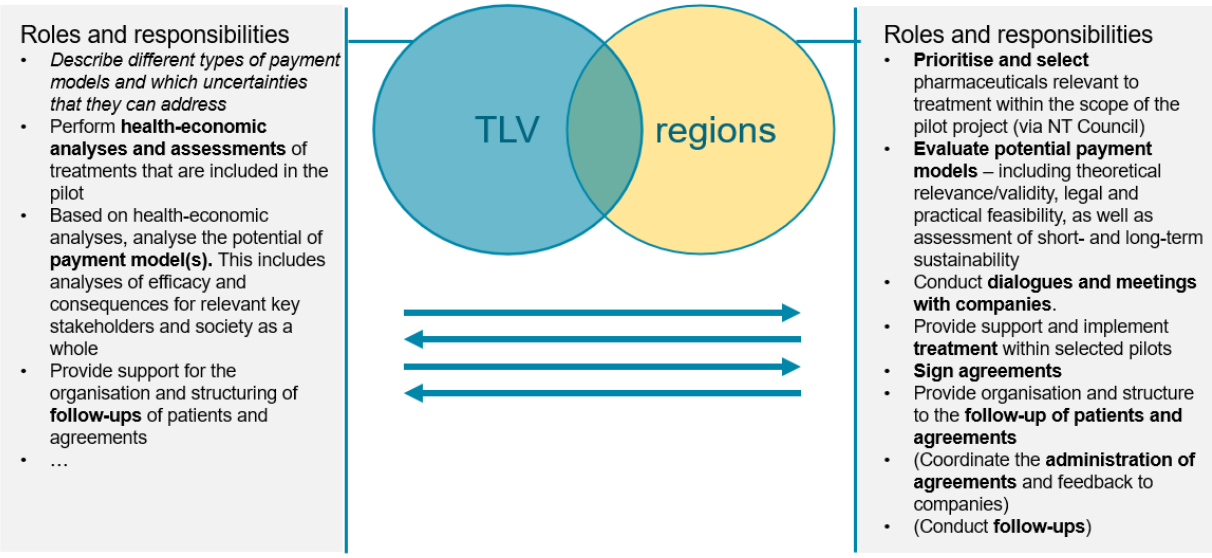


Figure 3. Roles and responsibilities within the framework of the pilot project

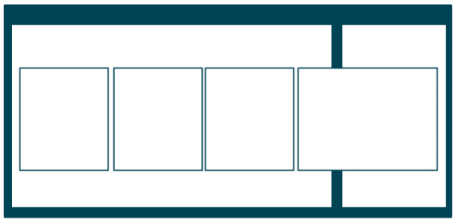
2.2.3 TLV has maintained an ongoing dialogue with most external actors

Issues related to precision medicines and ATMPs are investigated and discussed by numerous actors, both in the public and private spheres, and at a local, regional and national level. Upon the launch of this government assignment, it was clear that there were many parties who wished to have information about the work, and to contribute with their knowledge and perspective. With the aim of increasing consensus on the challenges and opportunities, TLV deemed that it was crucial to maintain active dialogue and collaboration with actors in the field. An additional motive was to – in a small country such as Sweden – avoid duplication of work and leverage potential synergies.

Collaboration has taken the form of activities organised by external parties, participation in collaborative groups, and (two) webinars and reference group meetings organised by TLV. Three reference groups were set up, where two of the groups consisted of representatives from the pharmaceutical industry and one, of representatives from patient organisations, interest groups and public-sector actors. Each group was assembled three times. At the webinars and reference-group meetings, discussions were held on the interpretation of our assignment, how we are expected to contribute within its framework, as well as on the identified issues.

TLV has also maintained a continuous dialogue with the Swedish Agency for Health and Care Services Analysis, by reason of its assignment to analyse the impact of precision medicines on health care.(14). Furthermore, in the course of its work, TLV interacted with Genomic Medicine Sweden (GMS) for knowledge acquisition and analyses of the operating environment. TLV has also participated in the working group for precision medicines and ATMPs, which is linked to the government's collaboration group for health and life sciences.

3 The characteristics of precision medicine



In this chapter, we expound on the following:

- The concept of precision medicine lacks a uniform and generally accepted definition. Consequently, there are many different uses of the term, from narrow interpretations based solely on genetic markers, to very broad interpretations encompassing nearly all kinds of complex or technically advanced medical interventions.
- TLV defines precision medicine in this report as 'diagnostics, treatment and prevention based on an individual patient's molecular profile'. With respect to pharmaceuticals and other therapies, TLV refers to precision medicine as 'molecular information about the individual or his/her disease governing the choice of treatment'. It is the precision of the method used to demonstrate the molecular (for example, genetic) properties that matters, not the underlying technology that is used.
- There are recurring characteristics for precision medical products, which have an impact on health-economic assessments. Examples of this are the testing procedure and associated costs, as well as the small patient populations that the molecular characterisation often leads to.
- The division of patients into smaller disease entities (stratification) also leads to more complex treatment routes, which may complicate the assessment of effectiveness in relation to other treatments or treatment sequences.

3.1 What are precision medicines and ATMPs?

3.1.1 Precision medicine – products where molecular information controls the choice of treatment

The concept of precision medicine is multifaceted and has many different interpretations in medical literature. It is often used interchangeably with the related term 'personalised medicine' and is essentially synonymous with stratified medicine. TLV has studied different definitions of precision medicine in order to delimit the government assignment in relation to TLV's scope of responsibility and the issues concerned.

What the term ‘precision medicine’ encompasses varies in medical literature, from relatively narrow definitions referring strictly to therapies linked to a genetic marker (often solely in reference to targeted pharmaceuticals), to broad terms that include other types of molecular biomarkers, complex algorithms and artificial intelligence (AI), high-resolution imaging techniques, digital health applications, prevention, lifestyle factors and more (15) (16) (17) (18) (19) (20) (21) (22).

Based on this, TLV has chosen the following simple description of what the term ‘precision medicine’ encompasses: ‘diagnostics, treatment and prevention based on the individual patient’s molecular profile’. For pharmaceuticals and other therapies, TLV refers to precision medicine as ‘molecular information about the individual or his/her disease governing the choice of treatment’.

The molecular information used in precision medicine today often consists of genetic markers or of aberrant protein expressions in the cells that can be studied under a microscope. The latter are often the result of a genetic mutation. However, other types of molecular information may also be relevant as a result of the ongoing achievements in the study of proteins and the breakdown products of metabolism (known as proteomics and metabolomics, respectively).

In this context, it should be mentioned that in practice, patient characteristics that do *not* consist of molecular information often form the basis for an individualised treatment choice. For example, this may pertain to how the patient has responded to previous treatments in terms of effectiveness and side effects. This is part of customary medical practice and is not usually included in the new concept of precision medicine. In theory, other more complex information from, for example, AI-based imaging diagnostics, could also influence therapy choices. At present, we are not aware of such examples that do not simultaneously demonstrate a molecular characteristic, nor of products that provide such information that has reached the market, which is why they are not included in TLV’s working definition above.

TLV’s regular tasks include conducting health-economic assessments of pharmaceuticals and medical devices. Examples of precision medical devices that TLV investigates may include diagnostic products in the form of molecular tests, various forms of medical technology equipment and IT applications. Prevention can also take the form of a pharmacological treatment of at-risk individuals who are identified by a molecular test, and could thus be the object of a health-economic assessment by TLV.

3.1.2 A regulatory definition exists for ATMPs

Unlike precision medicines, ATMPs have a legal definition under EU legislation for what constitutes an advanced therapy. (23) For the purposes of this regulation, the term ATMP covers products intended for medical use on humans and utilises gene therapy, somatic cell therapy or tissue engineering.

3.1.3 There is a partial overlap between precision medicines and ATMPs

An overlap exists between precision medicines and ATMPs, although it is by no means a complete overlap. The overlap is due to many ATMPs being part of a sequence of precision- medical treatments, such as when a molecular test is required to identify the patients with the potential to benefit clinically from the treatment. Zynteglo is an example of one such gene therapy and another is Zolgensma. These products are aimed at correcting a specific genetic defect in patients.

One notable type of ATMP that is *not a* precision medicine according to TLV's description, is CAR-T cell therapy. The treatment involves extracting the patient's own immune cells and genetically modifying them to become better at identifying and killing tumour cells, after which they are returned to the patient (24) (25). The treatment is not designed to remedy a detected molecular abnormality in the patient, but is a type of immunological treatment (24). Although this type of therapy involves a molecular-level modification of an individual's own cells, which could intuitively bring to mind 'precision medicine', there is no testing criterion as per TLV's definition. Consequently, the patient thus does not need to be diagnosed with any special molecular abnormality to be relevant for a CAR-T treatment.

There are also other ATMPs, where no molecular test is required to identify who might benefit from treatment, and which also do not yield a precision medical effect in that they do not address or are not directed at a specific molecular abnormality. One such example is Alofisel (darvadstrocel), which is used against anal fistulas and consists of cultured fat stem cells, which have immunomodulatory and anti-inflammatory effects on inflammation sites. Alofisel is not a gene therapy, but a somatic cell therapy.

3.2 Precision medicines have distinctive features

Although precision medicine is not a uniform concept, there are certain distinctive and frequently recurring features. Below is an attempt to provide a structure around some of the main components. A precision-medicine product does not have to have all these characteristics, and almost none of the characteristics are truly unique to precision medicine. It is the combination of characteristics – and that they are becoming increasingly common – that allows for us to talk about a shift to greater precision in health care.

Figure 4 is a summary of some distinctive and frequent features that may impact the assessments, which are further explored in the section below. The letters in parentheses indicate which of the features is being referred to in the figure above.

A key feature of precision medicine examinations is the molecular characterisation (A) and the resulting stratification of patients, i.e. the division of patients within a disease entity into smaller groups (E). This in turn results in smaller patient populations in the clinical trials. The smaller the trial populations, the higher the uncertainty surrounding measurement values, which often leads to other trial designs being used for market authorisation than those we usually consider to

provide the best evidence through the isolation of treatment effectiveness, relevant outcome parameters and safe point estimates (H). In practice, this often means that uncontrolled trials, i.e. trials without a comparison arm, also known as single-arm trials, are used instead of randomised controlled trials (RCT). The latter have a built-in control arm for comparison.

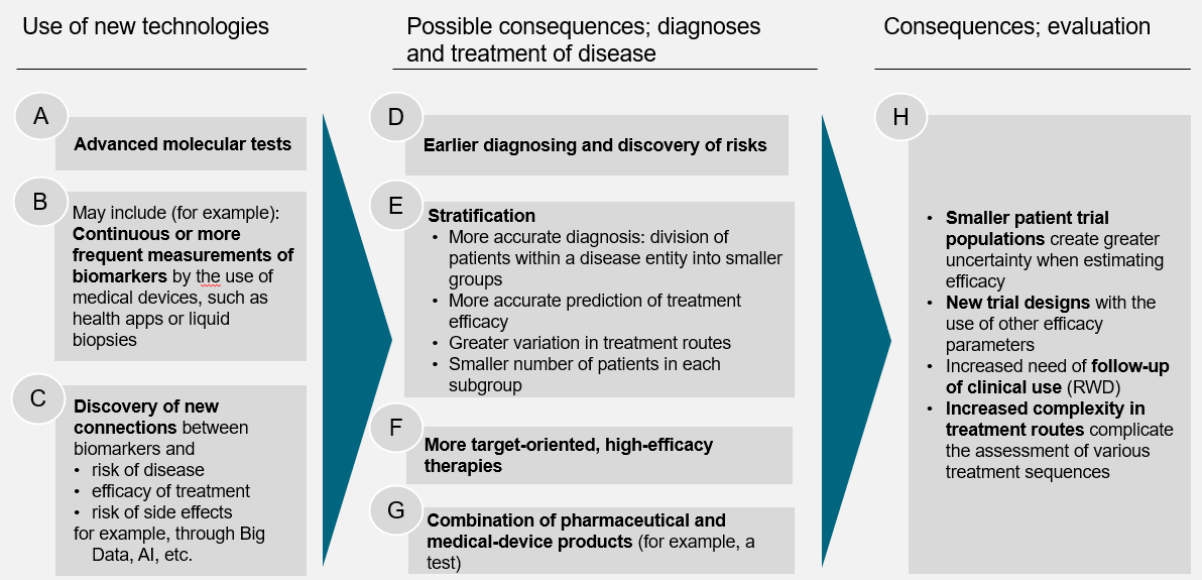


Figure 4. Common characteristics of precision medicine.

An example from oncology can be used to illustrate what this entails. In large patient populations, the basis for market authorisation and health-economic assessments usually consists of an RCT with survival (or other time-dependent effectiveness parameter) as the primary outcome parameter. Conversely, for a small patient population, a single-arm study with objectively established tumour shrinkage is often used as the primary outcome parameter. How tumour shrinkage relates to survival – the parameter that companies and TLV need for their QALY calculations – is unknown. This significantly complicates the assessment, even if it is obvious that the pharmaceutical has an effect against the disease. Since tumour shrinkage is a parameter that responds relatively quickly, shorter follow-up is possible within the study: follow-up periods are often significantly shorter than for an RCT with time-dependent outcome parameters. It should be noted that this is not unique to precision medicines, but is a known phenomenon from other unusual disease conditions with a small patient sample size.

Another consequence of increased uncertainties in effectiveness estimates is the increased requirement to follow up the utilisation of a pharmaceutical in routine medical care following its market authorisation (H). Such follow-up may subsequently be needed to ensure that the effectiveness modelled in the health-economic assessment, which was based on limited data from clinical trials, corresponds to the actual effectiveness achieved. Such information is known as ‘Real World Data’ (RWD) and consists of data generated from clinical practice in connection with the utilisation and effectiveness of a pharmaceutical. Although

access to infrastructure for the acquisition of such data may vary depending partly on the field of therapy concerned, in many cases, it is deficient.

When it is linkable to the clinical data on outcomes for patients, increased molecular testing (A) also generates increased knowledge (C). This could in turn give rise to continued pharmaceutical development, often in the form of selective and targeted therapies (F). Targeted therapies generally yield high effectiveness compared with pharmaceuticals with more non-specific modes of action. High effectiveness is often a characteristic of these biomarker-guided therapies. However, if the targeted pharmaceutical were to be administered to a molecularly unselected patient population, the effect would be 'diluted'. This is because only a small proportion of patients, i.e. those who express the target molecule for the pharmaceutical, would benefit from the pharmaceutical agent. The higher effectiveness observed in comparison with other types of pharmaceuticals, may thus be due to a more effective mode of action combined with the fact that molecular testing has succeeded in selecting the right patients for the treatment. A corresponding opportunity to select patients is rarely available for traditional medicines with a more non-specific mode of action; when spread across the entire population, the scope of effect is therefore generally lower.

Molecular tests can also be used to predict the risk of serious adverse events and thus increase the benefit of a treatment in relation to risks and costs (C).

The medical technology side of precision medicine is developing rapidly, including new methods of taking samples, including what is termed 'liquid biopsies' (B). Liquid biopsies entail molecular testing being performed directly on the patient's blood, instead of on tissue samples that are surgically removed. This allows for analysing circulating tumour DNA (ctDNA) in the bloodstream to determine whether the patient's tumour expresses the target molecule for a certain targeted anti-cancer pharmaceutical. The simplified sampling can also allow for the biomarker to be monitored through repeated sampling, in order to assess whether the ongoing treatment is effective and to allow for a quick switch of therapy if needed.

Another aspect of precision medicine that is expected to increase in the future pertains to *wearable health devices* (B) (26). These products comprise equipment for directly measuring the individual's health data. Examples of this are the continuous measurement of physical activity or heart rate. Devices for measuring heart rate and oxygen saturation in the blood via a skin sensor are already in use today within health care, and similar technology could be developed for home use with an uplink to a health care provider. Another conceivable example could be a device that continuously measures a diabetic patient's insulin levels and which in real time, via an insulin pump, delivers an insulin secretion to the patient that is more similar to the body's normal function than what is possible through a series of measurements and dosages spread over a day. In addition to the practical benefits, the use of such a device could provide health gains in that a dosage that is more similar to the body's normal insulin secretion will provide better blood sugar control and reduce the long-term adverse consequences of diabetes.

Precision medical technology can also pertain to computer or smart-phone apps, where individuals can personally register their health data (B). Such information could be used for self-care and exercise, and in some forms, can also be shared with health care providers for the follow-up of chronic diseases, side effects, etc. Such apps for following up chronic diseases and which have an uplink to health care are already available as 'medical devices' under the medical-benefits system.(27). This technical solution is also used in certain clinical trials, where the participants can personally report side effects and health-related quality of life to the study via an app on their own mobile phone or computer. TLV's report, *Follow-up of anti-cancer pharmaceuticals and other pharmaceuticals via alternative data sources*, describes an app for patient-reported data on antibiotic usage for patients with cystic fibrosis(28).

3.3 The treatments are conditional on adaptations by health care providers to varying degrees

The implementation of precision medicine and ATMPs requires adjustments to, and investments in, health care, depending on the product and treatment. (29) Their development is based on infrastructure being in place, providing access to data from various sources and staff with specific skills. Investments in the form of premises and equipment, and the recruitment and training of staff to correctly diagnose, treat and follow up patients may be required. For ATMPs, there may also be a need to establish special treatment centres.

The CAR-T treatments Kymriah and Yescarta are examples of resource-intensive implementations. The treatments have been on the market since 2018 and are used for the blood cancer diseases, acute lymphatic leukaemia and lymphoma. (30) (31) In order for clinics to be able administer these treatments to patients, the pharmaceutical companies impose high demands on skills, equipment and processes. Here, health care providers are integral to the production process and the requirements are set based on what the company needs to fulfil in order for the production and administration of the pharmaceutical agent to be safe. The utilisation of these therapies has thus entailed major changes to health care practices.

The above mainly pertain to costs that are currently borne by Sweden's regions. (29) In some cases, companies provide training to health care professionals when it comes to commercial products and services.

3.4 A sampling of TLV's completed assessments of precision medical products

3.4.1 Alecensa – a targeted pharmaceutical

Alecensa (alectinib) is an example of a precision medicine, as only patients who have a specific genetic mutation in their tumour can respond to this targeted

treatment. A molecular test is required to show that the patient has the mutation before treatment may begin.

Alecensa was approved in February 2017 for the treatment of adult patients with anaplastic lymphoma kinase (ALK) positive advanced non-small cell lung cancer (NSCLC) previously treated with Crizotinib. TLV's subsidy decision (93/2017) was made on 24 November 2017 following an application and customary health-economic assessment. Alectinib is an ALK and RET tyrosine kinase inhibitor that can induce programmed cell death in tumour cells that have an ALK fusion.[2] According to the indication's wording, the patient is assumed to have undergone a genetic test to show the presence of an ALK mutation before becoming eligible for treatment with the pharmaceutical.
Approximately 2 to 7 per cent of patients with lung cancer have this specific gene mutation, a fusion between two genes (EML4 and ALK).[3] This and other ALK mutations are more common in non-smokers, infrequent smokers and adenocarcinoma patients. It is a disease with a rapid progression that is often discovered only when the disease has spread to other organs. Patients may develop resistance and the disease may progress particularly in the central nervous system, resulting in impaired quality of life and survival. The degree of severity was therefore deemed to be very high.

In the course of its investigation in 2018, TLV deemed there to be a high level of uncertainties in the health-economic model. (32) They pertained mainly to the effect of Alecensa over time and the actual form that post-progression treatment would take in clinical practice.

Questions related to precision medicine

The health-economic assessment did not include any test costs in the model.
The main uncertainties in the investigation were not linked to the pharmaceutical's specific precision medical properties (see above).

3.4.2 Vitrakvi – a targeted pharmaceutical with a histology-independent indication

Vitrakvi (larotrectinib) is a pharmaceutical used to treat cancer. It is an example of a precision-medicine pharmaceutical, as a molecular test is required to identify the patients who are expected to benefit from the treatment. The pharmaceutical agent is targeted to the molecular structure that is (indirectly) detected in the test.

Vitrakvi is the EU's first example of a what is referred to as a 'histology-independent indication', which entails that in addition to the overall delimitation for solid tumours, molecular diagnostics are the only process used to delimit the disease. This is in contrast to all previous anti-cancer pharmaceuticals, the use of which has always been limited to the selected tumour type(s), traditionally based on the type of tissue for which usage was studied, such as lung cancer, breast cancer, prostate cancer and so forth. With the expected intensified development of precision

[2] ALK = anaplastic lymphoma kinase.
[3] EML4 = Echinoderm microtubule-associated protein-like.

medicines, such indications, also known as tumour-diagnostic or tissue-diagnostic indications, can be expected to increase.

Vitrakvi was approved in September 2019 for the treatment of adults and children with solid tumours with a fusion of the Neurotrophic Tyrosine Receptor Kinase (NTRK) gene, which causes a disease that is locally advanced, metastatic or where surgical resection would likely lead to severe morbidity, and which lacks satisfactory treatment alternatives. TLV's subsidy decision was made in October 2020 (33).

Larotrectinib is a TRK inhibitor used against cancer in patients whose tumours have a fusion in one of the three NTRK genes. The clinical basis for the product consists of relatively small and early Phase 1 and Phase 2 trial, through which individuals with different cancers are being studied together. The patient material only includes individual patients with some of the diseases studied, and many types of cancers included in the approved indication are not represented in the studies at all. For this reason, there are considerable uncertainties in estimating the scope of effect, compared with the large, Randomised Phase III trials of a single tumour type, which had previously been the normal basis for market authorisation and thereby, the health-economic assessments as well.

Questions related to precision medicine

When assessing Vitrakvi, test costs were included in the analysis, including the costs of the patients who were tested but who did not have an NTRK fusion and thus were not eligible for treatment with Vitrakvi. In other words, health care incurred the cost of detecting *one* individual who had the gene fusion that was included. However, test costs were not a decisive factor in the health-economic outcome. See section 4.2 for an in-depth discussion of this topic.

The limited clinical basis is due to the low incidence of the molecular abnormality and is thus indirectly linked to the precision medical treatment algorithm. The short follow-up period also contributes to accentuating the uncertainties before the decision and further increases the requirement for follow-up.

For this product, there were no expectations that the pharmaceutical would be able to lead to a cure in the primary indication, which concerns disease at a late metastatic stage. For other indications on the other hand, patients are included at an earlier, potentially curable stage, in cases where surgical resection would probably lead to severe morbidity. This was deemed to be applicable when curative surgery would involve, for example, amputation of an extremity or other impact on function or residual symptoms. One very good effect of the pharmaceutical in such an application could be the elimination of the entire tumour, possibly via a final minor surgery, so that the patient is cured.

3.4.3 Zynteglo – gene therapy (ATMP)

Zynteglo is both a precision-medicine product and an advanced therapy (ATMP) that is used against the blood disease beta-thalassemia. In order for the treatment to be effective, it is required that the patient does *not* have a certain set of genes (genotype), so a test must be performed to determine the absence of this genotype

before treatment is administered. This falls under TLV's definition of precision medicine. The treatment is both a gene therapy and an ATMP.

Zynteglo consists of autologous CD34-positive cells that express the βA-T87Q globin gene and was approved in May 2019 for the treatment of patients aged 12 years and older with transfusion-dependent beta-thalassemia (TDT) who do not have a β0/β0 genotype and for whom haematopoietic stem cell transplantation (HSCT) is appropriate, but who lack a human leukocyte antigen-matched (HLA) HSC donor.

Zynteglo is a gene therapy and autologous haematopoietic stem cell therapy and thus constitutes an ATMP. Treatment with Zynteglo entails that blood-forming stem cells are first extracted from the patient and subjected to genetic modification. The genetic modification causes the stem cells to produce the beta-globin protein, which patients with beta-thalassemia are deficient in. The genetically modified stem cells are then returned to the patient, whose disease condition will thus be improved or cured.

According to the indication's wording, the patient is presumed to have undergone a genetic test that shows that the patient does not have a β0/β0 genotype, before being eligible for treatment with the pharmaceutical. Patients who do not have the β0/β0 genotype produce little β-globin and in this group, symptoms and severity may vary between individuals. The degree of severity was deemed to be medium at a group level.

TLV conducted the health-economic assessment in the spring of 2020, within the scope of a collaboration between the HTA authorities of Norway, Finland and Sweden, called FINOSE. Zynteglo was then involved in a Nordic contract negotiation between the negotiating parties of Sweden, Norway, Finland, Denmark and Iceland, based on the FINOSE report. The Nordic negotiations did not lead to an agreement with the company, which is why the NT Council recommends that the regions refrain from using Zynteglo.

Questions related to precision medicine

Test costs for the genotyping of patients treated with Zynteglo were included in the model. Test costs for patients who did *not* meet the criterion for treatment, i.e. who do not have the β0/β0 genotype, were not included in the model.

Not all patients became transfusion-free from the treatment, i.e. not all patients were cured. In its 2020 investigation, TLV deemed that the main uncertainties in the health-economic analysis pertained to whether Zynteglo's effect (achieved transfusion independence) is sustainable in the long term, and the scope of potential survival gains caused by avoiding iron retention-related complications. (34) Furthermore, the health-economic model was highly sensitive to the benefit values attributed to treatment with iron-binding pharmaceuticals.

The small patient sample size and the short follow-up period contributed to the uncertainties prior to the decision and would have increased the need for follow-ups

of clinical use. Further costs were factored in due to the administration of this advanced form of therapy at highly specialised centres, which in many cases are not in proximity to the patient's place of residence.

3.4.4 FoundationOne CDx – a medical device

FoundationOne CDx is a CE-marked medical device that is based on a molecular test kit consisting of a gene panel. The information is compiled as decision-making data, intended for use in selecting patients for various targeted cancer treatments. It is thus a precision medical product. TLV conducted a health-economic assessment of FoundationOne CDx in spring 2019. (35).

FoundationOne CDx is a diagnostic service based on a broad gene panel that detects over 300 genetic markers that may be of significance to solid tumours. The service includes extraction of genetic materials from patient samples, (NGS) next generation sequencing-based genetic analyses, processing with bioinformatics and the compilation of decision-making data, which can be used to support the choice of treatment for cancer patients. Patients who, through the test, prove to have a genetic marker for which there is a specific (usually targeted) treatment are then eligible for such treatment. For patients who prove to lack such a genetic marker, the choice of treatment is instead directed towards non-targeted therapies. There are also genetic mutations that could affect the likelihood of responding to certain non-targeted therapies, and others that impact the risk of serious adverse effects from a particular type of treatment. Consequently, the choice of treatment does necessarily pertain strictly to targeted pharmaceuticals.

FoundationOne CDx and other NGS-based tests were used extensively in the trials that formed the basis of Vitrakvi's (see above) market approval to identify patients who could benefit from the treatment.

Questions related to precision medicine

The health-economic assessment was challenging and most of the difficulties were linked to the product's precision-medicine properties.

The product is intended for use on all solid tumours. However, depending on the tumour type, stage of disease, treatment situation and more, patients may benefit to different degrees from the testing. The lack of comparative trials of clinical outcomes using FoundationOne CDx compared with other types of tests, made it impossible to quantify the clinical benefit of the test. For this reason, only a cost comparison was made against specific tests for individual markers, for a small number of selected diagnoses (non-small cell lung cancer, breast cancer, cancer with unknown primary tumour, melanoma, colorectal cancer and ovarian cancer).

The health-economic analysis did not include any costs or health gains associated with the treatment that was administered based on the testing. TLV deemed that such an analysis would require a large number of assumptions and result in an extremely high level of uncertainties. The costs of generating data about treatment alternatives for decision-making support were also excluded from the health-economic analysis, as the assessment was limited to the testing itself. Consequently,

this type of assessment does not capture the future societal benefits or monetary value that could be generated through the knowledge provided by aggregated genetic data from numerous patients, such as the clinical optimisation of existing therapies, medical research and new pharmaceutical developments. However, the documentation from the investigation noted that the value of the tests increases if the data generated is owned and/or disposed of freely by the public sector.

On the whole, the complexity was the precision-medicine feature, which most significantly impacted the assessment of FoundationOne CDx. The complexity was compounded by the numerous alternative treatment routes and outcomes, which were dependent on factors such as the type of tumour and testing results. In addition, there were known challenges associated with the field of medical technology, such as the very limited availability of clinical data.

3.5 Assessments of precision medicines and ATMPs – some experiences and lessons learned

In summary, there are several distinctive frequently recurring features in precision medicine, although few of them are completely exclusive to these products, and the precision-medicine aspects are not always of great importance to TLV's health-economic assessment. In many cases, they bring new difficulties to the assessment that may require new methods of thinking and working to resolve. Some of these aspects are, for example:

- the testing procedure and associated costs
- small patient groups result in poorer evidence
- complex treatment routes
- the frequent lack of validated clinical data for medical devices.

With regard to the testing procedure, TLV's established practices are undergoing development – this is explored further in Chapter 4. The above examples of completed investigations of precision-medicine products indicate that testing costs for patient selection have developed over time. These had not previously been factored in at all (for example in the case of Alecensa in 2017). In subsequent assessments, the test cost for patients who, following testing, could actually receive the treatment, was included in the health-economic analysis (as in the case of Zynteglo 2020). With the assessment of the first histology-independent pharmaceutical (Vitrakvi 2020, see above), where the presence of the target molecule was very rare (less than 1 per cent) in some of the histologically defined cancers, attention was focused on the extensive testing that was required to sift for the molecule.

Molecular characterisation can lead to small or very small patient populations, which in turn impacts the design of trials and the general level of evidence that can be obtained. This increases the uncertainty in the assessments, which in turn potentially increases the need for following up clinical use.

The stratification of patients into smaller groups with different prognoses and/or treatment options results in more complex therapy routes, which can significantly

complicate the assessment of relative effectiveness, such as in relation to the next treatment in a treatment ladder.

The challenge when evaluating medical devices is often the lack of validated clinical data, because the product is yet to be introduced to the market. Empirical evidence may have demonstrated that the technology works, but this may not have been documented in a clinical study. If for example, the medical device is a prognostic or predictive test kit, the analytical validity can be ensured (that the product measures what it should), while the clinical validity (how the test result correlates with clinical outcome) is unclear. This increases the uncertainty in assessments of relative effectiveness and cost, and potentially complicates the introduction of innovative medical devices (36). In section 0 of this report, we describe the challenges in health-economic assessments of diagnostic tests and the specific parameters that are important for the outcome.

The development of precision medicine, as well as its assessment and follow-up, is based on an infrastructure that is in place, with access to data from various sources (medical records, registers, diagnostic tests, health apps), logistics, staff with special skills (e.g. bioinformatics), geneticists, pathologists etc.

In summary, the complexity and the new uncertainties that emerge with respect to the effectiveness of precision medical products have an impact on several stages of TLV's work, including the assessment of medical relative effectiveness and health-economic models, as well as decision-making. This is a perspective that is also shared by assessors in other countries (15).

4 Assessment of products in treatment combinations and treatment sequences

In this chapter, we expound on the following:

- If the introduction of a new pharmaceutical means that a new treatment-predictive test must be performed, the basic rule is that the cost of the test is included in the health-economic assessment of the pharmaceutical. However, if the test is already being performed for the patient group concerned, in order to steer patients towards other treatments, the test cost does not always have to be included.
- The value of a treatment-predictive test depends on the cost-effectiveness of subsequent treatments, which creates challenges to the health-economic assessment due to the frequent lack of knowledge about this.
- When two or more costly original pharmaceuticals are used in combination, the cost is often unreasonably high. It is important to find ways to provide companies with incentives and opportunities to sell their pharmaceuticals at a lower price when they are used in combination, compared with when they are used as a monotherapy. One of the problems that must then be resolved, is how the total value of the combination is to be distributed between the different pharmaceutical agents. However, TLV does not interpret this to be within its mandate, but that it should be resolved through negotiations between the companies.

4.1 In precision medicine products will increasingly be used together

One of the opportunities with precision medicine is that treatment sequences can to a greater extent be tailored to various patient groups. Precision medicine also entails that medical devices such as test kits are becoming increasingly integral to the treatment sequence – when assessing the risk of developing a disease, as an aid in performing a diagnosis and/or when choosing treatment.

The fact that individual products are increasingly being included as part of a whole entails challenges both in terms of valuation and payment. In this assignment, we have chosen to proceed from three issues to address some of these challenges:

- How and when should the cost of treatment-predictive tests be included in a health-economic assessment of the subsequent treatment?
- What are the basic factors that determine the value of treatment-predictive tests that provide information about which pharmaceutical to use?
- Should TLV develop guidelines for how the total health gain of combination therapies should be distributed between the individual pharmaceuticals?

These questions were selected based on the situations that TLV is faced with in the health-economic assessment of precision-medicine products. However, we would like to emphasise that there are many other issues in this regard that need to be addressed, moving forward.

A starting point for the discussion is that when different products are used together to achieve a health gain, there are no methods that can objectively separate the value and determine how much the different products contribute to health gains. For example: If a treatment-predictive test needs to be performed in order for a targeted pharmaceutical to be used, it is impossible to determine how much of the health gain should be attributed to the test or treatment. Both are needed to achieve the health gains. Similarly, it is impossible to objectively determine how much of the health gain is to be attributed to each pharmaceutical, if two of them had to be combined to achieve the health gain. Therefore, what can be assessed is one combination of interventions compared with another combination of interventions.

4.2 Inclusion of the cost of the test in the assessment of subsequent treatment

In the following section, we examine whether the cost of a treatment-predictive test should be included in the health-economic assessment of the subsequent treatment, in situations where the test is a prerequisite for the treatment to be administered. Or to put it in more concrete terms: under what circumstances is it reasonable to include the cost of a genetic test in the health-economic assessment of a targeted pharmaceutical?

The primary rule in health economics is that all costs related to treatment should be included in the calculation. However, it may be reasonable in certain situations to deviate from that rule, if the introduction of a new treatment does indeed presuppose a certain utilisation of resources, but does not displace other usage of the resource.[4]

[4] There is a comprehensive discussion about what costs should be included in an assessment and how the costs should be calculated. See for example (10). One question is how to factor costs that are fixed in the medium term. This pertains to capital costs (such as buildings, equipment with extensive useful life) and overhead costs (such as hospital administration). Another partly related question is whether it is the average, the variable or the marginal cost that should be included. A third question is how the cost should be calculated: Is it to be based on market prices (which often does not exist in health care), production cost or is it the alternative cost? Many believe that on

Three stylised scenarios are used below to address the issue.

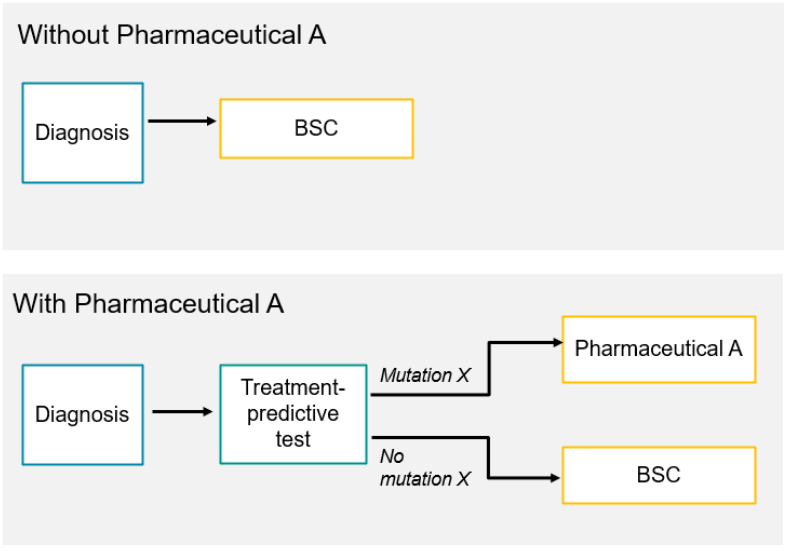
4.2.1 If the treatment requires a test, the cost of the test should be included in the assessment

Scenario I
A targeted pharmaceutical, 'Pharmaceutical A', receives market approval for a cancer indication. The use of the pharmaceutical is conditional on a treatment-predictive genetic test first being performed.

Conditions:

- The patient has previously been diagnosed.
- Before Pharmaceutical A is launched, there is no available treatment for the diagnosis that the treatment is aimed at.
- Pharmaceutical A only works if the patient has mutation X. Therefore, a genetic test must be performed before the pharmaceutical is administered, to find out if the patient has this mutation.
- Pharmaceutical A is priced so that from a cost-effectiveness perspective, it is not reasonable to empirically test it by administering it to all patients.

In this case, we want to compare 'Test + Pharmaceutical A' with the best supportive care (BSC); see figure below.



TLV's assessment in this scenario

TLV is of the opinion that the test cost should be included in the assessment. The reason being that the incurred cost is a direct consequence of the introduction of

a principled basis. it is the alternative cost that should be the starting point: the value of the care/intervention that is crowded out (10).

Pharmaceutical A into the market: resource usage occurs, which would not have occurred without the introduction of the pharmaceutical.

Cost per QALY is calculated according to the formula

$$ICER = \frac{C_{DrugA} - C_{BSC}}{Q_{DrugA} - Q_{BSC}} + \frac{C_{Test}/p}{Q_{DrugA} - Q_{BSC}}$$

where C stands for costs, Q for QALY and p for the proportion of patients who have mutation X (see footnote for how the formula was derived).[5]

The formula describes the cost per QALY for treating patients who have mutation X with Pharmaceutical A, compared with not testing and administering the BSC to these patients.[6]

The first term is the usual formula, i.e. the cost per QALY for administering Pharmaceutical A to patients who have been identified with mutation X. To this, we must add the cost of discovering that the patient has mutation X, which is captured by the second term. The second term shows that it is not only the cost of the test that is decisive but also the probability, *p,* that the patient has the mutation. The consequence is that the less common the mutation, the higher the health care cost incurred for identifying an individual who has the mutation. In practice, if the test costs SEK 10,000 and the prevalence is 10 per cent, it costs SEK 100,000 to detect one patient with the mutation. If the prevalence is only 1 per cent, it costs SEK 1 million to identify a patient with the mutation. The ratio $1/p$ is called the 'number needed to test'.

It is sometimes discussed whether the test cost should be calculated based solely on the patients who test positive or on all patients who are tested; see for example, NICE's discussion on Vitrakvi (37). We interpret the discussion as a question of whether or not C_{Test} should be divided by p. TLV's conclusion is that the test cost should be calculated based on all patients who are tested, as the formula above also shows: the test cost arises for all patients who are tested, not just for those who are found to have mutation X.

5

$$ICER = \frac{C_{Test} + pC_{DrugA} + (1-p)C_{BSC} - C_{BSC}}{pQ_{DrugA} + (1-p)Q_{BSC} - Q_{BSC}} = \frac{C_{DrugA} - C_{BSC}}{Q_{DrugA} - Q_{BSC}} + \frac{C_{Test}/p}{Q_{DrugA} - Q_{BSC}}$$

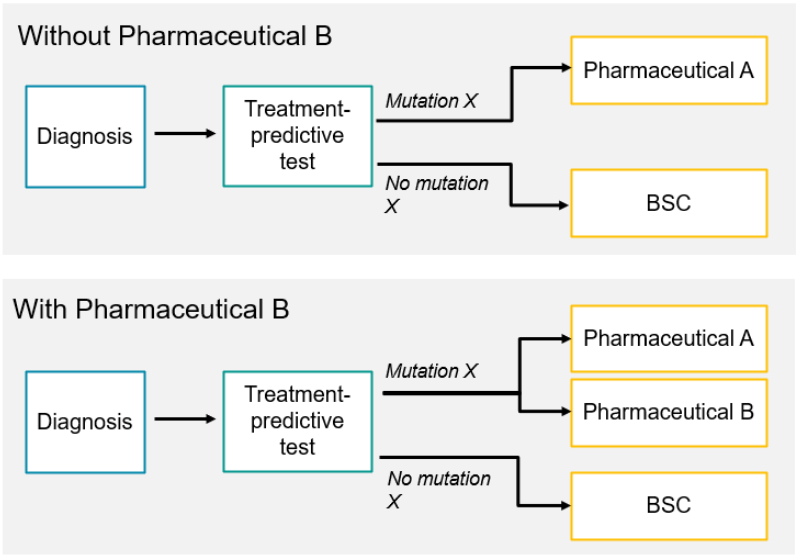
6 Here, we deliberately ignore questions about the sensitivity and specificity of the test – which should not impact whether and how the test cost should be included – so as not to complicate the matter unnecessarily. We return to those questions below.

4.2.2 If a treatment requires a test that is already used to steer patients towards another treatment, the test cost does not need to be included

Scenario II
Another pharmaceutical product, 'Pharmaceutical B', is granted market approval for the same cancer indication as Pharmaceutical A.

Conditions:
- Pharmaceutical B also works only if the patient has mutation X.
- The same diagnostic test used for Pharmaceutical A is used for Pharmaceutical B.
- Otherwise, the same conditions apply as described in Scenario I.

Now the two treatment strategies 'Test + Pharmaceutical B' and 'Test + Pharmaceutical A' should be compared against each other; see figure below.



TLV's assessment in this scenario

In this scenario, the test cost does not need to be included in the assessment. Therefore, only a comparison of the health gains and costs for the two pharmaceutical agents is made here. In the event that Pharmaceutical B is deemed to provide a greater health gain than Pharmaceutical A, the price may be set higher. Otherwise, it may not.

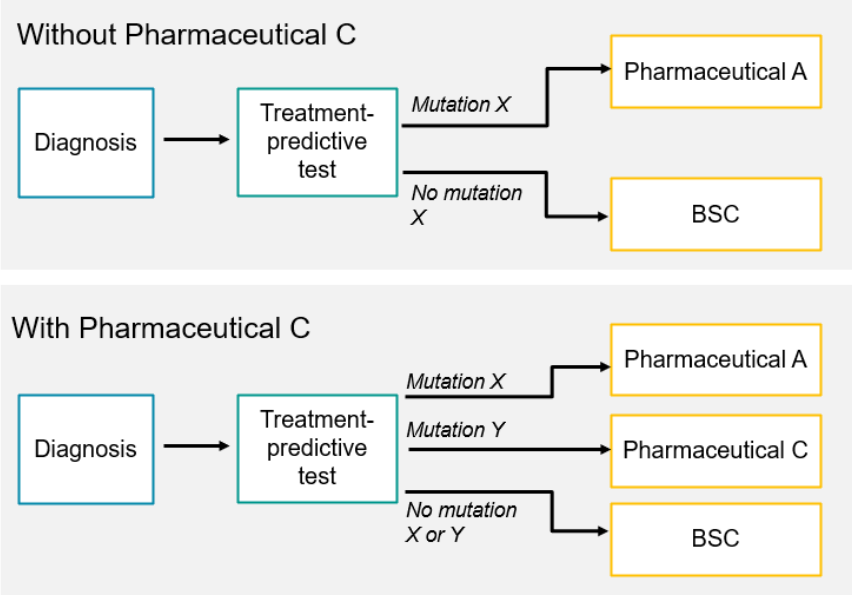
The logic behind the assessment is that since the test cost is the same for both treatments, they cancel each other out.

4.2.3 If the test has already been performed on the patient group, the cost does not always have to be included

Scenario III
Another pharmaceutical product, 'Pharmaceutical C', is introduced for the same cancer indication as Pharmaceutical A and Pharmaceutical B.

Conditions:
- Pharmaceutical C only works if the patient has mutation Y.
- The same test used in scenarios I and II can also identify mutation Y, at no extra cost.
- Otherwise, the same conditions apply as described in scenarios I and II.

We now want to compare the two treatment strategies 'Test + Pharmaceutical C' and 'Test + BSC'; see figure below.



TLV's assessment in this scenario

The test cost should be included, but in a manner that factors in that the results of the test can also be used to identify mutation X. If the test is sufficiently established and used to identify patients for several different treatments, the test cost does not need to be included.

In this case, it is more difficult to determine whether the test cost should be included. On one hand, the launch of Pharmaceutical C does not entail any additional test costs, since the patients are nevertheless tested, which suggests that the cost should not be included. On the other hand, such an approach means that A and C are not treated equally. C can be priced higher than A could at launch – and this holds true even if patients with mutation X derive as much health gains from A as patients with mutation Y get from C.

In other words, there are two different issues to consider: firstly, a methodological question of whether marginal costs or average costs should be used, and secondly, how desirable it is for an equally high price to be accepted for A and C if the achieved effectiveness is the same.

With regard to the first question, the marginal cost for detecting whether the patient has mutation Y is SEK 0, given that the test is already being performed and does not cost anything extra. On the other hand, the average cost is greater than SEK 0. TLV is of the opinion that established practice falters on this issue of whether it is the marginal or average cost that should be factored, but that it provides guidance to think in terms of opportunity costs: how much it displaces other forms of health care.

In Sweden, one of the regions' price lists for out-of-county care is most often used as a unit cost, i.e. what one region invoices when they have treated a patient who lives in another region. These price lists are based on the Swedish Association of Local Authorities and Regions' CPP (cost per patient) calculations, which include depreciation for buildings and equipment (38).This is thus a type of average cost that can be justified by the fact that there is an opportunity cost of utilising localised care premises or a medical device – they cannot be used for anything else for a certain period of time.

There is a crucial difference between utilising local care premises and tests to justify that the average cost is not so relevant to the test: testing for mutation Y does not displace anything else. If we then still include a certain test cost – the average cost – it results in an overestimate of the actual additional resource consumption from the introduction of Pharmaceutical C. In summary, a pragmatic line of reasoning is that the cost does not need to be included if the test was already sufficiently routine before the new pharmaceutical was introduced, and if there is no obvious displacement or opportunity cost.

This leads to the second question: how desirable is it to accept an equally high price for Pharmaceutical A and Pharmaceutical C, if the effect is the same? TLV is of the opinion that the conditions for pricing may change over time for a variety of reasons. An assessment is performed, given the conditions that apply at the time of the assessment, and according to TLV, it is unreasonable not to reflect the actual conditions just to achieve a higher degree of price equality. If A and C had different comparison alternatives with different prices and effectiveness, there would also have been a reason why the prices of the two pharmaceuticals could be different. Note that there is no question of unfair competition, because Pharmaceuticals A and C treat different patient groups and therefore do not compete for market share. Since this scenario is requisite on Pharmaceutical A already having been established as cost-effective, no patient group is unfairly impacted by limited access to pharmaceuticals with the same benefits.

Example: management of test costs in health-economic assessment of the anti-cancer pharmaceutical agent, Vitrakvi

The pharmaceutical agent Vitrakvi was discussed in section 3.4.2. This is an example of an application case submitted to TLV, where the question of test costs arose. Below, we describe how TLV and NICE (the HTA authority in England) managed the test cost.

NICE is of the opinion that test costs should be included in the health-economic analysis for Vitrakvi (37). The expert group appointed by NICE to assess cost-effectiveness made a calculation based on the costs of various methods and the proportion of tests performed using these different methods(39). In that analysis, the cost of positive and negative tests were factored against the number of patients expected to receive Vitrakvi, in accordance with the reasoning of 'Scenario I' above. Using this method, the expert group arrived at a test cost per treated patient of GBP 18,618. However, NICE ultimately chose a different route, which entailed a significantly lower test cost for the analysis.

In its application to TLV, the company did not include the cost of testing in the base-case scenario. For children, the company reasoned that clinical practice involves a routine analysis of all genes, known as 'whole genome sequencing'. Thus, there is no extra test cost for diagnosing children when choosing to possibly use Vitrakvi as a treatment. For adults, the company reasoned that the routine testing of everyone in connection with diagnosis will become standard practice within the next few years. In some scenarios, however, the company included a test cost that they calculated to be SEK 186,000 per patient.

TLV stated that if testing for the NTRK fusion is performed for all patients upon diagnosis of the disease, the introduction of Vitrakvi does not lead to any additional cost for testing. (40) However, for the patient groups where any treatment with Vitrakvi involves an additional cost for tests, TLV deemed that the cost of these tests should be included in the health-economic analysis. The calculation of the test cost must also take into account that many who do not turn out to have the NTRK fusion will also be tested. For children, however, TLV did not include any test costs, as most children already receive whole-genome sequencing upon diagnosis. Furthermore, NTRK fusion is common to most NTRK-driven tumour types that affect children.

However, test costs were not a driving factor in the health-economic analysis.

4.2.4 How and when should the cost of treatment-predictive tests be included in a health-economic assessment of the subsequent treatment?

In summary, if the introduction of a new pharmaceutical means that a new treatment-predictive test must be performed, the basic rule is that the cost of the test is included in the health-economic assessment of the pharmaceutical. However, if the test has already been performed to steer patients towards other treatments, the test cost does not always have to be included.

4.3 Methods of assessing treatment-predictive tests

In Section 4.2, we explored whether the financial assessment of a pharmaceutical should include the cost of requisite treatment-predictive tests. In this section, we address the question: How do we assess the cost-effectiveness of treatment-predictive tests, i.e. tests that provide information about which pharmaceutical to use?

4.3.1 A new test should sometimes be directly compared with another test, but sometimes with itself, depending on the various test and treatment strategies

The question, 'Is the new test cost-effective?' is relevant when there are several different tests with similar characteristics to choose from in a given situation. However, if the new test has a distinctly superior function and price compared with the test previously used, it could mean that a completely new test and treatment strategy is relevant. Such technological shifts frequently arise from the introduction of precision medicines. A concrete example is the broad gene panels that now provide more information than previously used tests, and which have become increasingly cheaper to use. In this scenario, it is more relevant to ask: 'Given the price and features of the new test, is the new test and treatment strategy cost-effective?'

In this section, we use two different sub-scenarios to explore what has an impact on the cost-effectiveness of a new test. In the first sub-scenario, the new test is compared with the one established for the same test-and-treatment strategy. We discuss how the test's costs, sensitivity and specificity, and the cost-effectiveness of the subsequent treatment impact the cost-effectiveness of the test.

In the second sub-scenario, a new test is instead compared in two different test-and-treatment strategies: testing all patients immediately following diagnosis is compared with first attempting the standard treatment and then only testing those that do not obtain an effect from the standard treatment.

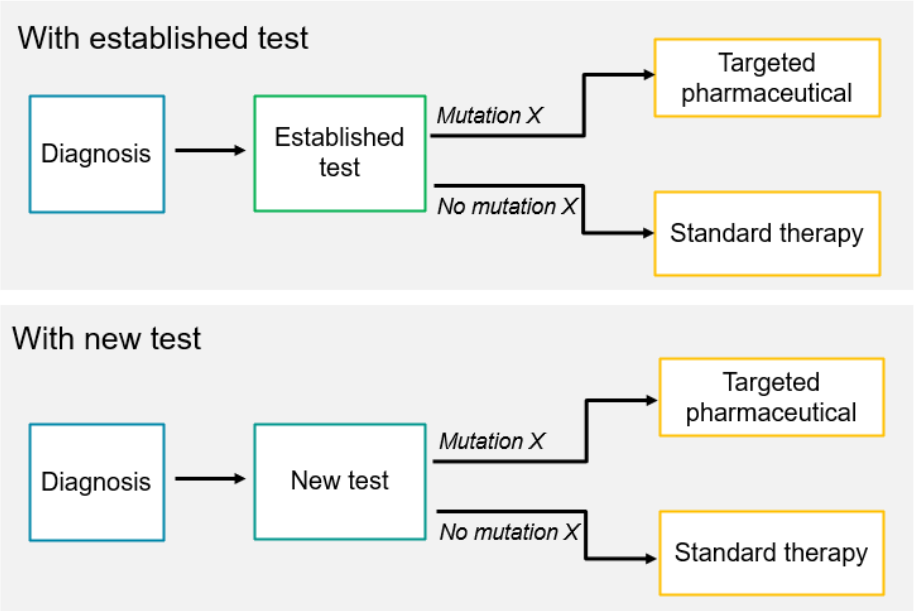
In a background report for this project (Henriksson and Gruneau), additional scenarios are analysed using health-economic model simulations (41).

4.3.2 Assessment of a new test within the same test-and-treatment strategy as the established test

Scenario IV
In this scenario, a new test is compared with an established test within the same test-and-treatment strategy.

A new treatment-predictive test has been developed which can identify mutation X through a particular diagnosis, and which replaces the established test. While the new test has a higher price, it also has better sensitivity and specificity.

Is the new test cost-effective compared to the established test?



In Appendix 1, we demonstrate how the cost per QALY can be calculated in this example scenario. We then see that the new test shows better cost-effectiveness compared to the established test when:

- the cost difference of the new test is smaller, in comparison with the established test (where all costs associated with the test are taken into account)
- the difference in sensitivity and specificity is greater for the new test compared with the established test
- the pharmaceutical is more cost-effective compared with the standard treatment for patients who are correctly identified as having the mutation
- the targeted pharmaceutical is less cost-effective compared with the standard treatment for those who are incorrectly identified as having the mutation.

The last two points suggest that in order to assess the new test, we must know what the cost-effectiveness is for the subsequent treatment, which significantly complicates the assessment. It is only if the new test is both superior (has higher sensitivity and specificity) and cheaper than the established test, that the cost-effectiveness of the subsequent treatment does not need to be taken into account. If the new test is costlier and superior, we need to know how much these superior features are worth, which depends on the cost-effectiveness of the subsequent

treatments. However, such a complete analysis can be overwhelming. TLV considers identifying reasonable simplifications to be an important aspect of its work.

If the choice is between two tests, where one has better sensitivity and the other better specificity, which property is most important? Or in other words, is it more important to have a high percentage correctly identified as having the mutation or to have a lower percentage that is incorrectly identified with the mutation? This is also dependent on the cost-effectiveness of the subsequent treatment. If we have a scenario where the targeted pharmaceutical is priced so that it is on the verge of being cost-effective for patients who are truly positive, then specificity is most important. The reason is that in such a scenario, the greatest importance is to minimise the proportion of patients incorrectly identified as having the mutation – this is where the most QALY can be gained. If, conversely, we have a scenario where the targeted pharmaceutical has a high cost-effectiveness, then it is important to ensure that as many true positives as possible receive the treatment, which will result from the test's high sensitivity.

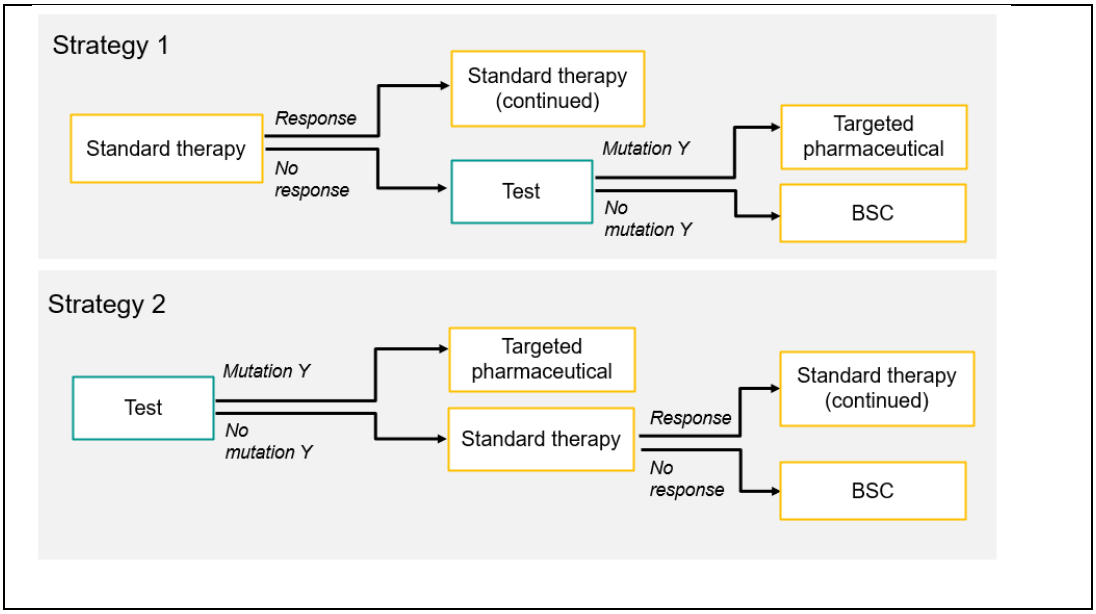
4.3.3 How do we determine whether it is more cost-effective to perform a test immediately following diagnosis or only after the standard treatment has been attempted?

Scenario V
A new test-and-treatment strategy is compared with another test-and-treatment strategy: to test all patients immediately upon diagnosis or to first administer standard treatment to the patients and then test only those who do not benefit from the standard treatment.

A new treatment-predictive test is being developed that can identify mutation Y in a particular diagnosis. The purpose of the test is to identify which patients have mutation Y and thereby the effectiveness of the targeted pharmaceutical.

The different test-and-treatment strategies for the scenario are illustrated in the figure. In *Strategy 1*, all patients receive the standard treatment first. Those who respond to and tolerate the treatment then continue with the same treatment. Those who do not respond to treatment undergo a genetic test to see if they have the right mutation to respond to the targeted pharmaceutical. In *Strategy 2*, all patients undergo the genetic test immediately following their diagnosis. Those with mutation Y receive the targeted pharmaceutical, while other patients receive the standard treatment.

The question we seek to answer here is: Is it more cost-effective to test all patients immediately following their diagnosis (Strategy 2), compared with waiting and seeing which patients respond to the standard treatment and test those who don't (Strategy 1)?



What are the decisive factors for whether it is Strategy 1 or 2 that is most cost-effective? We discuss this below. The scenario is deliberately simplified in order to highlight specific aspects. The background report by Henriksson and Gruneau presents a more detailed analysis (41).

In simplified terms, there are four categories of patients based on how they respond to each treatment:

- *'Target-oriented and standard'*. This group has mutation Y, so the target pharmaceutical works. However, the standard treatment also works for them. We assume that standard treatment is the cost-effective alternative – this is a key assumption for the following discussion.
- *'Strictly target-oriented'*. This group has mutation Y and responds to the targeted pharmaceutical, but does not respond to standard treatment. We assume that the targeted pharmaceutical is the cost-effective alternative.
- *'Strictly standard'*. This group does not have mutation Y, but responds to the standard treatment, which is cost-effective.
- *'None'*. This group does not respond to the targeted pharmaceutical or the standard treatment.

Figure 5 shows which treatment the different groups of patients ultimately receive, due to the different test strategies.

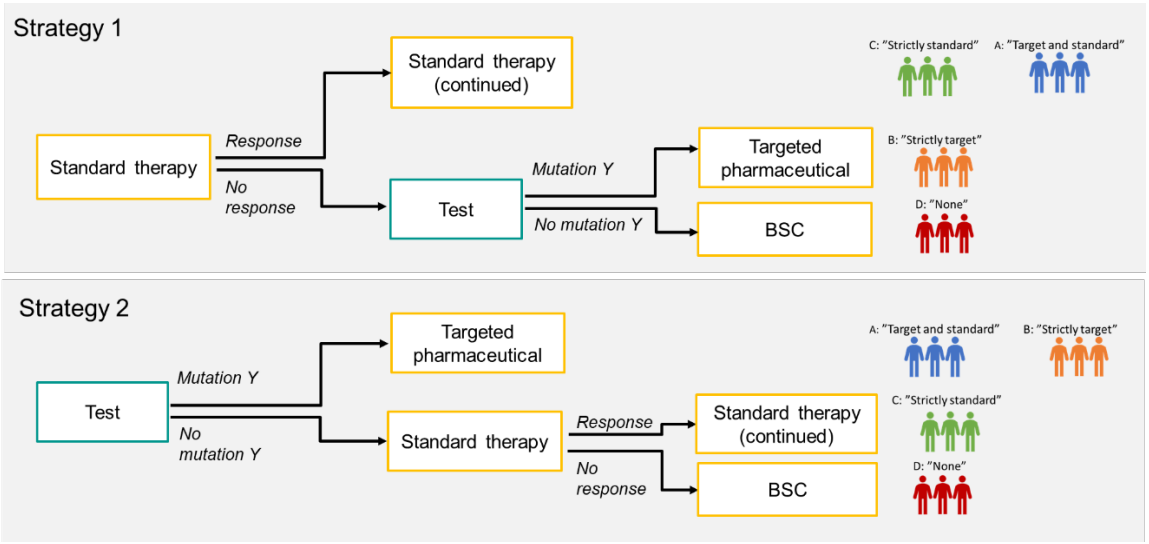


Figure 5. Distribution of different patient categories when the test has 100 per cent sensitivity and specificity

In this stylised scenario, only the patient group '*Target-oriented and standard*' receives different treatments depending on whether it is Strategy 1 or 2 that is chosen. Testing of all patients immediately following diagnosis, Strategy 2, therefore leads to this patient category receiving more expensive treatment than necessary. This is a disadvantage of Strategy 2. It is not possible to conclude that one or the other strategy is cost-effective without making quantitative assumptions about a number of factors, such as the proportion of patients in the different groups, cost per QALY for the different treatments and so forth. However, it is possible to establish how various factors impact the probability of Strategy 2 being the cost-effective strategy. If the group '*Target-oriented and standard*" constitutes a significant proportion of the total patient population, the probability decreases that it is more cost-effective to test everyone immediately (Strategy 2).

For the patient group, 'Strictly target-oriented', *Strategy 2 entails that they will receive efficacious treatment more quickly*. This is the advantage of Strategy 2. If the rapid insertion of treatment is a key factor, for example, because the disease has time to progress during the time that the standard treatment is assessed, the probability increases that Strategy 2 is cost-effective.

A number of on conlusions can be drawn from the simulation model in the background report (41). Strategy 2, to test everyone immediately following diagnosis, is more likely to be cost-effective:

- the smaller the price difference between the standard treatment and the targeted pharmaceutical
- the longer it takes to realise that the standard treatment does not work
- the faster and more irreversible a disease progresses
- the cheaper the test
- the smaller the proportion of patients who experience good effectiveness from both the targeted pharmaceuticals and standard treatments

- the greater the proportion of patients who have mutation Y and only benefit from the targeted pharmaceutical.

Low sensitivity of the test – may be supportive of Strategy 2

So far, we have assumed that the test can perfectly identify who has and does not have mutation Y, i.e. that the test has 100 per cent sensitivity and specificity. How is a cost-effective strategy impacted if the test does not have 100 per cent sensitivity and specificity?

Figure 6 illustrates what the outcome will be with a test that has low sensitivity, i.e. if the test does not find all the patients who have mutation Y. Perhaps somewhat surprisingly, a test with low sensitivity increases the probability that the strategy where we test everyone directly (Strategy 2) is most cost efficient. To clarify, if we have a scenario where Strategy 2 is not cost-effective if we have perfect testing (100 per cent sensitivity and specificity), then a test with poorer sensitivity could mean that strategy 2 is cost-effective.

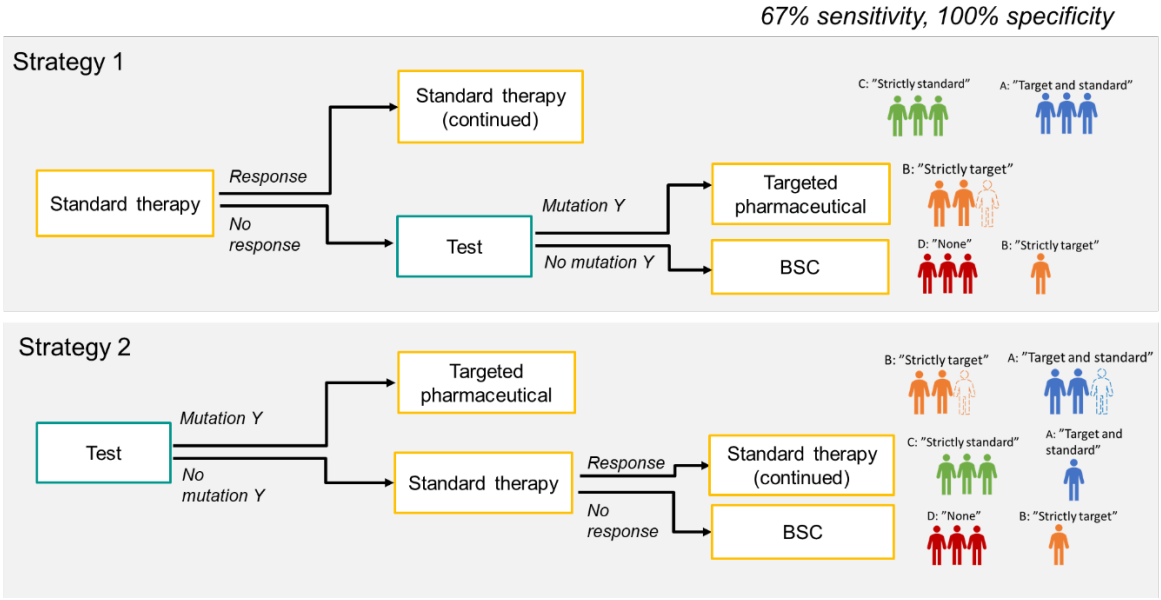


Figure 6. Distribution of the different patient categories when the test has low sensitivity

Why? As mentioned above, the disadvantage of Strategy 2 is that the patient group 'Both target-oriented and standard' will receive the targeted pharmaceutical, which is not cost-effective for this patient group. With a test of lower sensitivity, a certain proportion of these patients receive the standard treatment instead.

This should *not* be interpreted as meaning that a test with low sensitivity is a good thing. Low sensitivity leads to making the wrong decisions – some of the patients who can only respond to the targeted pharmaceutical will not receive it. However, this adverse effect of low sensitivity occurs regardless of whether we choose Strategy 1 or 2.

Low specificity of the test – does not support Strategy 2

Figure 7 illustrates what happens to a test that has low specificity, i.e. patients who do not have mutation Y incorrectly test positive for the mutation. Here, the sensitivity is at 100 per cent, which means that the test captures everyone who has the mutation.

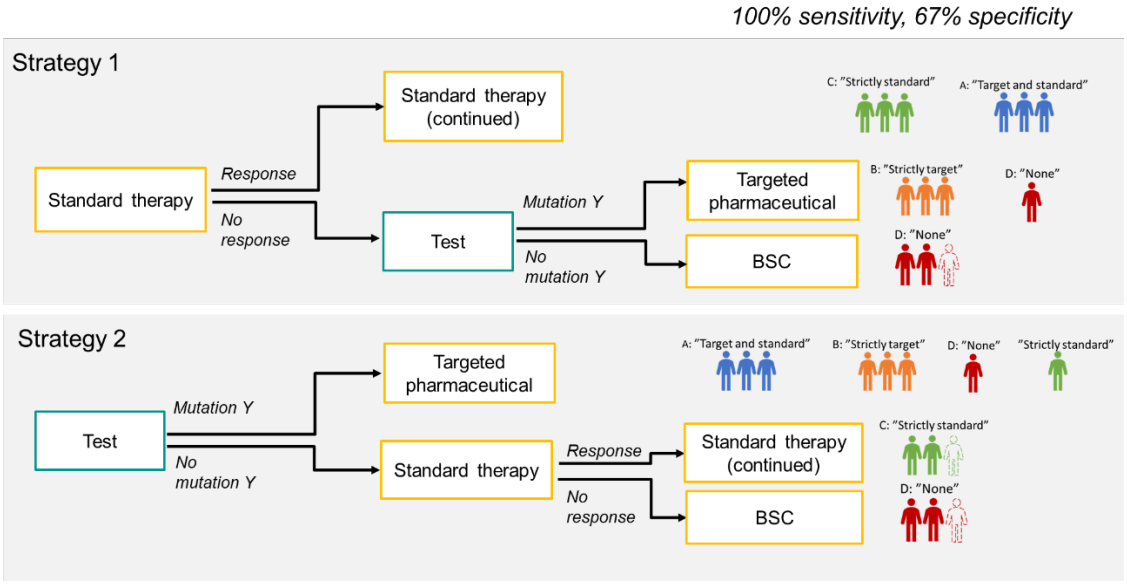


Figure 7. Distribution of the different patient categories when the test has low specificity

The conclusion here is that the lower the specificity of the test, the less likely it is that Strategy 2 is the more cost-effective strategy. This is because more people will test positive for the mutation, and with Strategy 2, more people will be treated with the targeted pharmaceutical but will not respond to it.

The importance of the accuracy of the tests is confirmed in an article (42). The authors are of the opinion that sensitivity and particularly, specificity, may be more important than the cost of the test.

4.3.4 Tests to diagnose and assess risk – the example of gene expression analyses to estimate the risk of breast cancer

In this chapter, we have so far focused on a certain type of test: treatment-predictive tests that are performed after a diagnosis has been made. Precision medicine also entails an increasing use of molecular-based diagnostic and prognostic tests. These are tests that allow for a more accurate and earlier diagnosis, or for an individual's risk to be better assessed. Of course, such information could also impact the subsequent treatment, but the test is not as closely linked to the pharmaceutical as a treatment-predictive test is.

One example of prognostic tests is what is known as 'gene-expression analyses', which are designed to estimate the risk of breast cancer relapses. TLV is currently evaluating several such tests. The idea is that the tests should be able to improve decisions about chemotherapy so as avoid both overtreatment and undertreatment. Some patients who, according to conventional clinical-pathological assessments, are

deemed to have a high risk of relapse may, through the gene-expression analyses, in fact prove to have a low genomic risk of relapse. The doctor can then consider refraining from chemotherapy – without causing significant deterioration to the survival rate. Other patients who with traditional methods are deemed to have a low risk may, on the contrary, prove to have a high genomic risk of relapse. This could be an indication that they would have benefited from chemotherapy, even if they are not indicated according to conventional clinical-pathological assessments.

There are several challenges to assessing these tests from a health-economic perspective, one of which is the lack of evidence. What is the health gain in terms of survival for those who would otherwise be undertreated with chemotherapy? What is the health gain in terms of higher quality of life for those who would otherwise be overtreated?

Useful evidence could consist of, for example, randomised clinical trials, where one group of patients is tested with a gene-expression test while the other group receives a traditional risk assessment. Some of the assessed tests had corresponding tests that utilised traditional effectiveness parameters, such as progression-free survival (PFS) and overall survival (OS). The advantage of using clinical outcome parameters such as PFS and OS becomes evident when there are discrepancies in the results of various tests that are assessed using intermediate parameters. One study compared five gene-expression analyses in the same population, and only 39 per cent of patients received the same risk assessment (low/intermediate/high risk) in all of the tests (43). It was also not uncommon for one test to show a high risk result and another test to show a low risk result for one and the same patient. Such discrepancies can be difficult to relate to on the basis of the usual parameters, such as sensitivity and specificity, since there is no well-defined ‘golden standard’ for such prognostic tests.

This further underscores the value of clinical trials covering both the diagnostic stage and the health gains of the treatment that is introduced based on previous diagnostics.

4.4 When costly on-patent pharmaceuticals are used in combination: How do we determine a reasonable cost?

4.4.1 Products used in various combinations can be challenging to assess

Combination usage may involve two or more products being used consecutively, in a sequence. It could also entail the simultaneous combined use of two different pharmaceuticals – a development that some believe will become increasingly commonplace, especially in the field of anti-cancer (44).

If two costly original pharmaceuticals are combined and one of them was originally priced based on its use as a monotherapy, the cost of the combination will often be

far too high to be considered reasonable.[7]Consequently, the main challenge is to incur a cost for the combination that is not the sum of the price of the included pharmaceuticals when they are used in monotherapy. A report by Towse et al. describes this as comprising four sub-problems (45):

1. *The incentive problem*. If the reduced price of a pharmaceutical when it is used in combination 'spills over' onto the price when it is used as a monotherapy, the company will often not have the incentive to lower the price, because overall sales revenues may fall.
2. *The value-allocation problem*. How do we determine the value of the individual pharmaceutical's contribution to the overall effect of the combination therapy?
3. *The antitrust law problem*. How do companies negotiate about how the total cost margin for the combination should be distributed between the individual pharmaceuticals – in a manner that does not contravene antitrust law?
4. *The implementation problem*. How do we implement the indication based pricing that must probably be applied, in order for the price of a particular pharmaceutical to be variable depending on whether it is used in monotherapy or in combination?

The problems of value allocation most closely pertain to the issues we are addressing here. An important starting point for the discussion is what was mentioned at the beginning of the chapter, that when products are used in combination, there is no objective way of determining how much the different products contribute to the total value. This is a complication of value-based pricing, because this method of price regulation, in simple terms, is based on the price corresponding to the value.

4.4.2 TLV is of the opinion that it does not have the main responsibility for allocating the total cost between the various products

TLV has assessed a number of combinations in recent years. As is the case with the corresponding agencies of other countries, TLV considers the price of the pharmaceutical that is already on the market and used in monotherapy as a given fact. If, for example, Pharmaceutical A in monotherapy is the standard treatment, and it is the combination of the new Pharmaceutical B and A that is to be assessed, there is already a price for Pharmaceutical A that can be referenced.

However, if the price of Pharmaceutical A is considered a given fact, a problem known as 'not cost-effective at zero price' may arise. This occurs as a consequence of the fact that for each additional month of survival that the combination provides, the patient will use the Pharmaceutical A for the same length of time. If Pharmaceutical A is then priced so that it is exactly on the verge of being cost-effective, Pharmaceutical B must have a negative price for the combination to be cost-effective (46). Towse et al. are therefore of the opinion that the price of Pharmaceutical A must be reduced when used in combination with Pharmaceutical

[7] The problem may occur even if neither of the pharmaceuticals are used in monotherapy, but both are only used in combinations. However, the problem is most obvious when one of the pharmaceuticals is used in monotherapy.

B (45). According to the authors, the amount to be reduced should be calculated using some method to allocate the total cost that is acceptable by the payer for the combination.

The report by Towse et al. proposes methods based on assumptions that the pharmaceuticals' effectiveness in monotherapy is leveraged: the effect in monotherapy either for both or only for one of the products. In simplified terms, the concept can be described as: If Pharmaceutical A provides 10 months of survival in monotherapy and Pharmaceutical B provides 5 months in monotherapy, then Pharmaceutical A is allocated 2/3 and Pharmaceutical B is allocated 1/3 of the total value when they are used in combination.

TLV can appreciate certain arguments for a public actor such as TLV to propose the allocation of the total cost, if this can facilitate accessibility. This could, for example, be justified in situations where companies have limited opportunities to negotiate due to competition rules. However, TLV believes that it will be difficult to allocate the value with reasonable precision based on effectiveness as a monotherapy, partly because all the requisite data will rarely be available.

A simpler alternative to the above-described method is therefore to divide the cost equally between the two pharmaceuticals. The weakness of this alternative is that it does not reflect what the two companies have to gain from utilising the combination. If the alternative to using the combination A + B is to use either A or B in monotherapy, but A provides superior effectiveness, then the company behind B has more to gain from finding a solution where the combination is reasonably priced and thus becomes available. As we understand it, the purpose of starting from the effect in monotherapy is not primarily about justice, but to reflect how urgently the different companies need to find a solution and what the result would have been in a regular negotiation. However, TLV is of the opinion that it is probably possible to find methods that allow for companies to negotiate on how the total cost should be distributed (see section 4.4.3 for further discussion), but then a distribution, as proposed by TLV, risks being both unnecessary and irrelevant.

To summarise our position on what we refer to as the value-allocation problem above, we are of the opinion that it should not be a priority task for TLV to utilise advanced methods to distribute the total cost between the individual products.

4.4.3 It is important to find methods for the reasonable pricing of combinations so that patients can have access to them

With regard to the larger complex of problems to find solutions to the four above-listed problems, TLV deems this to be urgent task.

Our assessment is that these challenges are best managed using models that allow for flexible payment and pricing mechanisms. Part of the solution may be for the pharmaceutical that is priced based on its use in monotherapy to obtain a lower price when used in combination. In this assignment, TLV does not take a position on whether the need for different prices for different uses is best solved through 'genuine' indication-based pricing, or by the pharmaceutical having the same price

for all uses, but one where the price reflects its usage in both monotherapy and combination therapy. Nevertheless, TLV estimates that the solution in the next few years will be based on agreements between companies and regions. TLV therefore proposes an in-depth collaboration between TLV and the regions to develop methods for managing the fact that a pharmaceutical is used in different situations and that the price of a product may sometimes need to vary depending on how it is used.

TLV has previously investigated the prerequisites for the negotiation and pricing of combination pharmaceuticals; a major challenge is the lack of data

The Pharmaceutical Inquiry addressed the pricing challenges created by combination therapies. (47) One of the possibilities mentioned was that TLV could set up a digital platform with cost frameworks, through which competing companies would be able to offer prices. This is similar to procedures sometimes used in public procurement, when no single company can deliver the product or service in question. In light of this, TLV conducted a pilot study on a national platform for price negotiation to identify possible methods for setting prices for combination treatments (48).

The initiative identified several challenges, mainly in terms of legal prerequisites and opportunities for follow-up. Differentiated pricing, where the price of a product varies between the different fields of application, is requisite on follow-up data at the individual level. Consequently, for the parties to enter into a meaningful agreement based on the fact that a certain price only applies if one product is used together with another, there must be an agreed method to identify this particular form of usage. Today, there is no possibility of tracking the use of hospital pharmaceuticals in a structured and automated manner, which limits the situations where such a model could be applicable.

The pharmaceutical industry also considers it a priority to find a solution to these situations

In a request to the Ministry of Health and Social Affairs, the Pharmaceutical Industry Association (LIF) proposed a joint project between the pharmaceutical industry, Sweden's regions and the state (TLV) to improve access to cancer treatments for patients. (49) The aim of such an initiative would be to – by enabling the signing and follow-up of agreements – report how many cancer patients have had access to combination therapies.

5 The treatment's added values – what does the assessment include?

In this chapter, we expound on the following:

- There is an ongoing discussion about whether the traditional health-economics method captures all the important values associated with medical treatments.
- We describe and discuss several of these aspects that are deemed to be particularly relevant to precision medicines and ATMPs. We do not draw any definite conclusions as to whether there are reasons to include these in decision-making processes, but note that there are currently no methods for capturing them adequately.
- TLV is of the opinion that most important for a health-economic assessment is to capture well the two aspects that QALY measures: the effectiveness of treatments on health-related quality of life and longevity, relative to the treatment alternatives.
- If additional aspect(s) are deemed to be important and ethically reasonable to take into account, these should be included regardless of whether they pertain to a precision medicine, ATMP or other type of treatment.
- The greatest obstacle to gaining a true picture of the value of new precision medicines and ATMPs, will be the uncertain evidence of relative clinical benefit – particularly in the long term.
- If a treatment improves the ability to work, productivity, it is uncontroversial that a higher quality of life should be included as a positive effect in the health-economic assessment. Although TLV previously factored in the monetary value of the extra production that gainful employment entails, it updated its methods several years ago. The reason is that we believe that it is not compatible with the human-value principle to prioritise health care based on how much the different patient groups contribute to production in society.

5.1 When the value of medical treatments must be captured in the health-economic assessment

There is an ongoing discussion in Sweden, as well as internationally, about whether traditional health-economic methods capture all of the values associated with medical treatments. The discussion is taking place both in scientific contexts and in more general health care debates (50). Precision medicines and ATMPs are sometimes mentioned as medical technologies for which today's assessments do not capture all the values.

Those who believe that the methods and bases for decision-making need to be developed do so, according to a few different points of departure. It is sometimes argued that the methods used to measure health-related quality of life leave out important treatment aspects. The solutions proposed are partly to apply other measuring instruments to better capture the patient's quality of life in the QALY parameter, and partly to use a measure other than QALY. Another line of argument is that there are aspects besides purely health-economic ones (costs and health gains) that should be taken into account in decision-making, but which are currently not considered. Currently, TLV factors the severity of the disease and in some cases, the rarity of the condition, but in the debate, it is proposed that certain other aspects also be taken into account. A third line of argument is that the average QALY gained is not always important to the patient. In some situations, a small chance of a big health gain may be more valuable than a big chance of a small health gain, even if the average health gain is the same.

Based on this, it has been suggested in the debate that methods should be developed to better ensure that all important values of medical treatments are quantified and taken into account. TLV is of the opinion that before the methods can be updated, some questions must be answered. First, should the value aspect be taken into account when prioritising public health care resources? The needs-and-solidarity principle states that serious health conditions must be prioritised over less severe ones. Does this also mean that certain types of values, more strongly linked to the patient's health-related quality of life and life expectancy, should be given priority over others? Secondly, if a certain value aspect should be taken into account, do we know that it is not already being captured by current health-economic methods and other decision criteria? Thirdly, if it is not already captured today, are there stable methods for quantifying or otherwise describing its extent?

Our ambition in this chapter is not to provide conclusive answers to these questions – that requires more work than has been possible within the framework of this assignment. Our purpose is instead to describe what patient values are particularly well-defined for precision medicines and ATMPs, and to describe and discuss some of the patient values that are highlighted by health-economics researchers as being important, but which they believe are not being captured by current methods.

Finally, we explore the socio-economic perspective: what it means to apply the perspective exhaustively and why TLV changed its approach several years ago and now applies a more limited socio-economic perspective.

5.2 Precision medicines and ATMPs – what values are added for the patient?

5.2.1 Precision medicines and ATMPs provide opportunities for increased benefits to patients

Some of the characteristics of precision medicines and ATMPs can be said to contribute to added values for the patient:

Diagnostics and risk forecasting

- Earlier and more accurate forecasting of risks. For example, by identifying a mutation that can lead to future disease.
- Earlier and more accurate diagnosis. For example, stratification of a patient population into smaller groups with different possibilities of responding to different treatments.
- For certain rare diseases, the possibility of diagnosis. For example, when patients, following several years of serious disease, uncertainty and numerous health care contacts place great value on being able to obtain a diagnosis, even if there is no available treatment.

Treatment

- Opportunity to implement preventive measures. For example, pharmacological or surgical prevention of a disease that the patient has a proven genetic disposition to.
- Faster effect or better treatment. For example, in the form of a targeted pharmaceutical against a target molecule identified in the patient. Targeted treatments often provides greater effectiveness than pharmaceuticals with a more non-specific mechanism of action.
- Opportunity to avoid ineffective treatment. For example, after the detection of a mutation that causes resistance to a certain targeted treatment.
- Opportunity to avoid side effects. For example, by choosing another treatment or lowering the dose for individuals with a proven elevated risk.

Opportunity for a considerably large health gain

- Potential cure, and thereby reduced anxiety and the need for lifelong treatments.

All of these characteristics are closely related to the patient's health, which QALY is aimed at capturing. This is not to say that they are always fully captured. The methods of measurement may sometimes be too blunt, especially for certain attributes. For example, TLV is of the opinion that it can be difficult to quantitatively capture the patient's reduced anxiety and frustration from finally receiving a clear diagnosis of his/her serious disease, or being cured of a lifelong disease. Two of the four value aspects discussed in the next section of this chapter concern this: the value of knowing and the value of healing. The two other value aspects that are discussed, *the value of taking risks in the hope of a good treatment effectiveness* and *the value of future treatments*, pertain to the expected number of QALYs gained not always revealing the whole picture.

Some precision medicines and ATMPs are used for rare disease conditions. From TLV's perspective, the argument that traditional health-economic methods do not capture all the values is even more pronounced when it comes to rare conditions. The reasons are that in these cases, there are often no validated outcome parameters, that there is larger heterogeneity in the disease, lack of knowledge about the natural course, short follow-up periods in the studies and that it is more difficult to study patient preferences with a small patient population (51).

The value aspect that has probably been most discussed in recent years – but which is not specifically associated with precision medicine or ATMP – is the effect a disease has on the quality of life of close relatives, i.e. whether an assessment of a treatment should take into account that the quality of life of relatives improves if their care burden decreases. Different countries differ in this regard. In some countries, the government agencies evaluating medical technology consider this aspect, while in other countries they do not. For example, TLV does not currently take this aspect into account, while NICE in England does (52). In addition to the question of *whether* the aspect should be taken into account, there are many uncertainties as to *how* it should be done in that case, and whether there is data that can credibly quantify the effect. The issue is not sufficiently closely linked to precision medicines and ATMPs and is too complicated for us to provide a true picture of the discussions about these issues. However, TLV sees a need to investigate the issue further in a different context.

5.3 TLV has selected four value aspects for in-depth discussion

TLV has reviewed the literature on value aspects with a focus on identifying those of particular relevance to precision medicines and ATMPs. A number of key scientific articles and reports have been selected as the basis for the review. TLV has assessed four aspects that are of sufficient interest and relevant for further analysis; see Table 1. For these aspects, we have presented a description of how they relate to current health-economic methods and decision criteria. Do we consider that the aspects are captured by current methods for measuring health-related quality of life and thus QALY? Are they otherwise captured in decision-making processes? What does the literature say about the possibilities of capturing the aspects? In the following section, the value aspects are defined and explained in more detail. 131

Table 1. Value aspects that TLV assessed in the course of this government assignment

Value aspect	Definition	Remarks
Value of knowing *Value of knowing* Relevant to precision medicine	The value for the individual to obtain knowledge about his/her risks, presence of disease or prognosis of an existing condition – completely regardless of whether there is an effective intervention	This aspect is relevant for evaluating certain types av tests. TLV deems that it can be difficult to capture this aspect with traditional quality-of-life instruments such as EQ-5D, despite the fact that the instrument contains a dimension aimed at capturing worry and anxiety. It is thus uncertain that this can be fully captured using QALY. There are examples of willingness-to-pay studies of this value. Different individuals may have different opinions about whether it is helpful or unhelpful to gain knowledge of a risk or a disease, if there are still no medical interventions available.
The value of taking risks in the hope of good treatment efficacy. *Value of having the choice among treatments with a different balance and timing of risks and benefits* Relevant to precision medicines and ATMPs[1]	The value for patients in taking risks on the choice of treatment in the hope of good treatment efficacy This aspect pertains to how the average QALYs gained is not always the relevant factor, but that a patient may be willing to take a risk: preferring a treatment that yields 5 QALY with a 10 per cent chance, over a treatment that yields 0.5 QALY with a 100 per cent chance, even though the average QALYs gained is the same.	The aspect may be relevant in special situations, e.g. in serious diseases with a very poor prognosis with currently available treatments, where there is an alternative of high potential but which is also asscoiated with a risk. This aspect is not captured by a traditional health-economic assessment, since it proceeds from the premise of the average QALYs gained. There are examples of willingness-to-pay studies of this value. It is likely that some individuals, contrary to the basic assumption of this value, may be reluctant to take risks.
The value of future treatments *Real option value* Relevant to precision medicines and ATMPs	The value of an existing treatment prolongs life so that the patient can be treated with pharmaceuticals that may be developed in the future.	This value is not captured by traditional health-economic assessment methods; the value of a possible future treatment is seldom calculable. It is a challenge to quantify the benefits of new treatments before they become available. To the knowledge of TLV, there are no studies that have attempted to capture this value.
Value of a cure *Value of a cure* Relevant to ATMPs.	The added value that comes from being cured, even if a patient, through current lifelong and continuous treatments, is asymptomatic and is expected to have a normal lifespan.	The psychological value of being cured is difficult to capture using the traditional QALY method. The value has not been described in detail in literature and neither is the concept of "cure" well-defined. Some believe that the value of a cure can be captured by other value aspects, while others believe that there is a psychological value that is not captured by other values.

5.3.1 The value of knowing

Definition and description

The value of knowing is discussed in connection with tests that provide a diagnosis or indicate an elevated risk. The reasoning is based on the fact that these tests could have a psychological value for the individual patient, in addition to the medical value of the tests that enable the introduction of an intervention. (53) (54) The value lies in the reduced state of worry and anxiety that the individual obtains from knowing the status of the disease or risk of suffering from a disease in the future. One example of this could be if close relatives have been affected by cancer and a person therefore suspects that they themselves are at greater risk. To then know that there is no increased risk can reduce anxiety. However, the psychological value of information from a test has been highlighted as something that can be perceived as both positive and negative (55) (56).

There are empirical studies on this value, which indicate that in certain situations, for a certain percentage of patients, there is a positive value of knowing, regardless of the medical opportunities to treat the detected disease or the existing risk. In a study by Neumann et al., 1,463 participants imagined hypothetical scenarios on the risks of contracting various diseases: Alzheimer's disease, rheumatoid arthritis and prostate and breast cancer. (55) The participants were then required to answer a questionnaire about how much they were willing to pay for a (prognostic) test that shows the risk of contracting the disease, regardless of the medical opportunities to treat the disease. The study showed that the participants had an average willingness to pay between USD 109–263 (equivalent to approximately SEK 1,000–2,500) to take a diagnostic test for these diseases. In another study by Lin et al., a total of 40 willingness-to-pay studies for prognostic tests were compiled in a literature review. (57) The authors concluded that the average willingness to pay was just under USD 100 (approximately SEK 1,000), but that there was a considerable variation between individual studies.

The value of a diagnostic or 75urrent75icc test for the individual can be impacted by the disease in question. There may also be variations between an individuals' ability to receive and process the information from a test. Through a literature review, Lee et al. compiled factors that were considered significant for the extent to which individuals appreciate information from a diagnostic test. (54) The most important factors that stand out are the individual risk of falling ill, how long it is expected to take before the disease occurs, the accuracy of the test and the individual's reluctance to receive a negative message.

Information from a test may also have a negative value for the individual patient if the result consists of 'bad' news, as mentioned above. A study by Denberg et al. examined the causes of incomplete compliance with screening for colon cancer. (56) The study reports that 7 per cent of all participants did not want to undergo screening for colon cancer for fear of being diagnosed.

Discussion

One concrete example of the value aspect could be a patient with a rare and difficult-to-diagnose condition that results in long-term uncertainty and many recurring health care contacts for the patient. A genetic test could facilitate a diagnosis that would make it easier for the patient to live with the disease.

The medical value of a prognostic or diagnostic test – if it leads to an intervention that yields a health gain – could be captured using TLV's current health-economic methods. The psychological value in the form of reduced anxiety and frustration is more difficult to capture. Although willingness-to-pay studies have been referenced, TLV is of the opinion that considerable uncertainty prevails about how the results of such studies should be interpreted. There is probably also a high degree of heterogeneity between patients and diseases in terms of value quantification.

5.3.2 The value of taking risks in the hope of good treatment effectiveness

Definition and description

Studies of patient preferences have shown that those with serious medical conditions may be willing to take risks in choosing between treatments, especially when the prognosis for survival is poor[8] (58) (59). Lakdawalla et al. posit that there is a value for risk-inclined patients to have the opportunity to choose a treatment alternative with a small chance of a large health gain, over an alternative that provides a high probability of a low health gain (50). This is true even if the average health gain, measured as QALY, is the same for both treatment alternatives. This means that the patient may prefer a treatment that has a 10 per cent probability of providing 5 QALY, over a treatment with 100 per cent certainty or providing 0.5 QALY, even if the total number of QALYs gained for both treatments is 1 QALY.

Lakdawalla has also conducted a study of 150 cancer patients who were undergoing chemotherapy or radiotherapy, or who were recently diagnosed (60). The participants were asked to rate two different treatment alternatives for an advanced form of cancer – malignant melanoma and breast cancer. The study showed that 71 per cent of the participants chose a treatment alternative that provided a chance of prolonged survival, while at the same time, a risk of poorer quality of life. A minority of participants chose the treatment alternative that guaranteed moderately high effectiveness. The treatments had the same average survival rate.

Garrison et al. have identified this value aspect as being particularly relevant to ATMPs (61). This is because the individual may be more inclined to take risks if there is a probability of being cured. Further studies have concluded that this value aspect could potentially be relevant to include in an assessment of ATMPs as a complement to QALY (58) (62) (63).

[8] The ICER (Institute for Clinical and Economic Review) in the US has reworked this value aspect somewhat by focusing instead on the value that arises from the patient having a choice between two alternatives with different risk-benefit balances [2].

Discussion

Based on the articles identified, it is reasonable to conclude that there may be situations where the patient prefers a treatment that is associated with a higher risk alongside a greater health gain, over a treatment with a lower risk and less health gains. This is true in cases of serious disease where there are no good treatments available.

The value of taking risks in the hope of a good treatment effectiveness is not captured by TLV's current health-economic methods, as the methods are based on average effectiveness. However, we deem that to date, no stable methods have been developed for how to capture the value or for determining the situations in which it would be relevant to do so.

5.3.3 The value of future treatments (real option value)

Definition and description

One value aspect that has been highlighted in the field of oncology in recent years is the value of the current treatment prolonging the patient's life, so that the patient can benefit from any future treatments that may be developed. Today's treatment might not be revolutionary, but if it can prolong life for a few years until a curative treatment is developed, that would in itself constitute a value. Those who advocate that this value be included in health-economic assessments thus believe that the value of any future treatment should be factored as a value of the current existing treatment (58) (59) (63) (64).

A report by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) states that in choosing between two treatments that provide equal QALY gains – one providing a life extension and the other an improved quality of life – a patient may prefer the one that prolongs life. This may be the case if the patient values the possibility of benefitting from future treatments (50). There are some sporadic studies that have quantified the value of future treatments. One example is a study by Sanchez et al. that retrospectively estimates the value of future treatments for patients with the disease, acute myeloid leukaemia (65). The authors used the survival data of two treatments used for the same condition: a first treatment that prolonged life for several years and a second treatment that was introduced several later and which further extended life. The patients would thus not have been able to benefit from the survival gain of the second treatment, if they had not received the first. In the study, the value of the first treatment was estimated by calculating the overall survival rate, presupposing the patient's subsequent access to the new treatment. A similar example has been illustrated by Snider et al., who evaluated an existing treatment for breast cancer by calculating the probability and duration that survival can be prolonged by new treatments in the future (66).

Discussion

There are several examples of fields of therapy where treatments have extended the lives of patients and where new, more efficacious treatments have been introduced at a later stage, which the patients were subsequently able to utilise.

TLV's health-economic assessments do not include the potential value of future treatments that do not yet exist. To our knowledge, neither is this the practice of corresponding government agencies in other countries. Although there are concrete examples of this value aspect being referenced in practice, it is a challenge to take into account the value of future treatments without any knowledge of what benefits these treatments may entail. The examples given to quantify the value aspect assume that data on the future treatments either already exists or that it is possible to statistically estimate the degree of innovation within a certain field of therapy over time, and enter such a factor as a template.

5.3.4 The value of cure – to be free from disease-related symptoms and subsequent treatment

Definition and description

The hope with some ATMPs is that they can cure the patient, i.e. completely eliminate the disease so that no symptoms remain – or at least no progression occurs – so that no further treatment is needed. There is a discussion about whether pharmaceuticals that lead to a cure should be attributed an extra value, in addition to the health gains captured by the QALY parameter. For example, if we compare two treatments for a chronic disease – one that provides continuous life expectancy vs. a cure – both of which lead to symptom relief and normal life expectancy, the curative treatment would have a higher value for the patient. The reason is that the patient avoids lifelong medication and the anxiety of harbouring the underlying disease.

Several researchers are therefore calling for new or complementary approaches to capturing this value (63) (67). At the same time, it is conceivable that this value aspect is captured by other value aspects that we have mentioned: 'the value of taking risks in the hope of a good treatment effectiveness' and 'the value of future treatments'. Garrison et al. and Pearson et al. provide examples of value aspects that can be associated with potentially curative treatments, while emphasising that there are currently no established methods that allow for weighing these aspects within decision-making processes (62) (63). The Institute of Clinical and Economic Review emphasises that it is challenging to include the value of cures, partly due to the risk of duplicate calculations and partly because there will be an imbalance, when the proposal is to include only positive value aspects and no negative ones (68).

Studies have been conducted on whether individuals are willing to pay more for curative treatments (63) (69), i.e. a value in addition to the direct health gain, in the form of symptom relief and life expectancy. The British Office of Health Economics has studied patient preferences for various outcomes of pharmaceutical treatments with *discrete choice experiments* among 1,000 participants corresponding to the general population in the UK. In the study, 'cure' was not a single factor that influenced the participants' preferences between different treatment alternatives (70).

Another aspect put forward in the debate is the lack of a generally accepted definition of cure (68). In the field of oncology, the term cure is used for patients who are in remission or when cancer is no longer detectable after a certain period of time, for example, five years. However, there are studies showing that oncologists nevertheless have different views on when a patient should be considered cured, as the concept is multi-faceted and complex (68) (71). This further demonstrates the difficulty of adding an extra value for cure.

Discussion

Knowing with certainty that you have been cured of a chronic disease that requires lifelong treatment is likely to be of great value to the patient. However, if an extra value for cure is to be included in the assessment, what it must capture is *not* increased life expectancy or relief from symptoms, as those aspects are already captured by QALY. Instead, it is factors such as reduced anxiety and avoiding the discomfort of lifelong medication that constitute the added value.

However, TLV is of the opinion that some circumstances make it doubtful whether an extra value should be included for ATMPs. The first is that it will take a long time before it can be established that a certain pharmaceutical truly leads to a cure. Given this, we find it difficult to see that reduced anxiety about gene therapy for example, is of significance to the assessment. Often, the patient will not know whether he/she has been cured and gene therapy could create considerable concern that the disease will return or that the treatment itself will lead to other diseases in the long run. Naturally, the fact that 'cure' is not clearly defined further complicates the matter.

5.4 The background of TLV's current application of the socio-economic perspective

The purpose of this section is to discuss the socio-economic perspective in a health-economic assessment: what it means and why TLV changed its approach several years ago and now applies the socio-economic perspective differently than before. One way of summarising the TLV's practice today is to express it as: TLV applies as broad a societal perspective as can be accommodated within its ethical platform.

A health-economic assessment is based on a certain perspective

A health-economic assessment is always based on a certain perspective: a choice of which sectors' costs, savings and values are to be included. The discussion is often in terms of two alternatives: the health care perspective and the societal perspective. While the health care perspective only includes resource usage (costs) paid for within health care services, the exhaustive societal perspective includes all resource usage that is impacted by the provision of medical treatment, regardless of who pays and regardless of the type of resource usage involved. Furthermore, an exhaustive societal calculation includes the impact on a patient's resource generation, i.e. the extent to which they work.

The Benefits Act states that TLV must assess whether a pharmaceutical has a reasonable cost from a medical, humanitarian and societal perspective, and with

regard to the ethical platform adopted by the Swedish Parliament. In the inquiry (72) that preceded the Benefits Act, the argument for the societal perspective was that for many diseases, the cost of health care constitutes a smaller part of the total cost. The emphasis in particular was that the inability to work constitutes a major cost to society. The lost production-output value when the patient is unable to work was thus factored here as a cost. The inquiry therefore found that applying a narrower health care perspective and only factoring health care costs would mean that a large part of the societal costs are not captured.

In the first few years after the new Benefits Act came into force, TLV applied a relatively comprehensive societal perspective, which entailed including the production-output value. In 2015, the TLV updated its practice on this matter. The change in practice was due to TLV revising its view on whether it is compatible with the ethical platform's human-value principle when the capacity of patient groups for gainful employment is allowed to impact the specific medical treatment they receive access to. We describe below what the exhaustive societal perspective entails and why TLV changed its course.

The exhaustive societal perspective includes all resource usage and resource generation

A medical treatment can, in simplified terms, impact the patient's quality of life and the patient's life expectancy.

Treatment that impacts health-related quality of life

A disease that is associated with, for example, pain, limited mobility or mental illness not only impairs quality of life, but can entail a limit to opportunities for gainful employment. An inability to work can have a double negative effect on those of working age: it can lead to a further deterioration in the quality of life and a reduction in resource generation for society. Consequently, if a new pharmaceutical product relieves the symptoms and improves the capacity for work, the quality of life and resource generation (production-output value) increases. That such higher quality of life should be included as a positive parameter in the health-economic assessment is uncontroversial. However, including the production-output value is more debated.

If an exhaustive societal perspective is applied, the production-output value is included, since according to this perspective, all resource generation and all resource utilisation must be included. This is achieved by adding the production-output value, approximated by gross income, as a saving in the calculation. Thus, krona for krona, a direct pharmaceutical expenditure for the regions is equated with an increase in the patient's gross income: a pharmaceutical that costs SEK 100,000 per year is considered cost-neutral if one can expect the patient's gross income to concurrently increase by SEK 100,000.

Treatment that impacts life expectancy

A treatment that increases life expectancy could also impact resource generation and resource utilisation – the latter both in the form of publicly funded services and private consumption. The exhaustive societal calculation must therefore include the

net of consumption and production during the extra years of life (73). The net result looks different for different age groups. Those who are retired do not work, which makes the net result negative – consumption is greater than production. Providing life-saving treatments to patient groups in retirement ages would then be considered more expensive than doing so for a patient group of working age. It would also be considered more expensive to provide life-prolonging treatments to groups with disabilities or others who are not expected to work.

TLV's previous approach factored in this effect. For example, in a health-economic assessment for utilising Zytiga against prostate cancer, a disease in which the majority of patients are in retirement age, TLV described the effect as follows (74):

> 'Indirect costs are added to this patient age group, because production-output minus consumption equals a deficit – the prolonged survival of this age group thus giving rise to increased societal costs.'

If calculation and prioritisation were to be based on such grounds, then groups that do not work and which will not start working after treatment risk having poorer access to both quality-of-life improvements and life-prolonging treatments than others. After examining the ethical appropriateness of this approach, TLV found that it was incompatible with the ethical platform's human-value principle. Consequently, TLV changed its general guidelines for health-economic assessments upon obtaining feedback through a circulation for comment to several organisations (government agencies, patient organisations, companies) and health-economics researchers. Some of the researchers did not approve of TLV's amendments. Nor did the companies.

Additional aspects of the exhaustive societal perspective

In this context, we would like to highlight a few more aspects of the exhaustive societal perspective. Firstly, it is sometimes explained that if a pharmaceutical puts patients back to work, it leads to a cost saving for society – the treatment pays for itself. However, we rarely see evidence of this – if ever. The usual situation is that the inclusion of the production-output value for a pharmaceutical that enhances quality of life reduces the cost per QALY, but not to below SEK 0, i.e. it does not constitute a cost saving. Consequently, the pharmaceutical does not pay for itself, but entails a cost.

Secondly, as mentioned above, in the calculation of the exhaustive societal perspective, it is considered that increased gross income can be offset against a direct pharmaceutical expense. We present three reflections about this:

- While the cost of the pharmaceutical is certain, the inclusion of the production-output value is based on an assumption that the ability to work must increase. Studies demonstrating that this actually happens are rare.
- The pharmaceutical cost has a direct opportunity cost for health care – it displaces other care. However, the patient's gross income is mainly used for private consumption and does not benefit health care. Private consumption is important, but the calculation should show where the opportunity cost ends up, which it fails to do through the usual method of including the production-output value.

- In societal calculations, the benefit of health care must be weighed against the benefit of private consumption. According to economic theory, the deadweight loss of taxation – that taxes impact behaviour – must then be taken into account. The Swedish Transport Administration uses this approach in its societal calculations and multiplies costs by a factor of 1.3 (75). From a health care perspective, the benefits of various care interventions are instead weighed against each other within a given budget, and the deadweight loss need not be factored.

Consequently, TLV now applies a narrower societal perspective than before its change in approach. However, TLV does not adopt a strict health care perspective. Costs and savings outside of health care can also be taken into account. For example, whether or not municipalities save money if the need for personal assistance decreases is factored in when TLV assesses. The disadvantage of TLV's approach is that socio-economic efficiency becomes less important to subsidy decisions. The narrower perspective can thus be explained as giving due consideration to what fits within the ethical platform.

5.5 TLV has presently not taken a position on whether there is reason to include additional value aspects

TLV has no definite stance on whether there is reason to include, in the future, any of the additional value aspects that have been proposed. In this chapter, the purpose is to describe them and briefly refer to the attempts made to measure them. Our conclusion is that there is currently a lack of any evolved methods for capturing them adequately.

The discussion on prioritisation proceeds from the premise that health care resources are limited, and that if more money were to be spent on treatments that improve a certain value aspect, it would also entail that less resources will be spent on treatments that do not impact this value aspect, but which benefit patients in other ways. If new value aspects are taken into account, there will be a redistribution of how resources are utilised, although this does not mean that more health care can be provided.

The quality-adjusted life years (QALY) parameter is aimed at capturing health gains. TLV is of the opinion that this is the primary parameter to be considered. Unreliable evidence of health gains will be the greatest obstacle to gaining a true picture of the value of new precision medicines and ATMPs:

- compared with the treatment alternative
- for the different relevant patient groups
- in the long term.

Undoubtedly, obtaining better data on health gains is what will most manifestly improve the quality of the assessments and facilitate decision-making processes. A final reflection is that if additional value aspects are to be factored, these should not be tied to a specific technology – for example, factoring solely precision

medicines and ATMPs – but should apply to all types of treatments. TLV has arrived at this conclusion, because it deems that favouring a certain technology is not consistent with the ethical platform.

6 How do we describe and manage uncertainties?

In this chapter, we expound on the following:

- The greatest challenge to performing health-economic assessments will be the lack of evidence for long-term health gains.
- In general, we cannot expect more accurate cost estimates per QALY gained (ICER).
- It is important to distinguish between uncertainties in the estimated ICER and the uncertainty as to whether the ICER is above or below the level that the decisionmaker considers reasonable.
- It will often be reasonable to perform separate calculations for smaller subgroups for a treatment, based on factors that we know differ between the groups: prognosis, cost of comparison alternatives and so forth. However, data on the difference in effectiveness between the pharmaceutical and the comparison alternative will often not be finely divided enough for making different assumptions for different subgroups.
- In situations where genuine uncertainty prevails about long-term health gains (such as with ATMPs), one approach may be to allow the basic calculation to reflect that there is a probability of different outcomes. This can be achieved by using a basic scenario that consists of a probability-weighted average of different ICERs, where different outcomes have been assumed.
- Increased discount rates have been proposed as another method of dealing with the greater uncertainties of ATMPs. However, TLV does not recommend this.
- One way to reduce the uncertainty for the payer is to hold off on utilising the treatment until there is better evidence. However, the consequences of holding off on treatments differs from disease to disease. Consideration should therefore be given as to whether the long-term health effects of holding off on treatment should influence how much uncertainty is acceptable.

6.1 Uncertainty about clinical effectiveness leads to uncertainty about cost per QALY

Health-economic assessments are very data-intensive. In addition to capturing all the costs, the ambition is to capture the extent of health gains – measured in terms of health-related quality of life and life expectancy – that the patient achieves through a medical intervention.

In this chapter, we address a number of issues with regard to uncertainty:

- Are precision medicines and ATMPs associated with greater or different types of uncertainty in the estimated cost per QALY (ICER), compared with traditional treatments?
- What should be the basis for which level of subgroup analysis to choose for an assessment: access to evidence for subgroups or relevance to decisions about usage?
- How can uncertainties in health gains be reflected in the health-economic assessment? The focus of this question is on ATMPs.
- Is there a reason to estimate the future consequences for patients who hold off on treatment, if this is considered as an alternative to obtaining better information about the effectiveness of the pharmaceutical before it is used? If so, how do we describe and estimate the consequences?

6.1.1 Uncertainty in estimated cost per QALY *versus* decision uncertainty

It is not uncertainties in estimated ICER that are problematic for decisionmakers, but decision uncertainty – the uncertainty as to whether ICER is above or below the level that the decisionmaker considers reasonable. Estimated ICER may be very uncertain, but if the estimate is well below what the decisionmaker's reasonable threshold, it may still be clear that the pharmaceutical cost of is reasonable. Similarly, an uncertain ICER that is well *above* the level of reasonableness can clearly show poor cost-effectiveness; see Figure 8.

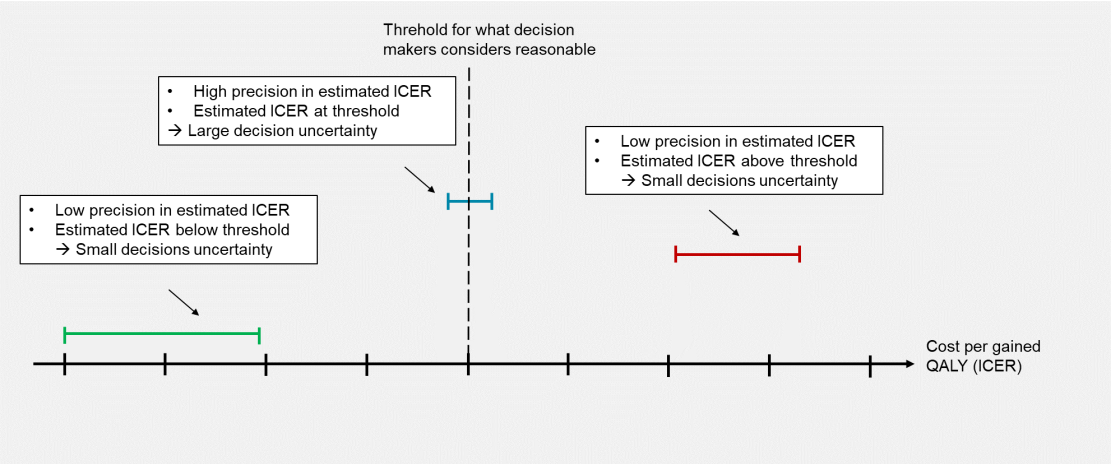


Figure 8. Illustration of uncertainty in estimated ICER and decision uncertainty

6.1.2 The designs of pharmaceutical trials provide scant evidence of the treatment's effectiveness

Today, pharmaceuticals are often granted market authorisation based on more limited data on clinical effectiveness than previously, as discussed in Chapter 3. The evidence is sufficient for the regulatory body to assess that the expected benefit outweighs the risks. However, it is challenging to assess the extent of long-term health gains relative to the comparison alternative, which is what authorities such as TLV must form an opinion about (76). Much of the uncertainty is generated by the design of the trials:

- Trial design – that the test frequently has no control arm.
- Outcome parameters – that surrogate endpoints are used instead of hard outcome data.[9]
- Sample size – that a small number of patients are included in the trial.
- Duration – that the trial is not conducted for such a long time.

That the trials are designed as such is not unique to precision medicines and ATMPs, although is more commonplace in these fields. There are several reasons for this. The products are aimed at health conditions that affect few patients, while there is a great need for new pharmaceuticals. A small patient sample size makes it more difficult to conduct larger trials. The immense requirements for new treatments make it crucial for patients to have quick access to the pharmaceuticals, which entails that larger Phase III trials with a control group are not necessary for obtaining market approval.

6.1.3 Precision medicine leads to more precise treatment, but not to less uncertainty in assessments

Part of precision medicine involves the use of molecular testing to obtain knowledge about which patients will potentially gain a treatment effect – and those who will not gain any effect. This entails an opportunity to be more confident that the treatment will work when it is administered to a patient, and in the long run that money is saved by not treating those who will not obtain any effect. Despite all of these factors, TLV finds that this does not result in less decision uncertainty than for other types of pharmaceuticals. Estimated ICER will not achieve higher precision, and the cost-effectiveness will obviously not be improved, despite avoiding the administration of treatments to patients who will not benefit.

That the estimated ICER does not increase in accuracy is due to the often limited clinical evidence at the time of approval. Although a molecular test can show who will and will not obtain an effect from the treatment, it does not show how efficacious it will be on those for whom the treatment works.

Due to price adjustments by companies, the pharmaceutical's cost-effectiveness does not necessarily improve even if treatment is avoided for patients who will not

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A surrogate endpoint is a laboratory value or a physical marker that is used as a replacement substitute for what is actually intended to be measured.[9] The hope is that changes in the surrogate endpoint will reflect changes in what is actually intended to be measured – the hard outcome data (105). Surrogate endpoints often capture the activity of a pharmaceutical instead of health outcomes.

derive any effect. In a value-based pricing system, companies set prices based on the average effectiveness for patients who are expected to receive treatment and who are included in the trial. If a pharmaceutical that is not subject to a test is administered to 100 people and 50 of them gain 1 QALY while the others obtain no effect, the average health gain is 0.5 QALY. If the company knows that the payer normally accepts a cost per QALY of SEK 1 million, it will in all probability choose to price the pharmaceutical at SEK 500,000. The cost of health care will then be SEK 50 million (SEK 500,000 * 100 patients). If we instead have a situation where an available test can indicate in advance which 50 people will be obtain an effect from the pharmaceutical, the average health gain for these patients is calculated at 1 QALY. In all probability, the company will then choose to set the price for the same pharmaceutical at SEK 1 million, and the health care cost will again be SEK 50 million (SEK 1 million * 50 patients). Both cost-effectiveness and the total cost will thus be the same.

6.1.4 Considerable uncertainties for ATMPs, if entire payment for lifetime effect is made in connection with onset of treatment

For ATMPs, there is an additional factor that increases the uncertainty of long-term cost-effectiveness: that payment cannot be terminated if, for example, the effect does not turn out as expected. We address some of these aspects later in this chapter, but primarily in chapter 7.

6.2 At which subgroup level should assessments be made?

In order for a health-economic assessment to be relevant to the health care system when making decisions on treatment, the assessment should be sufficiently adapted to the specific situation and the patient group. At the same time, there will often be a lack of sufficiently fine-grained effectiveness data for different subgroups of patients. We address this below, based on a specific situation. The background report by Henriksson and Gruneau presents a more detailed discussion (41).

Example: A new anti-cancer pharmaceutical with histology-independent indication is approved

Most anti-cancer pharmaceuticals are approved for use against a specific tumour type. Their specific usage is studied in clinical trials. An anti-cancer pharmaceutical with a histology-independent (also knowns as ‘tumour agonistic’) indication is characterised by the indication being based on the presence of a certain genetic abnormality in the tumour, regardless of the organ in which it originated. Although the pharmaceutical may be used for different tumour types, the cost-effectiveness of the pharmaceutical may vary between the types. In a health-economic assessment, it may therefore be expedient to report separate calculations for the different tumour types.

Variations in cost-effectiveness between tumour types may be due to:

- *Difference in effectiveness compared with the standard treatment.* Although the tumour-diagnostic pharmaceutical has an effect on all tumour types that express the mutation in question, the magnitude of the effect may vary.

- *Mortality*. The higher the risk with the standard treatment, the greater the absolute risk reduction achieved through a superior treatment.
- *The cost* of the tumour-diagnostic pharmaceutical may vary between tumour types, if the dosage and duration of treatment are different.
- *The cost difference compared to the standard treatment*. If there are different standard treatments for different tumour types, the cost of the alternative to the new tumour-diagnostic pharmaceutical may vary.
- *The prevalence of the mutation*. This impacts the amount of health care costs incurred for a test to detect patients with the relevant mutation, since many who do not have the mutation must also be tested (see Chapter 4). However, this is a non-issue if broad genetic testing is already performed for the patient group.

It is often possible to form an idea of how some of these factors will differ between the tumour types in order to justify separate calculations: mortality with the current treatment, difference in cost from the standard treatment and how prevalent the mutation is. However, the most important factor in a health-economic assessment is the difference in effectiveness from the standard treatment; but when the pharmaceutical product is new, there will rarely be separate information about effectiveness differences for the different tumour types. A clinical trial without a control arm with, for example, 25 patients, where a certain tumour type may only be represented by an individual patient, can hardly form the basis for conclusions about the difference in effectiveness. Therefore, TLV is of the opinion that it will often be reasonable to perform separate calculations for the different tumour types, which will vary depending on the available information. However, the difference in effectiveness between the pharmaceutical with a histology-independent indication and the standard treatment will usually not be based on tumour type-specific data.[10]

Numerous research projects are currently being conducted based on the question of how to perform relevant health-economic assessments in situations where patients are stratified into various subgroups. Hopefully, this will lead to the development of methods that will be applicable to future assessments.

6.3 ATMPs: How should uncertainties be reflected in the estimated ICER and how should it affect the decision?

There are different methods of calculating and describing the uncertainties in a health-economic assessment: sensitivity analyses, scenario analyses and probabilistic sensitivity analysis. This is described in more detail in one of our background reports (41).

However, the expert group that assessed Vitrakvi on behalf of NICE did not share the company's view in that case (39).[10]

In the following sections, we address specific issues of particular relevance to ATMP-class pharmaceuticals that are based on the additional uncertainties about long-term cost-effectiveness created by the fact that treatment cannot be undone and payment cannot be terminated. We mainly address two proposals: firstly, how the uncertainty should be reflected and secondly, the decisionmaker's approach to uncertainty:

- That the base-case scenario, base case ICER, should reflect the long-term uncertainty by weighting different possible outcomes, such as assumptions that the duration of the effect will probably be 5, 10, 15, 20 and 25 years, respectively.
- That greater decision uncertainty should be acceptable, the greater the health loss caused by holding off on treatment.

For both ideas, the conditions and consequences need to be investigated before they are formulated as concrete proposals.

6.3.1 How can uncertainties about critical ATMP cost-effectiveness factors be reflected in the health-economic analysis?

Given that payments for ATMPs cannot cease even if key conditions were to change, the uncertainty about long-term cost-effectiveness increases significantly with respect to these pharmaceuticals.[11] This raises some questions about how the uncertainty should be reflected in the health-economic assessment.

The main uncertainties for ATMPs consist of limited information about the following parameters:

- Uncertainty linked to clinical outcome:
  - percentage of patients who respond to treatment
  - the effectiveness relative to other available treatment alternatives
  - duration of effect
- Market uncertainty:
  - other upcoming treatment alternatives
  - price changes on the comparison alternative

In traditional health economics, the base-case ICER should correspond to the expected ICER – it is a *mean value* rather than a value at the fringe of the distribution of possible ICERs (10). However, TLV sometimes deliberately presents conservative ICER calculations in order to demonstrate the 'worst possible case' in the outcome. If this worst case scenario is not particularly adverse, the decisionmaker may feel more confident at the point of decision.

However, the expected ICER does not mean using the most *probable* values of the included parameters. If there is a 90 per cent chance that the effect's duration is lifelong and a 10 per cent chance that the duration is 5 years, then the lifetime effect is the most likely value but not the expected one. Therefore, in the expected duration, the probability of a shorter-term effect must also be factored in. This means, for example, that an assumption of lifetime effect from an ATMP treatment

[11] A more detailed description of the characteristics of ATMPs can be found in Chapter 8.

is often unreasonable, as this is based on the assumption of a zero-per-cent probability that the effect will be shorter than a lifelong one. It is important to calculate ICER in a manner that does not entail that all uncertainty is funnelled in one direction, i.e. that all deviations in clinical practice from what has been assumed in the calculation will result in higher ICER.

The challenge with ATMPs is that we have very little knowledge about some of the decisive factors – perhaps in particular, the duration of effect – and thus what assumptions are reasonable to make, both for base-case and sensitivity analyses. What then, is the best estimate of the expected ICER?

Below, we present some different methods for dealing with this predicament. One method is to report a base-case scenario that leverages assumptions about a certain duration of effect, a certain response rate, price development, etc., and in addition to this, several different scenarios, including worst case and best case. The second method is to weight possible outcomes with probabilities in the base-case scenario calculation. The third method is to apply a higher discount rate.

Method 1: Supplement the base-case scenario with best case and worst case scenarios, as well as a threshold analysis of how long-lasting the effect must be in order to achieve a reasonable ICER

The US Institute for Clinical and Economic Review advocates using these methods in a report on how to assess 'single and short-term therapies', which encompass ATMP-class pharmaceuticals (68).

The best and worst case scenarios must therefore represent a more positive and negative outcome than what is normally reported. The idea is not to vary all the parameters in the model, but to focus on a number of parameters linked to the effectiveness of the treatment, such as:

- the duration of the treatment effect
- the scope of the effect relative to the treatment alternative
- the proportion of patients in different health conditions (such as seriously ill, mildly ill, cured)

as well as tests of various mathematical functions for survival curves.

Nor is the idea to always assume in the best case scenario that all patients will be cured for the rest of their lives, or to always assume in the worst case scenario that the effect disappears the day after the follow-up period of the clinical trial. The assumptions in the best and worst cases should not be extreme but reasonable, with outcomes that may be realised in practice. The assumptions must be made after careful consideration and after obtaining the views of medical experts, patient organisations, manufacturing companies and more. These analyses should not replace the usual sensitivity and scenario analyses, but be supplementary by reason of the extra uncertainty that will characterise the assessments of 'single and short-term therapies'. The base-case scenario should continue to reflect the best individual estimate of benefit.

According to TLV, the advantage of this approach is that the decisionmaker gains a clear picture of how much the cost per QALY will be, based on different assumptions, including in the worst and best cases. The disadvantage is that it can be difficult for the decisionmaker to know which scenario the decision should be based on. Often, some scenarios will demonstrate solid cost-effectiveness while others will indicate poor cost-effectiveness, and the risk is likely that it will be more difficult for the decisionmaker to form an opinion about what is the most probable scenario.

The report from the Institute for Clinical and Economic Review contains a supplementary proposal that a threshold analysis should always be presented for how long-lasting the effect must be in order to achieve a reasonable cost per QALY (68). TLV considers this to be an interesting supplementary analysis.

Method 2: The base-case scenario consists of a weighted average of several different calculated ICERs

This idea is based on several reference points. When forming an opinion about what are reasonable assumptions, all available knowledge should be utilised. This pertains not only to the outcomes of clinical trials, but also what is probable, based on medical and biological considerations. The experience of experts may also be an important source of knowledge. With ATMPs, however, there is still so much uncertainty about critical factors, in particular the duration of effect, that would render such knowledge inadequate. No one can make a fully qualified assessment.

Therefore, as a first point of departure, it is not only important to utilise all the knowledge that is available; it is equally important to use one and the same approach when there are no objective reasons for utilising different assumptions – for example, due to a lack of knowledge about the duration of the effect. Different cases should be handled differently, but similar cases similarly.

A second point of departure is that the base-case calculation is of special significance in decision making. It is therefore important that the base-case scenario is a well-balanced core value rather than a value at the fringe of the distribution of possible values. Base-case scenarios are normally based on a duration of a certain number of years, a certain proportion of cured patients, a certain future price for the comparison alternative, and so forth. However, there is a risk that the base-case calculation does not sufficiently reflect the possibility of different outcomes.

The idea here is that for certain factors, where it is difficult to determine a specific value based on available empirical data and theory, the base-case calculation should partly reflect that different outcomes are possible, and partly start from standard assumptions to some degree. Instead of choosing either 5, 10, 15, 20 or 25 years' duration, ICER is calculated using different assumptions about duration, and the base case is allowed to consist of a probability-weighted average of these different ICERs. If we make the assumption that the probability is the same for all five

outcomes, the weights will be 20 per cent for all of them.[12]A weighted ICER then better reflects the fact that at the time of the decision, all outcomes appear to be possible with a certain probability. This means that the assumptions in the base-case scenario have a lesser either-or character.

The idea is not to weigh in different possible outcomes for all the parameters in the base case, but only those that are decisive in the long term; and wherever it is also difficult to assess a reasonable outcome. Examples of such parameters may be the duration of effect, the probability that the comparison alternative decreases in price and the probability that another superior treatment will be available in the future.

To determine which weights to use, a starting point may be from the shared probabilities of different ATMPs – or at least the same type of ATMP – followed by corrections based on the available evidence, clinical and biological bases, and so forth. Hopefully, this can facilitate consistent assessments and increase transparency about which assumptions will be made.

In other words, the method has two components. First, that the ICER in the base-case scenario consists of a weighted average of a few different ICERs based on different values for two to three variables. These variables are crucial in the long run, while there is very little evidence. The idea is to avoid the probability of certain possible outcomes being set to 0 per cent. Second, that the assessment is based on a standard distribution of probabilities for these two to three variables. Deviations from this distribution can then be made based on the situation.

This method does not really need to be regarded as an alternative to Method 1 above, but rather as a complement, since Method 1 is about which scenario analyses are to be performed while Method 2 is about how the base-case scenario is to be calculated.

Before this method is applied, a more detailed impact assessment must be performed and a number of issues resolved, in particular, which probabilities should be utilised. One prerequisite for an application is that the companies' health-economic models are flexible to allow for TLV to assume that certain events occur with a certain probability at certain times.

Method 3: Apply a higher discount rate

Some argue that a reasonable method of dealing with long-term uncertainty in socio-economic calculations – as an example of a health-economic assessment – is to use a higher discount rate (11). This is also something that has been suggested in the Swedish discussion on how long-term uncertainty about ATMPs should be addressed (77).

[12]Calculating an ICER based on the average of 5, 10, 15, 20 and 25 years, i.e. 15 years, usually does not yield the same result, since the ICER parameter will often be non-linear in duration.

However, TLV is of the opinion that this will be a relatively crude manner of dealing with uncertainties. The health gain calculated in an assessment depends on a number of factors: quality of life at different health stages, probabilities of going from one health stage to another, risk of death. In a health-economic analysis, there are opportunities to transparently adjust the factors considered to be most uncertain, to see what happens. Although, a higher discount rate broadly affects all factors in a manner that is not always readily transparent. And how do we choose a discount rate for a specific pharmaceutical based on the uncertainties of that product?

A background report to this assignment discusses various aspects of what should impact the discount rate in a health-economic assessment (78). The discussion is not limited to ATMPs, but the issue of discount rates and uncertainties is raised and the author posits that the discount rate should not be higher for treatments with greater uncertainty. It should also be mentioned that there is an ongoing discussion as to whether a lower discount rate should be used for ATMPs, but for other reasons than addressing the uncertainties (59). Also in the above-mentioned background report, the author states that a lower discount rate for both for health gains and costs should be used than the one that TLV applies – 3 per cent (78). The author's conclusion pertains not only to ATMPs but to all pharmaceuticals.

An additional problem with a higher (or lower) discount rate is that there will be difficulties with demarcation: for which pharmaceuticals should a higher or lower discount rate be applied?

TLV proposes further investigation and the development of a method to reflect the uncertainties

In summary, TLV is of the opinion that a higher discount rate will be an imprecise way of dealing with uncertainties and that there are better alternatives. Here, we present a proposal for an approach, where the basic calculation in the health-economic analysis reflects that there is a probability for different outcomes. This can be achieved by using a basic scenario that consists of a probability-weighted average of different ICERs, where different outcomes have been assumed. However, this needs to be further investigated, both in terms of method and application – an initiative that TLV intends to continue with as soon as possible.

6.3.2 The consequence of holding off on utilising the pharmaceutical should impact the degree of acceptable uncertainty for ATMPs

Since there is frequently great uncertainty about cost per QALY, the decisionmaker's attitude to uncertainty has an impact on whether the pharmaceutical becomes available. Consequently, it is important that TLV and the NT Council use a well thought-out and consistent approach to uncertainties when deciding on subsidies and recommendations.

It should be considered whether the long-term health consequences on the patient group that waits for several years before utilising the new pharmaceutical should impact the level of acceptable uncertainty. Holding off on usage until better evidence has been provided may be a strategy for the decisionmaker to reduce

uncertainty. However, certain medical conditions progress rapidly and irreversibly, which makes such a strategy less attractive. In these situations, it may therefore be reasonable to accept greater uncertainty than when it pertains to medical conditions that do not progress irreversibly. This idea can be operationalised by calculating what the extent of health losses will be – measured in terms of quality of life and life expectancy – for patients by holding off on treatment for, for example, five years.

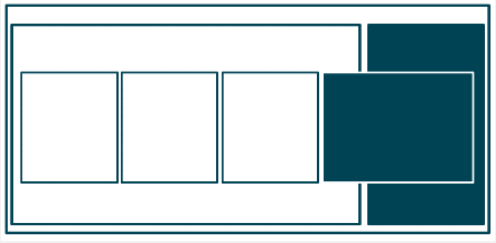
However, it is important to apply this in a manner that does not entail that the same factor being taken into account several times in the decisions, i.e. so that no calculations are duplicated. The parameter, *health loss from holding off on treatment for five years,* will to some extent depend on the extent of health gains from being treated with the pharmaceutical. The reason is that the greater the health gain from treatment, the more the patient loses by not receiving treatment. To some extent, the parameter will also depend on the severity of the condition, since holding off on treatment entails a greater loss of health for serious conditions than mild ones. There is thus a risk of repeatedly considering the same factor. Therefore, the parameter should not be used as a separate decision criterion in addition to cost-effectiveness and severity of disease. Consideration should be given to whether it is usable to determine how much decision uncertainty to accept.

To clarify: Although the severity, calculated ICER and uncertainty are the same in assessments of two pharmaceuticals used for different disease conditions, there may be reason for the decisionmaker to arrive at different decisions. This is because the consequences can still be different for patients waiting for better evidence before the utilising the pharmaceutical.

TLV believes that this concept is compatible with both how individuals actually behave and with formal decision theory. Most patients are probably more inclined to use a pharmaceutical with uncertain effectiveness, if currently available treatments for the disease cause rapid deterioration in health. The concept is thus related to one of the value aspects discussed in chapter 5.3.2 (the value of taking risks in the hope of good treatment effectiveness). In terms of formal decision theory, *value of information* is the established theoretical framework that describes how to approach the value and consequences of holding off on the introduction of new treatments in anticipation of better evidence. One factor that has an impact on these analyses is precisely the health loss for patients from waiting (41).

We wish to emphasise that this concept needs to be further analysed before a concrete proposal for practical application is presented and agreed upon. However, some challenges are already identifiable at this point. Perhaps the greatest challenge is determining what the balance should be between the uncertainty and health loss from holding off on treatment, since applying the concept could result in changes to which particular pharmaceutical products are given higher priority and which are given lower priority.

7 Challenges to the cost-effective utilisation of ATMPs



In this chapter, we expound on the following:

- From a payer's perspective, there are mainly two challenges that must be addressed for pharmaceuticals that are administered as one-time treatments and where the price is set based on the assumption of excellent long-term health gains: the irreversibility problem and the budget problem.
- The irreversibility problem arises as a consequence of the fact that payment cannot be terminated if the pharmaceutical does not prove to have sufficiently positive and long-lasting effectiveness to justify its price. Payment would then have been made for an unrealised health gain.
- The budget problem is that the regions may find it difficult to afford the treatments, even if the pharmaceutical is likely to be cost-effective in the long term.
- If the challenges are not met, it could result in an irrational utilisation of the pharmaceuticals – both overuse and under use.
- TLV is of the opinion that the challenges should be addressed partly by testing the potential of payment models that spread the cost over a number of years and which are dependent on actual health outcomes, and partly by allowing the unaddressed uncertainties in a payment model to be clearly reflected in the health-economic assessment.
- TLV sees stronger reasons for state (co-)financing of ATMPs than for other hospital pharmaceuticals. TLV therefore deems that there is reason to investigate this further.

In the preceding chapters, TLV described several distinctive features of precision medicines and ATMPs and the manner in which these products challenge current methods of health-economic analyses and pricing. The next chapters will focus on ATMPs.

7.1 Two key challenges to the rational and cost-effective utilisation of ATMPs

TLV finds that there are two main challenges with ATMPs: the irreversibility problem and the budget problem, the combination of which can result in the suboptimal utilisation of these pharmaceuticals.

7.1.1 The irreversibility problem – the payment cannot be terminated if effectiveness discontinues or is lower than expected

The early assessment of a new pharmaceutical nearly always comprises uncertainties. An important difference between 'regular' continuous treatments and nonrecurring treatments such as ATMPs, is that the payment of the former can be terminated if they do not yield the intended effect or if better treatment alternatives are developed. However, if a patient who has received an ATMP needs to switch to another medication, but the entire payment was already made in conjunction with the administration of treatment, the payment cannot be discontinued.

The problem of irreversibility therefore arises through the combination of

- existing uncertainties about decisive factors for cost-effectiveness
- full payment issued in conjunction with the administration of the treatment or for a few years thereafter
- the pharmaceutical being priced at a level that presupposes health gains for many years

Examples of decisive factors for cost-effectiveness are relative clinical effect, proportion of patients who respond to treatment, duration of effect, future costs and the potential development of new and better treatment alternatives.

TLV and the regions often face the challenge of addressing the above three factors – either individually or two of them combined. Although it has so far been unusual to address a combination of all three, this will frequently be the case with ATMPs.

Figure 9 and Figure 10 below illustrate the problem by comparing an ATMP with a continuous treatment. If the effectiveness proves to be as expected, the cost and health gains are the same for both treatments; see Figure 9. If the effectiveness decreases after ten years for both treatments and the patients have to be treated with a different pharmaceutical, the standard treatment, the loss for the payer will be greater for the ATMP alternative; see Figure 10. In one of the background reports, this dilemma is specifically addressed (79).

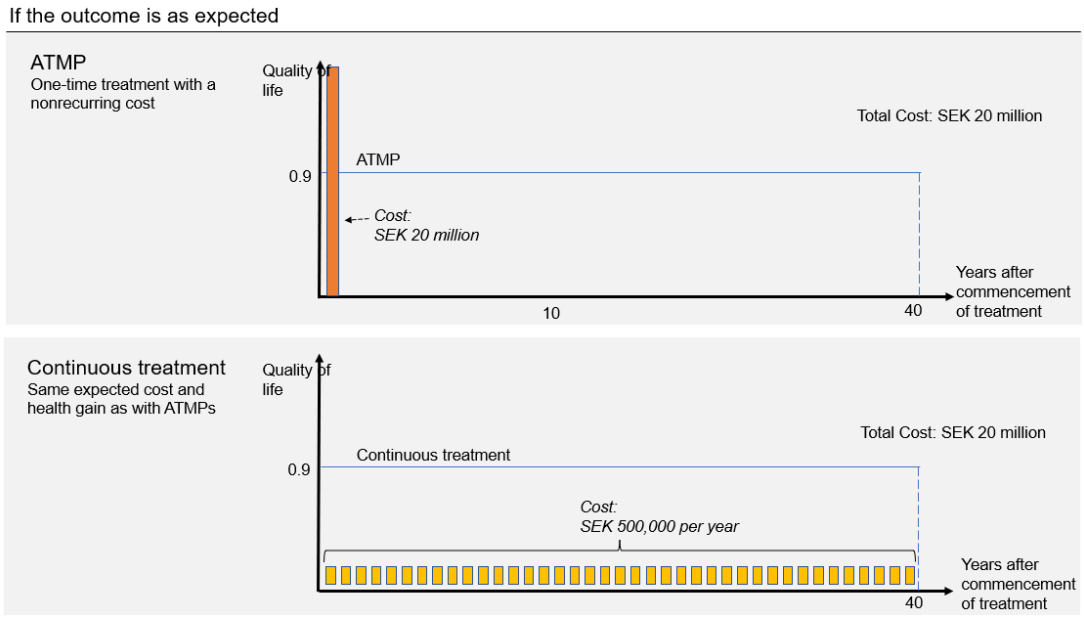


Figure 9. Illustration of the consequence of the irreversibility problem: what we expect in the early assessment

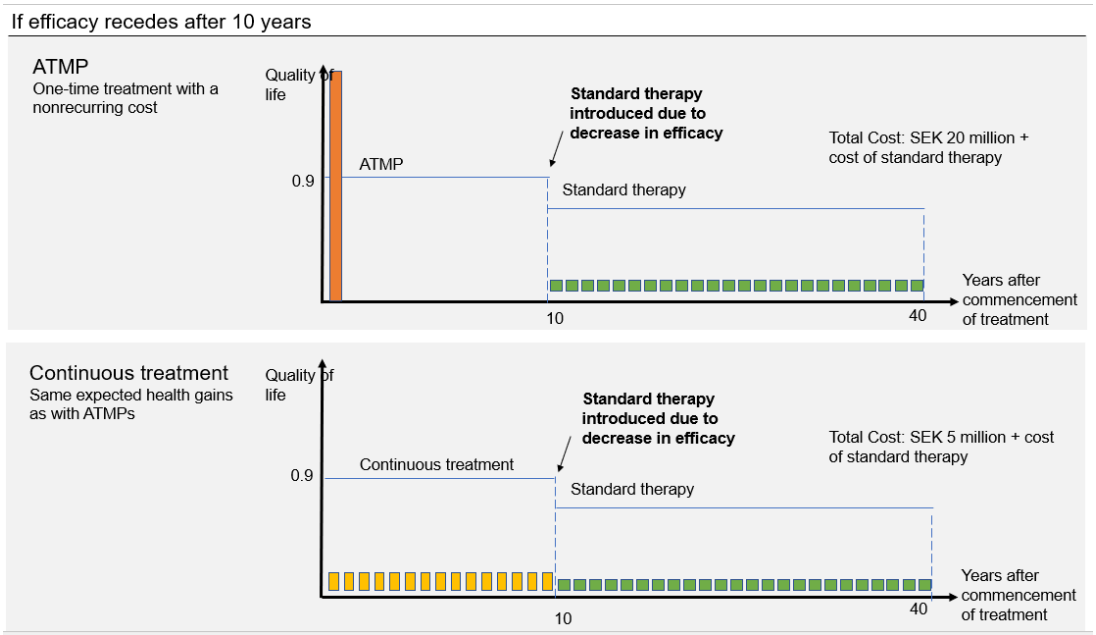


Figure 10. Illustration of the consequence of the irreversibility problem: if treatment effectiveness does not last more than 10 years

In summary, the estimated cost per QALY for ATMPs with a one-time payment entails more uncertainty than the estimated cost per QALY for a corresponding continuous treatment. One way to reduce this decision uncertainty is for ATMP payments to be split up and made contingent upon the actual outcome of the treatment. We return to the this later in this chapter.

7.1.2 The budget problem – one-time payments for pharmaceuticals priced on the basis of very long-term effectiveness create budgetary challenges for the regions

By budget problem, we are referring to the challenge for the regions to be able to afford one-time payments for an ATMP, even those that are deemed to be cost-effective. To have to pay for several decades' worth of health gains for a substantial group of patients within a short period of time, the total cost for the regions can be so substantial that the treatments are either not provided or other important care is marginalised. This problem was highlighted in the White Paper prepared by the Västerbotten Region (29). The Local Government Act (2017: 25) states that regions and municipalities must pursue sound financial management, which entails, among other things, that revenues cover operating expenses. Costs for pharmaceuticals fall under current operating expenses, and very highly priced treatments thus risk generating an economic imbalance in the regions.

If the patients are unevenly distributed across the country, the budget problem could also arise in an individual region, despite the fact that the total number of patients and thus the total cost in the country is not large. This is particularly pronounced for requisitioned hospital pharmaceuticals, as is the case with ATMPs, since each region has its own funding responsibility for these pharmaceuticals. (80).

Zynteglo and Zolgensma are two ATMPs that were launched in the past few years. Zynteglo is a gene therapy approved for the treatment of patients with transfusion-dependent beta-thalassemia, a rare inherited disease that results in chronic anaemia. (81) The pharmaceutical received market approval in 2019. The price per treatment per patient was set by the company at SEK 17 million. Another example is Zolgensma, which is a gene therapy for the treatment of spinal muscle atrophy, SMA. (82) The company's price per treatment is SEK 21 million. In comparison, the total cost of hospital pharmaceuticals in 2020, which was SEK 10 billion. Region Västerbotten, which is a 'medium-sized' Swedish region (approx. 300,000 inhabitants), had a total cost for hospital pharmaceuticals of just under SEK 300 million.

The affordability problem is being discussed internationally – the general problem for the payer to afford new effective pharmaceuticals (83). Our usage of the term 'budget problem' is somewhat narrower, i.e. we refer to the extra challenges created by ATMPs, in that they are nonrecurring treatments. Although the payment challenges faced by the regions with other types of pharmaceuticals should not be diminished, they are not the focus of this report.

7.2 The challenges may lead to both the overuse and underuse of ATMPs

We have found that the irreversibility problem and the budget problem are two obstacles to the rational and cost-effective utilisation of ATMPs. In the following section, we present a general discussion of how these obstacles could result in overuse and underuse. An expression of overuse might be Sweden's utilisation of ATMPs, which ultimately proves to too costly in relation to the health gains. If, on

the other hand, we do *not* utilise ATMPs that prove to be of a reasonable cost in relation to the health gains, that would be an example of underuse.

One reason for overuse or underuse may be related to incorrect estimates of health gains and costs. Institutional conditions could also lead to incorrect incentives or counteract optimal use from a socio-economic perspective. In the sections below, we describe some of these factors.

7.2.1 Underestimated or overestimated health gains or costs may constitute an obstacle to efficient utilisation.

The calculation of cost per QALY is based on an estimate of the pharmaceutical's health gains and costs. An underestimation of the health gain could lead to underuse, while an overestimation could correspondingly lead to overuse. An incorrect calculation of costs or savings could also lead to an underestimated or overestimated cost per QALY, and result in suboptimal utilisation. However, it is only when the error entails that the result ends up on the wrong side of what is considered a reasonable cost per QALY that it impacts the decision; see Figure 8 in Chapter 6. In other words, it is the decision uncertainty that is the critical factor, not the uncertainty in estimated cost per QALY.

An incorrect picture of the probability that better treatments will be developed in the future could also lead to an underestimated or overestimated ICER, which in turn could contribute to a suboptimal utilisation. A health-economic assessment considers the long-term perspective and makes comparisons across the entire time horizon – often lifelong for ATMPs – where there are differences in health gains and costs between the new pharmaceutical and the established treatment. For ATMPs, it may be relevant to such long-term analyses to consider the probability that new and improved pharmaceuticals will be launched in the future, because an ATMP treatment today often entails that the patient group does not have the opportunity to be treated by the superior treatment that might be developed in the future. This may be due to medical reasons or cost reasons, as the cost of an ATMP treatment today can only be justified if it provides a very long-term health gain and there are no requirements for additional costly treatments in the future. With continuous treatment, that limitation does not exist.

As mentioned above, due to the irreversibility problem, the consequence of an incorrect assessment of the cost per QALY for ATMPs is greater than for pharmaceuticals administered as part of a continuous treatment. The payer assumes a greater risk if the nonrecurring cost is SEK 15 million, compared with if the annual cost for a terminable continuous treatment were to be SEK 500,000.

7.2.2 Institutional conditions may hinder the efficient utilisation of ATMPs

The budget problem may result in underuse, i.e. even though a pharmaceutical is deemed to be cost-effective from a socio-economic perspective, the pharmaceutical will be utilised to a limited extent – or not at all. This is because the cost does not fit within the regions' budgets.

A second institutional obstacle that could result in underuse is when a region decides to utilise and pay for the pharmaceutical but does not partake of the entire benefit or savings. This could happen, for example, when patients move to a region other than the one that paid for the treatment. The problem is not unique to ATMPs, but more accentuated, due to the fact that payment is made on one occasion, for effects that are to span perhaps several decades – at a price that is set accordingly. This could lead to the insufficient utilisation of ATMPs where the main benefit is future savings on other forms of health care. We deem the problem to be smaller for ATMPs where the benefit consists of substantial health gains. There is a risk that the regions will be reluctant to pay for a very expensive treatment where the main benefit is not health gains but cost savings far into the future, and which may then be transferred to another region.

The party – state or region – that is responsible for paying for the established treatment may also impact the incentives for utilising a new ATMP, and therefore create an obstacle to rational utilisation. In the current structure with parallel systems for benefit pharmaceuticals and hospital pharmaceuticals, it is the different principals who hold the financing responsibility. Hospital pharmaceuticals are procured and paid for by the regions, while prescription pharmaceuticals that are covered by benefits schemes are financed by the state through a state subsidy to the regions (see section 1.3.5). This could also lead to the underuse of an ATMP that is funded by the regions as a hospital pharmaceutical, the main benefit of which is that it replaces an expensive lifelong treatment with a pharmaceutical covered by a benefit scheme.

A fourth institutional condition that could result in the underuse of ATMPs is the limited possibilities to sign agreements on payment models that have the potential to reduce the payer's risk. This is described in more detail in Chapters 8 and 9.

7.3 What have other actors proposed to reduce the risk of overuse and underuse?

7.3.1 Performance-linked payment models have been proposed to address both payment challenges and the risk of cost-inefficiencies

A number of methods have been proposed in Swedish and international literature for addressing the irreversibility problem and budget problem. The most frequent proposal is to utilise payment models where the amount paid is conditional on actual clinical outcomes, combined with dividing the payments over several years (often referred to as annuity payments) (84) (85).

Towse et al. discuss two different variations of payment models. (86) The first is Outcomes Related Payment and involves annual payments provided that the treatment is still effective. The second is Amortisation and involves annual payments for as long as the patient lives. In our further discussion of payment models in chapters 8 and 9 below, we refer to both of these models as performance-linked, since in both cases payment is conditional on the patient's clinical outcome.

Towse et al. are of the opinion that the Outcomes Related Payment model could create a financial equivalence between ATMPs and continuous treatments, and therefore could resolve the irreversibility problem. (86) This is because the payment is made per year that the medicinal product has an effect, for example as long as the patient is asymptomatic. The model requires that it be possible to measure whether the pharmaceutical is still efficacious, which can be a challenge. On the other hand, the *amortisation model* has the advantage that it is easy to measure and ascertain whether the patient is alive or not. The disadvantage is not necessarily a strong connection between whether the patient is alive and how good the treatment is, i.e. what type of health gain the cost-effectiveness is based on. Furthermore, Towse et al. argue that if companies and payers cannot agree on a payment model that reduces the payer's risk, the payer should demand a lower price in order to reduce the decision uncertainty that the payment model would otherwise have addressed; they suggest that the buyer should demand a lower price to 'buy out' the decision uncertainty that better evidence could have reduced. The authors also point out that the payment flow may need to be adjusted to address price changes to the treatment alternative or if other treatments are launched in the future. This is reminiscent of the idea of adaptive pricing as put forward in a report prepared by Västerbotten Region (29).

In one report, Persson proposes several performance-linked payment models with annuity payments as one of the solutions for making ATMPs available in a Swedish context (77). The authors highlight these models as a solution first and foremost for the treatment of the influx of new patients from small patient populations. They are of the opinion that this reduces the payer's risk, while spreading the payment over several years, and reduces the budget problem, i.e. it reduces both the irreversibility problem and budget problem.

7.3.2 Previous inquiries have proposed flexible budgets and loan structures to alleviate the budget problem

The Pharmaceutical Inquiry examined whether it would be appropriate to amend the law to enable the regions to record curative pharmaceutical treatments as an investment in their financial statements, in order to address the municipal balance requirement. (47) If the entire payment to the company were to be made in conjunction with treatment, the region's financial results would only be charged with a part of the cost each year – the annual amortisation. The municipal balance requirement entails that municipalities and regions must maintain a zero balance. However, the inquiry deemed that there was no reason to put forward such a proposal, partly because a patient cannot be considered an investment, and because payment and financing of curative pharmaceutical treatments can be addressed through current regulations. One suggestion was to invoke what is termed 'special reasons' to allow for an economic imbalance, i.e. a negative balance in the accounts.

A report by Persson et al. proposes flexible regional budgets that could allow the regions to run deficits for several years, as a solution to enable treatment of existing patients at the time the pharmaceutical is approved (prevalence) (77). They are also of the opinion that health care loans can be an alternative to annuity payments and flexible budgets, in cases where these proposals cannot be implemented. With such

a loan, the company would receive the full payment in conjunction with the administration of the treatment, while the region pays an instalment to the loan issuer for several years. The authors refer to the Pharmaceutical Inquiry, which states that it is permissible for a region to have a financial imbalance, provided that a plan is created to address the imbalance and there are 'special reasons' for the imbalance, as mentioned above, which may include curative treatments.

TLV is sceptical of these proposed solutions, primarily because the proposals seem to assume that the budget problem for ATMPs is temporary – which could then potentially justify deficits and loans. However, TLV is of the opinion that the problem is not temporary; further arguments are presented below.

7.3.3 There are arguments both for and against state financial responsibility

ATMPs will usually be administered via inpatient care by medical staff and thus handled as a hospital pharmaceutical. As mentioned above, the regions hold the financial responsibility for hospital pharmaceuticals, in contrast to 'benefit pharmaceuticals', which are paid for through a targeted state subsidy to the regions.

In the debate on the budgetary impact of ATMPs and the ability of health care to pay, various arguments are frequently in favour of state (co-)financing of ATMPs (29) (80) (77). The following hypothesis describes some of the theoretical reasons for and against government funding. This should not be seen as a complete review – there are several more arguments, both for and against government funding. Furthermore, TLV has not taken a position on the issue, but is of the opinion that it needs to be investigated. See also the background report of (79).

A first argument is based on the budget problem: if ATMPs are developed for more common diseases and there is an existing patient stock that should be treated, and there is therefore a need for temporary large expenditure, then the state has better opportunities to manage this than individual regions. The reason is that the cost is a much smaller proportion of the state budget compared with an individual region's budget. The state also has better opportunities for borrowing, as well as more tax instruments to utilise (79).

If the state considers that for research or commercial policy reasons it is important for Sweden to rapidly and broadly utilise ATMPs, a shared state responsibility for financing could be a means for the state to provide the resources and prioritise these issues. The regions have difficulty assuming full responsibility for this.

There are also arguments that are linked to the institutional barriers discussed above and which are in favour of state (co-)financing. One is the twist in incentives, partly due to different bodies holding the financing responsibility for hospital and prescription pharmaceuticals, and partly due to the financing responsibility of hospital pharmaceuticals being divided amongst 21 regions. If ATMPs are paid for by the region while the treatment alternative is a prescription pharmaceutical that is financed through government subsidies, this could incentivise the region toward underuse. And if the region where the patient lives at the time of treatment pays the full cost, even if the patient were to move to another region, this could also

contribute to underuse. This is also something that SKR highlights in a position paper from April 2021 (80). State (co-)financing could mitigate these effects. An alternative to overcoming this obstacle might be co-regional funding.

There are also arguments against state funding. One is that it could create the wrong incentives when choosing a treatment. If the choice of treatment is between an ATMP (paid for by the state) and another hospital pharmaceutical, the regions could be directed toward state-funded ATMP treatments instead of choosing less costly treatments. This could lead to an overuse of ATMPs. Another argument is that a state co-financing model may impede the price competition of therapies, between ATMPs and the treatment alternative, if they have two different financiers. It is the regions that negotiate with the companies, and in a situation where the regions do not pay for ATMPs, there are fewer opportunities to negotiate for lower prices.

TLV is of the opinion that there are stronger arguments for state (co-)financing of ATMPs than for other hospital pharmaceuticals. This is due to the irreversibility problem and budget problem. TLV therefore deems that there are reasons to investigate whether the state should have a shared responsibility for the financing of ATMPs, or if the solution is co-regional financing.

7.4 Health-economic assessments should utilise payment models and clear reporting methods

TLV finds that payment models that *avoid* one-time payments of the same amount for all patients – regardless of the effectiveness – could be part of the solution for rationally utilising ATMPs. This could be combined with allowing for reflecting the uncertainties that are *not* addressed by the payment model in the health-economic assessment. Figure 11 illustrates how the uncertainties addressed in a payment model could interact with the health-economic assessment.

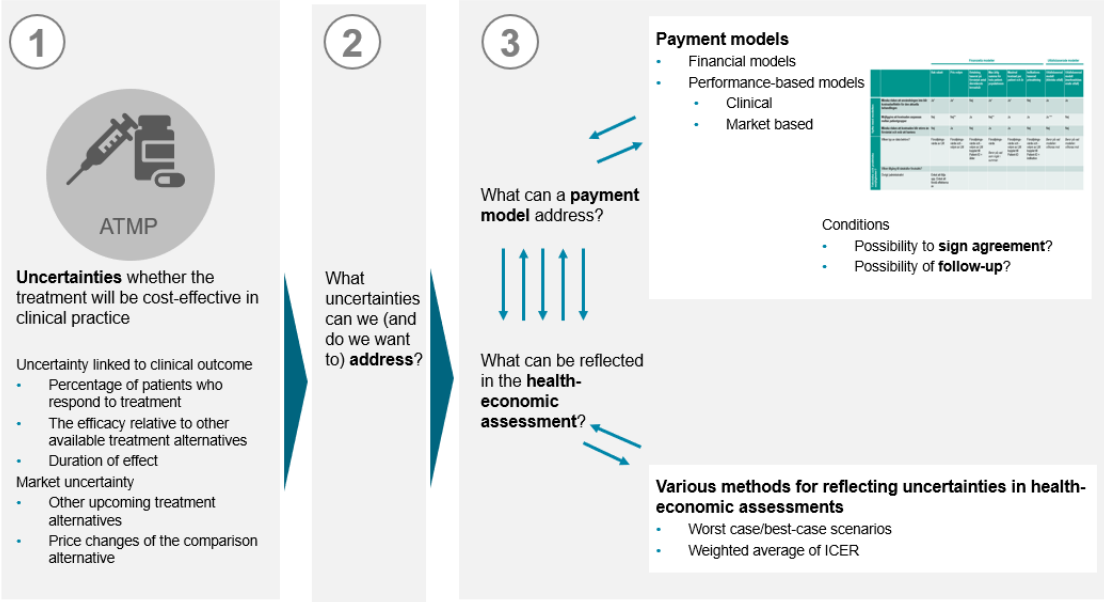


Figure 11. Challenges with ATMPs. The uncertainties can be reflected in the health-economic analysis and addressed through payment models

Allowing for the uncertainties to be reflected in the health-economic assessment

In section 6.3.1, we reviewed how uncertainties could be reflected in the health-economic assessment. We established that in order to avoid the overestimation or underestimation of health gains and costs in the calculation, it is crucial that the uncertainty is not strictly funnelled in one direction. The health-economic calculation needs to allow for the actual realised cost per QALY – when it is observable in the future – to be higher or lower than that what was estimated upon the introduction of the pharmaceutical. This means that the calculations should be performed so that the outcome of actual utilisation, if it should deviate from what was assumed in the initial calculation, does not always lean toward a higher cost per QALY. If, for example, the assumption in the health-economic analysis is lifetime effect, the uncertainty goes strictly in one direction – it cannot be more long-lasting than that.

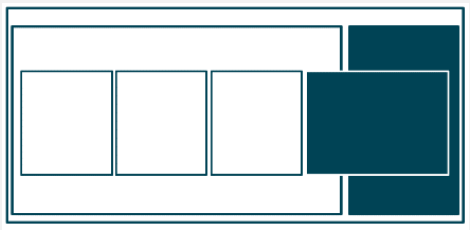
The discussion in Chapter 6 resulted in a proposal that the cost per QALY in the base-case scenario (basic calculation) should reflect the probabilities of *different* outcomes. With some probability, the duration of effect is long and short, respectively, and with some probability, superior treatments will be developed in the future.

Payment models as part of the solution for the rational use of ATMPs

Depending on the situation – the uncertainties that are to be addressed and the specific conditions – payment models may be of varying relevance.

Chapter 8 contains a review of various payment models, what they aim to resolve and their usability in terms of ATMPs. An overview of what is required for each model to fulfil its purpose is also presented. Chapter 9 provides an in-depth study of a fictitious situation with different payment models based on clinical outcomes.

8 Payment models – what problems can they solve?



In this chapter, we expound on the following:

- A payment model could have different purposes for the payer, where the payment for a pharmaceutical is not a constant amount per package, but is variable depending on the health outcome, field of application, purchased volume or other factors. Depending on the design, it could address uncertainties about cost-effectiveness, variations between patient groups with regard to, for example, health gains or large budgetary effects.
- Today, there are several challenges associated with the implementation of performance-linked payment models. One key challenge is the limitations in observing and measuring the relevant outcomes. Another is ambiguity about the actual opportunities for the public sector to formulate agreements that are sufficiently clear and which do not leave room for interpreting what payment a particular health outcome should lead to.
- Although there are examples from other countries of contractual solutions within the framework of performance-linked payment models, at this stage, it is difficult to assess the degree of success these have been met with. There are only a few examples of models with a long-term follow-up that address the payer's long-term uncertainties.
- TLV's assessment is that performance-linked payment models with instalments and a relatively long follow-up period, are the models most relevant to ATMPs, and that they should be tested on actual products in the next few years.

8.1 What are payment models and what are they designed to address?

8.1.1 Payment models are aimed at enabling the use of a pharmaceutical

The need for payment models may arise if the payer (the public sector) and the pharmaceutical company cannot agree on what is a reasonable cost based on current knowledge about the benefits of the pharmaceutical. An agreement between

the payer and the company to make the treatment available under specific conditions could then allow for the pharmaceutical to be utilised. Such an agreement or contract could be based on a payment model, which means that the payment for a pharmaceutical is not a constant amount per package, but is variable, depending on health outcome, field of application, volume purchased or other factors. A simpler form of agreement is when the payer and the company agree on a percentage-based reimbursement, in the form of a direct reimbursement for the cost of the pharmaceutical.

A payment model may have different purposes for the payer:

- addressing uncertainties as to whether the cost is reasonable in relation to the health gain (the term cost-effectiveness used below)
- addressing variations between patient groups in terms of health gains or dosage
- addressing the risk that total expenditure for the region will be unmanageably large

Addressing uncertainties about cost-effectiveness is about reducing the risk of paying too high a cost for the treatment in relation to the realised health gain from actual utilisation. This may be the case, for example, if the effect does not meet expectations, if the proportion of patients who respond to treatment is lower than expected or if future costs and/or future treatment options change. If there is a great risk that actual usage will not be cost-effective, this may result in the payer not utilising the pharmaceutical.

In other situations, there may be a need to address the variations between different patient groups. If a pharmaceutical provides different health gains for different indications, the risk with a uniform price is that utilisation for indications with lower health gains will not be cost efficient. By allowing for the cost per package to vary between patient groups in relation to the expected health gain or dosage, utilisation could be cost-effective in different situations. This, in turn, could provide patients with access to the pharmaceutical.

By reducing the budgetary effect, a payment model could reduce the risk that the total cost to the patient population will be greater than expected and thus difficult for the payer to manage. The payer does not need to hesitate about utilisation and patients are provided access.

Companies may also benefit from the application of a payment model by enabling early availability, thus generating revenue, in addition to providing an opportunity to generate further knowledge about the pharmaceutical's effectiveness in day-to-day clinical practice. The agreements may comprise sections that are not transparent, which will provide opportunities for confidential prices that do not impact the reference prices in other countries and also enable pricing strategies with differentiated prices between countries. Confidential prices are something that companies often consider to be a prerequisite for offering a lower cost than the official price of the treatment.

At present, regions are signing agreements with pharmaceutical companies on behalf of the public sector. The state is not a contractual party. Since ATMPs will mainly be requisitioned within health care, the payment models and agreements will primarily be used within the framework of public procurement.

8.1.2 Which payment model is useful depends on the situation

In Chapter 7, we gave an account of some specific challenges in achieving the cost-effective usage of ATMPs and the ways in which these challenges could result in both overuse and underuse of these products. What role could payment models play in overcoming these obstacles?

The choice of payment model should be determined by the primary problem must be solved in the situation concerned. Is the aim to reduce the risk that usage of the pharmaceutical in clinical practice will not be cost-effective? Is the purpose to enable the cost to be adjusted based on the extent of health gains that can be expected in a specific patient group? Or is the purpose to reduce the risk that the total cost to the payer will be greater than expected and not financially sustainable?

If the primary goal is to reduce the risk that usage will not be cost-effective, there needs to be knowledge available about which uncertainties are most pronounced and/or most urgent to address with the help of payment models. This could pertain to both uncertainties about future effectiveness among patients or future market changes, such as the arrival of new treatments or a change in the price of the comparison alternative.

Various models can be combined if one model alone cannot solve the most pronounced challenge(s). Table 2 provides an overview of what the different models can address.

Table 2. Overview of different payment models, what they are intended for and their conditions of use

		Financial models						Performance-based models		
		Reimburse-ment	Price volume	Payment based on the expected remaining years of life	Maximum annual total for the entire patient population	Maximum cost per patient per year	Indication-based pricing	Outcome-based model (clinical outcome)	Outcome-based model (market-based outcome)
Purpose of the model	**Reduce the risk that usage will not be cost-efficient?**	Yes*	Yes**	No	Yes*	Yes*	No	Yes	Yes
	Make the cost adaptable to different patient groups	No	No**	Yes	No**	Yes	Yes	Yes**	No
	Reduce the risk that the total cost for the region will be greater than expected and difficult to manage	No	Yes	No	Yes	Yes	No	No	No
Is the cost impacted but the actual outcome?		No	No	No	No	No	No	Yes	Yes

* However, the model does not reduce the risk associated with, for example, lower-than-expected efficacy from actual application.
** A certain degree of (on the assumption that the sickest are prioritised for treatment)
*** In theory, but difficult in practice

8.2 Financial models – the cost of the pharmaceutical does not depend on future outcomes

Depending on which financial model is chosen, the purpose may be one of the three mentioned above. Below, we describe several different financial models, the challenges that they aim to address and the relevance they are deemed to have in making ATMPs available. We also mention some of the challenges to and opportunities for implementation. With regard to the latter, we would like to point out that this is a theoretical review and not a complete analysis of the conditions, as only a few of the models have been tested in a Swedish context.

8.2.1 Percentage discount

In this type of agreement, the company undertakes to give a certain percentage of the sales value in discount. The discount level is usually confidential. This is the model mainly applied by regions and the company in Sweden today, for both pharmaceuticals under benefit schemes and hospital pharmaceuticals.

In what way can this model contribute to a pharmaceutical's availability?

The model lowers the cost of utilisation and thus improves cost-effectiveness. This reduces the decision uncertainty and increases the chances of patient access. However, the model does not reduce the payer's risk associated with, for example, lower-than-expected effectiveness from actual use.

The model does not allow the cost per package to vary between patient groups in relation to the expected health gain or dosage, since the percentage of reimbursement is the same regardless of how many or which patients are administered the pharmaceutical. Furthermore, the model does not reduce the risk that the total cost to the patient population will be greater than expected and difficult for the payer to manage, as there is no ceiling amount or any price/volume component.

What are the practical possibilities and the challenges of implementing the model?

Direct reimbursements are easy to implement because only sales-value data is required as a follow-up to the model. Since the cost per package becomes constant, it facilitates communication to health care providers and an understanding of the effects.

Is the model considered useful for making ATMPs available and if so, how?

Since the same price is paid regardless of the effectiveness or whether there are changes in the market, the model does not address the often highly pronounced uncertainties associated with ATMPs.

If the percentage reimbursement is sufficiently substantial, the need for other types of payment models decreases. However, TLV's assessment is that in many cases, the payer will not reach an agreement with the company on a sufficiently large reimbursement that will make other payment risk-managing models more explicitly superfluous.

8.2.2 Price volume

A price-volume model entails the application of a specific unit price to a specific sales volume. For sales above this volume, a lower unit price is paid, regardless of which patients receive the treatment.

In what way can this model contribute to a pharmaceutical's availability?

Under certain circumstances, the model enables the cost per package to vary between patient groups in relation to the expected health gain or dosage. The idea is that the model should contribute to the control of usage, so that the patients who have the greatest need of or greatest effectiveness from the pharmaceutical should be prioritised. Therefore, the payment model can increase the chances that the utilisation will be cost-effective in situations where an existing subgroup of the patient population will derive greater benefit from the treatment than others: a higher cost is acceptable for those who receive the greatest health gains. If these patients are prioritised for treatment, when the cost is higher, the cost will be lower for patients with smaller health gains, which could make it cost-effective for this population. However, it is difficult to ensure that in reality, the patients who will have greatest health gains will be the ones who are treated in the first place.

The model does not reduce the payer's risk associated with, for example, the effectiveness in actual use being worse than expected.

The model can to some degree reduce the risk that the total pharmaceutical cost for the patient population will be greater than expected and difficult for the payer to manage. However, this is requisite on the price falling sharply with increased volumes.

One disadvantage of this model is the locking effect that it creates, in that the larger the volumes prescribed, the lower the unit cost will be. In a situation where there are different pharmaceuticals to choose from competing companies, the payer with a price-volume agreement has an incentive to utilise only one of the products. This could have an inhibiting effect on competition in the field of therapy and result in poor pricing dynamics.

What are the practical possibilities and the challenges of implementing the model?

Applying the model requires – in addition to the sales value of the pharmaceutical – information about the volume sold. Since the cost of the pharmaceutical varies depending on utilisation, somewhat higher requirements are imposed for both the communication and follow-up of the model in health care, compared with a direct discount. This model also entails that it is not fully predictable how much the pharmaceutical will cost per patient and how the budget will be impacted. The current structure of 21 regions with their separate budgets creates challenges for such volume-based agreements on how to divide the reimbursement between the regions. In a situation where some regions start utilising the pharmaceutical earlier and others later, when a specific volume has been reached – should these regions then have different costs for the pharmaceutical?

Can the model be useful in making ATMPs available and in what way?

This model is expected to be of limited relevance to ATMPs, at least as long as the patient groups are small. If an ATMP for a more common disease is launched, this model could potentially be useful.

8.2.3 Payment based on the age group's remaining life expectancy

This model entails that treatment costs vary with the patient's age: higher prices are paid for younger patients than for older ones. The cost, which is not pegged to actual health outcomes, but is determined in advance, will therefore be different for different patient groups based on the expected health gains.

In what way can this model contribute to a pharmaceutical's availability?

A one-time treatment with a lifelong effect will, for natural reasons, be more cost-effective for younger than for older patients, if the price were the same. By enabling an adjustment of the price to different age groups, the pharmaceutical can be made cost-effective regardless of age and be accessible to more people.

This model does not reduce the payer's risk associated with, for example, effectiveness in actual use being worse than expected. Neither does the model reduce the risk that the total cost for the patient population will be greater than expected and difficult for the payer to manage. Consequently, the model does not manage risks linked to future cost-effectiveness, nor does it manage potentially large costs with a large budget impact or uncertainties about future market changes.

What are the practical possibilities and the challenges of implementing the model?

When following up the model, information is required about the sales value and sale volume of the pharmaceutical, as well as the age of patients receiving the pharmaceutical. TLV sees a risk that implementing such a structure will be perceived as complicated by the regions, partly due to the fact that the cost will not be predictable.

Is the model considered useful for making ATMPs available and if so, how?

For a one-time treatment with an expected long-term (lifelong) effect, this model could entail reducing the risk that older patients will not have access to the treatment because they are not expected to benefit from the treatment for a sufficient number of years. The model should therefore be considered in a situation where patients suffering from a condition vary greatly in age and there is currently no effective continuous treatment available.

8.2.4 Fixed annual sum for the entire patient population regardless of volume utilised and no – or low – unit cost (the 'Netflix model')

This model works as a subscription for an entire patient population, and entails that the payer and the company agree on a certain annual amount and what is to be included for this amount.

In what way can this model contribute to a pharmaceutical's availability?

The main advantage of this model is that, from the payer's perspective, that the marginal cost of administering the treatment to a patient will be low. This means

that the payer has the opportunity to offer the treatment to all patients who can benefit from it – both those who will benefit greatly and those who will derive little benefit. An additional strength of the model is that it eliminates the payer's risk that the total cost to the patient population will be greater than expected.

However, the model does not allow the cost per package to vary between patient groups in relation to the expected health gain. On the other hand, the model solves the problem that a treatment may often be too expensive for certain patient groups, because the unit price is low for everyone.

The model does not reduce the payer's risk associated with, for example, effectiveness in actual use being worse than expected. The fixed amount is based on a certain expected health gain, and if it should turn out to be less than assumed through actual usage, the pharmaceutical is not cost-effective. A new type of risk also emerges, that fewer people than expected will use the pharmaceutical. The fixed sum is then distributed among fewer people and the average cost per patient becomes high. This could result in overall usage *not* being cost-effective.

This model could also be constructed in such a way that costs associated with the treatment – such as diagnostics, other treatments and follow-up – are included in the fixed sum, in addition to the costs of the treatment itself. Therefore, depending on what the agreement looks like, uncertainties will be reduced about what additional costs may arise. This could pertain to costs that are added if the effect ceases; for example, other pharmaceutical treatments. In addition, if several different treatments are included in such a package, uncertainties about which of these treatments (or which combination of treatments) is most cost-effective for the individual patient could also be reduced.

What are the practical possibilities and the challenges of implementing the model?

The model is easy to follow up, provided that only the cost of the pharmaceutical is included in the fixed sum. If the package is to include costs associated with the treatment, information about the costs must be registered on an ongoing basis. If the package is to include all patients with a certain diagnosis, information about this must also be registered. The model is thus requisite on the possibility of some form of follow-up, which compounds the complexity during implementation.

However, one advantage of the model from the regions' perspective, is that it is easy to communicate to health care services and to understand its effects, and that it offers predictability about what the treatment cost will be. The challenge described above for the price-volume model, which concerns aspects of fairness between regions when they sign their own agreements, also creates challenges for this model.

Is the model considered useful for making ATMPs available and if so, how?

Several features of ATMPs indicate that the model may be appropriate in some cases. The uncertainties linked to the duration of effect can be managed if the costs for a supplementary treatment are included in the agreed fixed sum. The rapid development of screening and gene diagnostics are allowing for the earlier detection

of more patients, who thus become relevant for treatment, and a model that shares the risk of this budgetary effect could reduce the uncertainties for the payer.

What makes this model unfavourable is that the 'production cost' of providing an ATMP is often relatively high. If the low unit price is lower than the production cost, the company's profit decreases for each additional patient treated.

8.2.5 Maximum cost per patient per year

This payment model entails that payers and companies agree on a maximum cost per year per patient. If the consumption or cost exceeds this level, the company provides the pharmaceutical to the patient free of charge.

In what way can this model contribute to a pharmaceutical's availability?

The model enables the cost per package to vary between patient groups in relation to dosage and duration of treatment. Thus, it is suitable for pharmaceuticals that are dosed based on body weight, and the cost risks being very high for heavier people. It is also suitable if there is uncertainty about how long a treatment will last.

The model does not reduce the payer's risk associated with the effectiveness from actual usage being less than expected. However, to some extent, the model reduces the risk that the total cost to the patient population will be greater than expected and thus unmanageable. However, the risk is not completely eliminated, because the more patients who are treated, the higher the cost.

What are the practical possibilities and the challenges of implementing the model?

When following up the model, information is required on the volume of the pharmaceuticals sold and which patients have received the medication. The model provides a predictability of what the cost will be for each patient, which facilitates communication in health care. The current structure, with 21 regions having their own budgets and own agreements, also entails certain administrative challenges for this model and raises questions about aspects of fairness.

Can the model be useful in making ATMPs available and in what way?

The usefulness this type of model for ATMPs is doubtful. Given the characteristics of the treatment, there will rarely be uncertainties about the amount of pharmaceuticals used per patient during a year. However, it is interesting if the maximum cost could span several years and the patient, when needed and if it is medically feasible, could receive another treatment free of charge.

8.2.6 Indication-based pricing

Variable prices depending on the indication, i.e. indication-based pricing, may be justified when the cost-effectiveness varies depending on the health condition or stage of a disease when the pharmaceutical is used. Often, the situation is that a pharmaceutical is already approved and subsidised for one indication, then subsequently approved for a second indication with less health gains. The price must then also be lower for its utilisation to be cost-effective and for patients to have access. See also the discussion on combination treatments in section 4.4.

This model can be implemented in different ways. If there is information about the specific indication a pharmaceutical is used for, and there are otherwise legal and practical opportunities to do so, strict indication-based pricing can be applied. If this is not possible, a variation with weighting is possible: the price for all usage is adjusted when a new indication is approved. The weighting can be based on the expected disease prevalence or market share for the various indications.

In what way can this model contribute to a pharmaceutical's availability?

The purpose of the model is to enable the cost per package to vary between patient groups in relation to their health gains. This increases accessibility.

The model does not reduce the payer's risk associated with the effectiveness from actual usage possibly being less than expected. The model also does not address the risk that the total cost for the patient population could be greater than expected and thus unmanageable.

Can the model be useful in making ATMPs available, and why?

Initially, most ATMPs will probably only have one indication, which makes them irrelevant to pure indication-based pricing. However, there are exceptions, for example the CAR-T pharmaceutical Kymriah has several indications.

On the other hand, if the 'indication-based' concept were to be expanded and ensure that the price is generally able to vary with the expected health gains – not only on the basis of indication but also on the basis of other conditions – such a model could improve accessibility and be useful to ATMPs. The model where the price is variable according to age, as discussed above, is an example of such an application.

8.2.7 Coverage with evidence development

In some cases, the payer may make the payment conditional on additional evidence after a certain period of time. For example, the company may be required to provide additional data for the subsidy's continued validity at the current rate, after five years for example, which may require either data from clinical trials or data from clinical practice (RWD). This is usually referred to as Coverage with Evidence Development, CED. These models can be described as being equivalent to the follow-up conditions that TLV occasionally imposes on its subsidy decisions.

In what way can this model contribute to a pharmaceutical's availability?

By ensuring continued follow-up of the pharmaceutical, CED manages the uncertainties in clinical effectiveness for future patients who may be relevant for treatment, and thus reduces the payer's risk that the treatment will be used for a long time despite its cost-inefficiency.

CEDs are considered in some contexts to constitute performance-linked payment models. However, one important difference between what is referred to in this report as performance-linked payment models and CEDs is, that the latter only addresses uncertainties in clinical effectiveness for future patients, i.e. not for the patient groups that are currently receiving treatment. Performance-linked models

reduce uncertainties as to whether the treatment being administered today will prove to be cost-effective.

The CED model also does not reduce the cost of the treatments being administered today and thus does not reduce the budgetary effect. Therefore, it does not allow health care providers the scope to treat additional patients.

Can the model be useful in making ATMPs available, and why?

The payer needs to reduce the risk that the cost – in relation to the health gains of patients being treated today – will be unreasonable in the long term. Availability could otherwise be impacted. The model does not reduce that risk. Neither does the model reduce the budgetary effect.

CEDs thus do not reduce the pronounced uncertainties of ATMPs to any appreciable extent, and are considered to be of limited relevance to these pharmaceuticals.

8.3 Models based on clinical outcomes

8.3.1 Models that are based on clinical outcomes allow for the cost to vary in accordance with the effectiveness

In this assignment, we refer to 'performance-linked payment model' as a model whereby the cost of the pharmaceutical becomes dependent on the health gain that the pharmaceutical provides. The health gain is calculated using specific predetermined outcomes.

In what way can this model contribute to a pharmaceutical's availability?

The purpose of a performance-linked model is to manage the risk that the treatment will not be cost-effective when used in clinical practice, or to manage the variation in health gains between patient groups. A payment that is proportionate to the demonstration of a specifically agreed effect reduces the payer's risk, which in turn increases the probability of accessibility to the treatment.

However, the model does not address the risk that the total cost to the patient population will be greater than expected and thus unmanageable.

What are the practical possibilities and the challenges of implementing the model?

Performance-linked agreements require that the payer and companies agree on what specific outcome parameter(s) to use, how they are to be measured and how frequently. The treatment effectiveness (outcome) can be demonstrated by the companies or the payer, at a group or individual level, via experimental studies or observational studies.

In section 8.6 we review some of the prerequisites for choosing outcome parameters and follow-up, and in chapter 9, we expound on this reasoning by using several examples.

Is the model considered useful for making ATMPs available, and why?

This model has the potential to be particularly useful for ATMPs, due to the great uncertainty about long-term effectiveness, above all.

As mentioned in section 7.3.1, previous publications have proposed that payments for ATMPs can be made using a performance-linked model combined with payments being allocated over several years, known as an annuity payment. This is said to reduce both the payer's risk that effectiveness will be less than expected, as well as the budget problem (77). However, the budget problem will not decrease in every situation. The budget problem may instead increase, if risk reduction entails that the health care provider chooses to offer treatment to more patients, despite a limited knowledge of its effectiveness. Since performance-linked payment models do not provide any relief to the regions' budgetary impact – if all treatments meet expectations, the regions will pay the full price for everyone – the regions could still find that they do not have the financial resources to offer patients the treatment.

In summary, performance-linked models with instalments are useful for reducing the payer's risk that the actual health gain will not be sufficient to justify the cost. However, the model does not reduce the budget problem.

8.3.2 Different methods for acquiring data from clinical outcomes – from clinical practice or from clinical trials?

There are variations to what data sets the outcome can be based on:

- Data from clinical practice:
  - at the individual level, i.e. the payment for a patient's treatment depends on the outcome for that particular patient
  - at the population level, i.e. the payment for a patient's treatment depends on the average outcome in Swedish clinical practice for the right patient category
- Data from clinical trials: the payment for a patient's treatment is dependent on the results of clinical trials (not necessarily conducted in Sweden).

Whichever variation is most appropriate and feasible will depend on the situation. Below is a review of the advantages and disadvantages of each method.

Payment models based on medical outcomes in Swedish clinical practice

Payment models that are based on data from utilisation in clinical practice (real world data, RWD) entails that the payment correlates with the actual clinical outcome. This model therefore addresses any uncertainties in assumptions and extrapolations from the clinical trial. It also addresses other uncertainties generated by differences between clinical practice and clinical trials, for example, which patient groups are receiving the pharmaceutical and how is the pharmaceutical being administered.

One of the disadvantages of this version may be that it is administratively demanding and thus entails large transaction costs. This is especially the case when the collection of data for outcome parameters requires extra efforts. If health care providers are responsible for collecting data, these costs fall on the regions, i.e. the

payer. The payer then needs incentives to bear the costs, for example by embedding these costs into the payment model. There is also a risk that some patients cannot or do not want to be followed up on. Another disadvantage is that data will only be generated for a relatively short period of time in relation to the period in which health gain is expected; with a follow-up period that spans five years, for example, only the outcomes that occur within the first five years will be captured in the payment model (however, see further discussion in section 9.3).

What are the advantages and disadvantages for follow-up at the individual level compared with the population level if it is to take place in Swedish clinical practice?

Since the regions can spread the risks across many individuals, what is most important for the regions is to reduce the risk that the pharmaceutical is not cost-effective for the average patient. In other words, a region does not have to pay the correct amount for each individual patient, but it suffices that it is the correct amount on average. This suggests that the payment could just as easily be based on a measurement at the population level (average effect) as at the individual level. Payments based on the population level should also greatly facilitate data acquisition, by eliminating the need for comprehensive examinations where all the patients must be followed up on, allowing for an indicative sampling instead.

However, if a region only has one or a few individual patients, there are advantages to individual-based follow-up. A payment model that entails that the cost on average corresponds to actual effectiveness will then be unable to compensate any region that treats a patient who has an outcome that is below the average. In theory, this could entail the region deeming the risk to be too excessive and thus not providing access to the treatment. The conclusion is that the smaller the patient population within a region, the better the performance-linked payment models at the individual level in clinical practice: if a region only has a few patients, it is more important that they know that for these patients, the cost will be reasonable in proportion to how large the actual health gain will be in the long run.

Payment models based on data from clinical trials

Performance-linked models can also be based on data from clinical trials, for example, in follow-up studies.

Why would this model be preferable over a model based on data from Swedish clinical practice? One advantage is that the clinical trials are often ahead of time compared to the data acquired from usage in clinical practice. The test that forms the basis for a pharmaceutical to be approved for sale often continues to be valid and is then perhaps more than two to three years ahead. For example, despite the fact that the follow-up period in the performance-linked payment model is only five years, the payment could then be conditional on an outcome of at least seven to eight years after the treatment has taken place. Another advantage is that the problem of acquiring data from usage is circumvented and that the agreement defines exactly how an outcome is to be measured, as this is already defined in the protocol of the clinical trial. Such a model thus enables the leveraging of more specific outcome parameters that are not normally generated in clinical practice. At

present, it is difficult to apply payment models based on outcomes in clinical practice due to the lack of access to the right data.

One of the disadvantages of this model is that the trial population does not always fully correspond to the patients who are treated in Swedish clinical practice. Differences between trials and practice are well known and have led to efforts to conduct more studies of effectiveness in clinical practice (87). The extent of difference varies and must be assessed on a case-by-case basis.

Another disadvantage is that the follow-up will depend on how the company has chosen to set up the clinical trial. For example, a single-armed study does not generate any additional data about the pharmaceutical's relative treatment effectiveness, regardless of the duration of the follow-up period. The payer also has limited influence over which outcome parameters are followed up on and how this is conducted. Another disadvantage is that there are also uncertainties in what happens if a study is terminated prematurely.

8.4 In a market-based outcome model, the cost varies depending on the future market situation

Another type of outcome on which payment can be conditional is future market events.

The particular outcome parameter that would be appropriate to base such a payment model on depends on the expected future developments within the field concerned. If the introduction of new, cheaper or more efficacious treatment alternatives is expected in the immediate future, the payment for the ATMP that is under consideration for use today could be linked to the eventual price of the new treatment. Conversely, in a situation where it may be relevant for the health care providers to offer patients the treatment in an alternative manner at a (significantly) lower cost, the agreement could be made continent on this cost. This could also be applied if there is an indication that the price of the treatment may fall.

In a situation where the payer is reluctant to utilise a new ATMP due to the potential arrival of a more cost-effective alternative within a few years, a model like this could reduce the payer's hesitation and contribute to the use of the available ATMP. Consequently, such payment models could be important to all parties concerned – the payer's the risk is reduced, which thereby increases their willingness to use the ATMP; the patient gains access to treatment; the company has sales.

However, the model requisite on the possibility of the systematic monitoring of market developments and the assessment of new pharmaceuticals. In practice, what will set the limits are restrictions such as contract length and contract costs, which allow for specifying or agreeing on what will happen in response to future market events.

Market uncertainty is discussed in detail in one of the background reports for this project (79).

8.5 Instalments do not solve the budget problem, but are an important component of the performance-linked (outcome based) model

Instalments entail dividing the cost of a patient's treatment over several years. For example, five years. Instalments are highlighted in various contexts as a potential solution to the regions' budgetary problems (77). However, TLV has difficulty seeing how instalments reduce the budget problem more than marginally, as there is a continuous influx of patients. If a region has treated patients for a period of four years, in Year 4, they will be paying instalments for all patients who commenced treatment in Years 1–4. Consequently, a pure instalment payment, which is not conditional on a certain outcome, often results in the same annual cost for the payer as a one-off payment, when the product has been on the market for several years. To clarify: any benefit that a private individual could derive from instalments when buying a car does not exist for a public-sector actor who buys a car a month for several years.

If the overall prevalence of a not-uncommon disease is to be treated in a very short time, such as one year, instalments could reduce the regions' costs for the pharmaceutical this year. But, firstly, we are of the opinion that it will not be a usual situation for the health care system to choose to treat the entire prevalence for such a short period, partly due to the lack of staff and capacity for such implementation. If instead, the entire prevalence is treated for four years and the payment for each patient's treatment is spread over three years, the partial payment does not reduce the regions' annual cost by much. Secondly, it is not just a single ATMP that will be introduced in health care, but ATMPs will probably be launched continuously for several years. Postponing the payment of the first ATMPs that are launched does not do much good if there are additional future costs, when the regions' budgetary situation is equally strained.

To sum it up, instalments could reduce the budget problem if it is deemed that there will be a 'cost hump' for only a few years, where several costly ATMPs will be administered to large patient groups, after which the budget pressure will decrease. However, TLV assesses that this will not be the actual situation and that instalments will not reduce the budget problem. TLV finds that combining instalments with outcome-based payments is part of the solution for reducing the irreversibility problem, as the payer is not required to assume as great a risk, which is the case with one-time payments.

In this context, an alternative to instalments is reimbursement: the full payment is made upon the occasion of treatment, but the company will repay all or part of the sum in the future, if the outcome is not as expected. However, TLV considers this to be riskier for the payer, as there is a risk that the company may no longer exist when

the time for repayment is due. This is expounded on in one of our background reports (79).

8.6 Payment models are requisite on opportunities to sign agreements and follow up on them

In this section, we will focus on two important prerequisites for payment models in a Swedish context: signing agreements and follow-up.

Several of the above-described payment models are requisite on agreements on payment flows following the 'purchase' of the pharmaceutical and the patient's receipt of treatment – when the product's extent of utilisation or effectiveness is known. To regulate these payment flows, a contractual solution is required between the pharmaceutical companies and the payer (currently the regions). The possibilities of payment models are thus dependent on the payer's and pharmaceutical companies' terms for negotiating a sufficiently explicit agreement, which takes into account all the uncertainties, including the long-term prerequisites, so as to eliminate any doubt about what the parties have agreed on.

Another important aspect pertains to the possibilities for follow-up: in order to be able to retroactively regulate the payment, we need to know the extent of utilisation and the eventual health outcome. What are the opportunities to identify, collect and analyse data for the outcomes that are important to the patient, and on which the payment should be based? The opportunities for follow-up govern what outcome parameters we can set and thus, what performance-based models we can construct.

TLV deems these two aspects to have the most significant consequences from a health-economic perspective. They thus impact the opportunities for reaching a contractual solution. We would like to point out that there are several other challenges of both a practical and principle nature, that are not addressed here.

8.6.1 What are the possibilities of contractual solutions between the public sector and the pharmaceutical companies?

Hospital pharmaceuticals are purchased through public procurement

As a rule, ATMPs will be administered through inpatient care and thus requisitioned and procured by the regions. The public sector's purchases, including pharmaceuticals, are mainly made through public procurement. (88) Procurement is regulated by the Public Procurement Act (2016: 1145) (hereinafter referred to as the 'LOU'). The Act is aimed at ensuring competition and that public funds are used as efficiently as possible, and applies to both government agencies and regions.

An ordinary procurement contract refers to one or more actual procurements. However, pursuant to the LOU, the procuring agency has the opportunity to sign framework agreements: under Chap. 1 Sect. 20 of the LOU, an agreement signed between one or more procuring agencies and one or more suppliers for the purpose of determining the contractual terms that will later be awarded during a given period of time. Through framework agreements, the procuring agency could thus

award contracts for a specific product or service whenever the need arises. For pharmaceuticals, in practice, this means that the regions do not procure a certain amount of the product, but that the quantity is sub-ordered from what has already been procured, as the regions see the need for it. For new pharmaceutical products covered by patent protection, for which there is only one pharmaceutical company (supplier), the procuring authority may, in accordance with Chap. 6 Sect. 14 of the LOU, use what is referred to as 'negotiated procedure' without prior announcement. However, such a procedure may be used only if there is no reasonable alternative and the lack of competition is not due to a contrived delimitation of the conditions for the procurement.

Pursuant to Chap. 7 Sect. 2 of the LOU, a framework agreement is only valid for longer than four years if there are special grounds. The LOU's legislative history cites as one special reason, that a supplier requires equipment with a depreciation period of longer than four years, and which must be available at any time during the entire term of the framework agreement.[13] A special reason for a term of longer than four years, may be that extensive investments are required, for example, through the construction of treatment centres or the acquisition of certain equipment. *Contracts* based on a framework agreement must be awarded before the framework agreement expires. However, the term of the individual contract does not have to coincide with the term of the framework agreement, but may be shorter or longer, taking into account for example, the time required for fulfilment, when maintenance of equipment with an economic service life of more than four years is included, or when extensive staff training is required to fulfil the contract.[14]

However, the parties should be free to regulate the rights and obligations that are important even after the end of the contract period in accordance with the general principles of contract law; for example, that one of the parties must submit follow-up data. Further analyses is required on how such agreements should be prepared for ATMPs and what rights and obligations they might comprise.

The regions' practical conditions for long contractual and follow-up periods

We provided a comprehensive description above, of the public sector's prerequisites for signing agreements in accordance with the LOU. To further assess which agreements are possible, the practical conditions must also be taken into account.

The regions have informed TLV that several aspects need to be factored in, in order for them to perform an assessment of what the actual possibilities are and what contractual solutions are suitable from their perspective. One example is the possibility of finding and agreeing on contract wording that is sufficiently clear and which does not allow for differences in interpretations between the pharmaceutical company and the payer. This is closely linked with the opportunities for follow-up. Certainty about which outcome should be constitute a successful treatment,

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Prop. 2015/16:195, p. 1008 f. and reason 62, first and second paragraph, Directive 2014/24/EU of 26 February 2014 on public procurement and repealing Directive 2004/18/EC.[13]

[14] Ibid., P. 1009.

combined with the availability of robust methods for measuring and assessing this outcome, creates confidence in the agreement.

According to the regions, the question of what the future market looks like for the field of therapy should also be taken into account. What research and development is ongoing in the field concerned? What method development is taking place for these treatments? With ongoing rapid developments, it may be relevant for health care providers to offer equal or superior treatments to patients by other means. When parties sign agreements, the primary rule is that each party bears the risk of future sequences of events. It may be difficult for contractual parties to anticipate the development of events over time and therefore, difficult for them to word the agreement to cover various circumstances that may arise, even if the parties are entitled to renegotiate in certain situations. This can be particularly complicated in the case of long-term agreements and in situations where the parties have agreed on conditions that are to apply even after the agreement has expired.

Another aspect put forward by the regions is what is protected by secrecy and for how long. As we stated above, it is an important input value for companies that there is an opportunity to keep information about contractual content confidential. In accordance with Chap. 19, Sect. 3 of the Public Access to Information and Secrecy Act (OSL), absolute secrecy applies during the procurement process. Thereafter, secrecy pursuant to Chap. 31 Sect. 16 of the OSL may apply to certain information, including the price, if a company enters into a business relationship with a government agency by means of a public procurement, if it is assumable that for special reasons, it would be detrimental to the company if the information were to be disclosed. However, the protection of secrecy is only valid for a certain period of time. The regions prefer public prices and see several challenges and problems with the wishes of companies to have confidential reimbursement levels and pharmaceutical prices. They also express that this problem becomes more pronounced in situations with long-term agreements.

The regions have some guiding principles for contractual relationships with companies

As described in section 1.3.4, the regions act jointly to develop conditions and prices for pharmaceuticals that are relevant for national collaboration. Within the regions, however, there is no shared approach to the principles that should form the basis of the trade-offs described above. Previous experience has also shown that there are differences between the regions in their application of the rules on sound financial management and in their decisions on priorities (89). These differences can be a challenge in situations that require national cooperation and unity.

The regions have – based on experiences from recent years in joint negotiation, co-signing and the follow-up of agreements – identified several conditions and principles that TLV is acquainted with and which have guided this assignment. One of the principles is that the payment solution and the agreement must be functional within and be accepted by all the regions – regardless of the region's size and what knowledge and capacity is available, for example in follow-up operations. Another principle is that the agreement's implications must be logical and easy to

understand and communicate to those concerned within the regions. This could entail that the agreement applies to all usage for the relevant patient group and that it complies with current therapy recommendations. A third principle concerns the follow-up of agreements. If there is a need for special follow-up data for contract design or payment solutions, these should be based on registrations that are already made and available, with a high contribution ratio and quality.

One issue of key significance to the regions is transparency in both the process of drafting agreements and their content. The regions express the importance that as many as possible of the main principles of the agreements be transparent, particularly with respect to agreement solutions that include a greater degree of complexity.

As we have already noted, ATMPs create challenges for the regions. This is the background to SKR's development assignment concerning the review of opportunities to develop new contractual structures and payment models. In the response to the motion that forms the basis for the assignment, SKR states that experience from regional joint negotiations indicates that payment models based on the follow-up of outcomes have been difficult for the regions to manage. (13) Examples of challenges include the administrative burden and lack of a functioning infrastructure for obtaining the data required for follow-up. The development work will be aimed at driving the development of innovative payment models for ATMPs that are financially and practically sustainable in the long term for Swedish conditions. As mentioned above, TLV and the regions currently cooperate by working with the companies concerned, to try to develop new payment models for actual ATMPs that are launched.

The Västerbotten Region has produced documentation to support continued dialogue about the challenges of making advanced therapies and new innovative pharmaceutical treatments available to patients with rare and serious diseases in Sweden, which sometimes involves the drafting of agreements (29).

8.6.2 What are the opportunities for follow-up?

Follow-up requires that data is available and that there is infrastructure in place for data acquisition and analysis.

Conditions vary, depending on how data is acquired and the source from which it is acquired

Different types of data are required, depending on which follow-up variables are chosen for conditional payment. How data is generated can be divided into primary data or secondary data. Primary data entails the need to generate completely new data. This may entail contacting the patient for separate examinations, strictly for the purpose of generating the requisite data for the payment model. The cost of generating this data as well as the risk of data dropouts when patients choose not to come to the examination can be high and must therefore be weighed against the advantages of designing a payment model based on the collection of such data.

On the other hand, secondary data refers to data that has already been generated through interactions with the health care system. This data may either be in the form of medical records or data that is collected in other registers, such as the Patient Register or the Pharmaceuticals Registry.

Although it is possible to extract data from existing registers, it can still be a tremendous task to make the data available. If the data is to be retrieved from medical records, work is required to locate the data, which is often fragmented among different systems in the different regions. It can also be challenging to follow up on the data of patients who move between different regions. If treatment with one therapy occurs in one region, but follow-up data is generated in another region, following-up on the data via medical record systems will be challenging, because the coordination of different registers may require comprehensive confidentiality management. If data is stored in medical record systems, there will also be an imbalance in who has access to the data. Among the implications are that the company will not be able to easily verify the payer's claims in terms of, for example, outcomes.

If the data is stored in a national health data register, it is a small matter to create a data set that is available to all stakeholders. In TLV's report of government assignments on follow-up and RWD, we report on available health data registers, what data these registers comprise and the legal prerequisites for utilising the data in these registers (90). What is important to note is that today, there is no national register that consistently registers pharmaceuticals that are administered directly to patients by health care providers or prescribed as hospital pharmaceuticals. This makes it impossible to systematically identify which patients have received an ATMP treatment. This problem must be resolved before a national-level follow-up is possible. The NT Council attempted to solve this problem for the CAR-T treatment, Yescarta, by calling for all treatments with the pharmaceutical to be registered in the Patient Register in their issued recommendations on the use of the pharmaceutical (91). However, the regions did not fully comply with this recommendation.

Sweden maintains numerous quality registers. These registers could potentially be used to acquire usable data for follow-ups and payment models. However, quality registers are based on voluntary contributions, from both the patient and the care provider. Data from a patient who chooses not to share their data must not be included in a quality register. Therefore, it cannot be guaranteed that data is available for every patient who has received treatment, which means that there is a risk that some patients will not be included in a payment model. This raises questions about whether such a position should be allowed to impact a patient's opportunities to access the treatment.

The particular actor who is responsible for acquiring data may be significant to the effectiveness of the agreement

The party responsible for acquiring data should have an incentive to do so if new evidence causes a change in the agreed price. If the agreement leads to a reimbursement in the face of new evidence, the payer has an incentive to collect

new data. If instead, the agreement provides a 'bonus' for new evidence, it is the company that will be incentivised to collect new data. Regardless of who has the main responsibility, transparency is important, so that all parties who the data concerns have the opportunity to assess the results and their bases, and that quality can be assured so that all parties feel secure about how the agreements are regulated.

The usage of health data that is automatically acquired is preferable to data that is acquired solely for the payment model.

To ensure that all patients who have received a treatment can be followed up on in connection with a payment model, it is preferable that the data be collected automatically and then transferred to a national health data register. This will not only reduce the cost of generating data but also reduce the risk of missing out on information requisite to the regulation of a contract. Another advantage of the data from these registers is that the company could also request an extraction if they wish to verify outcomes, and that the data is comparable with sales data. One obvious disadvantage is that this limits the selection of possible outcome parameters and thus the flexibility in the construction of a payment model.

8.7 Application of payment models in other countries

This section comprises a description of performance-linked agreements used in different countries. The focus is particularly on ATMP agreements. The description is mainly based on two sources: a recent survey of performance-linked agreements conducted by the OECD (92) and data from a database maintained by a research group at the University of Washington (93).

8.7.1 Performance-linked agreements – different terminology with partly different meanings

In the OECD report as well as in the database, the term 'performance-linked agreement' is used partly in a broader sense for agreements linked to some form of follow-up, and partly in a narrower sense, where payment is linked to the (health) outcome. The following terms are used in the sources cited:

- *Payment-by-result* (OECD) or *Performance-linked agreements* (the database). These refer to agreements based on health outcomes.
- *Coverage with evidence development (CED)*. This refers to agreements with follow-up terms.
- *Financial utilisation*. This refers to financial agreements, such as agreements with volume discounts.[15]

In this report, the term 'performance-linked payment models' is used in the sense that the payment depends on the outcome; see definition in section 8.1.2. These payment models/agreements correspond to the concepts of *payment-by-result* or *performance-linked agreements*. This type of agreement is the main focus of the description below.

[15] According to the OECD, a third contract form is conditional-treatment-continuation. This type of agreement is similar to payment-by-result. The difference is that manufacturer pays for continued treatment with other pharmaceuticals if the on-patent pharmaceutical does not yield any results.

8.7.2 The OECD has mapped the use of performance-linked payment models and agreements

In December 2019, the OECD published a broad survey of the literature on performance-based managed entry agreements (92), for which the OECD conducted a literature review and conducted a written survey with OECD member states on their use of performance-linked agreements, and structured interviews were conducted with twelve member countries.[16]

The OECD asked member states what products and indications there are performance-linked agreements for; see Table 3. The information was available for 14 countries.

Table 3. Products with performance-linked agreements in at least two countries (the agreements were valid in 2019). Source: OECD.

ATC codes	Product	Indication	Countries
L011X	Yescarta	B-cell lymphoma	England, Spain
L01XC12	Adcetris	Hodgkin's lymphoma	Estonia, Italy (contract type confidential in Australia, Belgium)
L01XE02	Inessa	Lung cell cancer	England, Italy (contract type confidential in Australia)
L01XE11	Votrient	Renal carcinoma	England, Italy (contract type confidential in Australia)
H01CB05	Signifor	Cushing's disease	Italy, Lithuania
L01	Kymriah	B-cells leukaemia	England, Spain (contract type confidential in the Netherlands)
L01XE16	Xalkori	Lung cell cancer	England, Italy (contract type confidential in Australia)
L01XE23	Tafinlar	Melanoma	Estonia, Italy

Most performance-linked agreements were in the field of cancer. England and Italy were the countries with the most agreements. Australia and the Netherlands stated that there were agreements but the type of agreement was confidential.

8.7.3 The survey identified how data for performance-linked agreements is collected

In the interviews, the countries were asked about how data is acquired and utilised. The interviewees indicated that a wide range of data sources are used. For routine data, electronic health registers, e-prescriptions, data linked to health insurance and disease registers were mentioned. Of these, data from health registers and health insurance systems were the most common. Some countries have created special registers to handle performance-linked agreements. Italy is the best-known example, where the country's pharmaceutical agency AIFA has created a web-based platform in 2005 for registering data for the assessment of performance-linked agreements.

For performance-linked agreements, follow-up usually takes place at the individual level, while agreements with follow-up conditions (CED) are usually conducted at the group level. This is illustrated in Table 4.

[16] Australia, Belgium, the Czech Republic, Estonia, France, Hungary, Italy, Korea, Lithuania, the Netherlands, Sweden and the UK (only England).

The OECD also requested information on which actor is responsible for collecting data. The most common is that the payer is responsible for data collection, but there are some examples where the company has sole responsibility for this and several others where both the payer and the company collect data.

Table 4. Follow-up at the patient level and at population level in different countries for different agreements formats. PbR = payment-by-result, CED = coverage with evidence development, CTC = conditional treatment continuation. Source: OECD.

	Patient level			Population level	
	PbR	**CED**	**CTC**	**PbR**	**CED**
Australia					Yes
Belgium	Yes			Yes	Yes
Czech Republic	Yes				
Estonia	Yes		Yes		
France	Yes				Yes
Hungary	Yes		Yes		
Italy	Yes				
Korea		Yes	Yes		
Lithuania	Yes		Yes		
Netherlands					Yes
Sweden	Yes		Yes		Yes
UK (England)					Yes
Total	8	1	5	1	6

8.7.4 Based on the countries' experiences, the OECD report draws a number of conclusions on the usefulness and value of the agreements

Based on the interviewed countries' experiences of performance-linked agreements, the OECD arrived at several conclusions in its report. First and foremost, they note that it is difficult to assess the extent to which performance-linked agreements have been successful, partly because only a few countries have formally assessed their experiences. One obstacle to independent assessment is the confidentiality that often covers the content of agreements. Another obstacle is that at present, there is only limited experience and evidence of using these agreements.

Payment-by-result agreements continue to be widely used, but they do not always generate evidence of product efficiency, since the data used to trigger payments is not always collected and analysed. Another conclusion is that the administrative cost of collecting and analysing data on pharmaceutical effectiveness can make the agreements costly to implement.

Despite the lack of evidence on the value and usefulness of performance-linked agreements, there are, according to the OECD, some good reasons for applying them under certain circumstances. In its conclusions, the OECD provides a number of guidelines for use. First and foremost, the use of performance-linked agreements should be limited to situations where it is clear that the value of new evidence exceeds the costs of renegotiating and applying the agreement. A type of investment

calculation should therefore be performed, whereby all the costs associated with the use and follow-up of the agreement are factored in. Furthermore, the uncertainties for each individual decision about the agreement should be clearly identified, and the agreement should be designed to ensure that data sources and the creation of evidence are appropriate to addressing the uncertainties of the decision concerned.

With regard to structure and policies, the OECD proposes the introduction of a framework that ensures a transparent process to allow payers the opportunity to act on the new evidence created by the agreement. The OECD also recommends that the payer strive for transparency regarding the content of the agreements, so that only the information that is commercially sensitive is withheld and that content is not unnecessarily classified.

8.7.5 Database containing information on approximately 170 performance-linked agreements for pharmaceuticals and medical devices

A research team in Washington maintains a database of agreements for pharmaceuticals and medical devices, the *Performance Based Risk Sharing Database*, PBRSD (93). In February 2021, the database contained data for 746 agreements. The agreements are mainly classified according to performance-linked agreements, agreements with follow-up terms (CED) and financial agreements (FU). The database contains information on, among other things, the length of the agreement, fields of therapy and the purpose of the agreement. There is also a brief description of the design of the agreements and, in some cases, information about the type of outcome parameter used. Although the database is probably the best compilation of agreements are used in the world, it does not constitute a complete description of which agreements are used, and the data must be interpreted with this in mind.

The focus of the description below is the agreements that have been classified as *performance-linked agreements*.

8.7.6 Two years is the typical contract period, but there are examples of longer and shorter agreements

For the years 1998–2021, 169 agreements were classified as performance-linked agreement in the database. Of these, the majority (89) are in the field of cancer therapy.

Of the 169 performance-linked agreements, information is available on the contract period of 50 of the agreements. The agreement period is an important parameter, as it sets limits on how much uncertainty can be resolved through a payment model. In the reasoning presented in section 8.6.1we describe the relationship between the contract period and opportunities for follow-up.

The typical contract length is two years; see Figure 12. Longer contracts are relatively rare. Four (of five) of the five-year agreements are agreement proposals for Zynteglo; see below. There are some examples of six- and seven-year contracts, and these are for medical devices, and were signed in the US.

The longest agreements in the database are for ten years, for interferons in the UK. These agreements were signed relatively early, as early as 2002. The agreements stipulated that the use of the pharmaceuticals would be monitored and reconsidered every two years, whereupon a new price would be set, which guaranteed an agreed ICER. According to information in the database, these agreements were not repeated. Although the agreements are classified in the database as performance-linked, it is not clear whether the agreements are aimed at correcting the price of treatments already sold or only the price of future treatments.

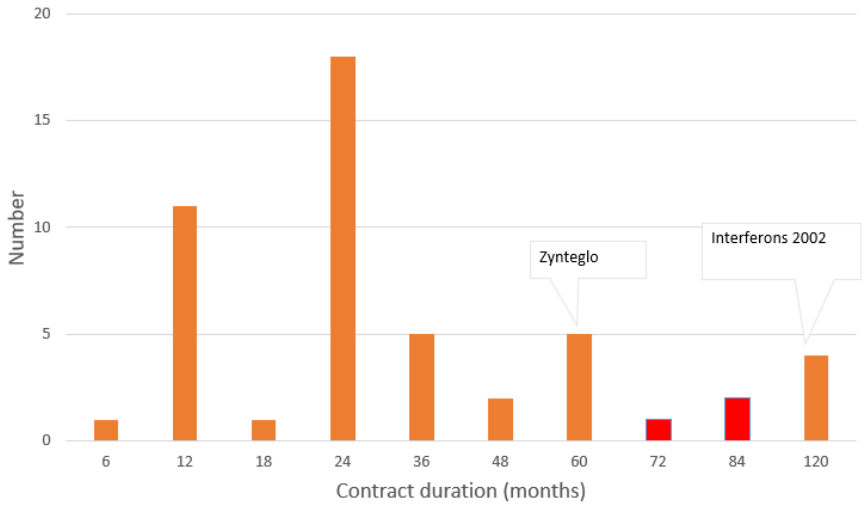


Figure 12. Contract lengths for performance-linked agreements (or proposed agreements), 1998-–2021. Orange = pharmaceuticals; red = medical devices. Source: PBRSD. Zynteglo on draft agreement.

8.7.7 Choice of outcome parameters and assessment at the individual or group level – important choices when following up agreements

For performance-linked agreements to be useful, a key factor is that the outcome parameters must be clear and easy to measure, see section 8.6.2 and chapter 9. Some outcome parameters have elements of subjective assessment, while others are more objectively measurable. Furthermore, an important variable for the construction of an agreement is whether the effectiveness assessment is conducted at the individual or group level, which was discussed in section 8.3.2. The breakdown of collection at the individual/group level and whether the outcome parameters are more or less objectively measurable is not included in the PBRSD. TLV has therefore attempted to review the performance-linked agreements from 2016 onwards in more detail, and attempted to classify them as above. About 22 agreements were identified, where it was possible to classify the agreements based on these aspects.

Of the 22 performance-linked agreements, 18 were deemed to have objective outcome parameters, while four were deemed to be less objective. Examples of objective outcome parameters are survival for cancer therapies (Kymriah), missed blood transfusions (Zynteglo) and standardised lab values such as viral response (Hepatitis C). An example of a less objective parameter is disease progression for MS (Tecfidera).

For 17 of the 22 agreements, the outcome measurement was deemed be at the individual level, and for four agreements, the follow-up was deemed to take place at the group level. Measurement at the individual level is easier to perform in terms of contractual technology, since agreements at the group level require agreeing on complex factors, such as what constitutes the relevant group to measure the outcome for. Measurement at the group level also has the advantage that for the payer, it is group level cost that is often the most relevant.

8.7.8 Limited experience of performance-linked agreements for ATMPs, but there are some examples

Pharmaceuticals classified as ATMPs are relatively new; of the pharmaceuticals currently on the European market, the first was approved in 2015. Today, there are just over ten products registered with the EMA (94). The very recent lunch of these pharmaceuticals probably accounts for the relatively few agreements available for them. In January 2021, the database contained data on agreements for five products (Strimvelis, Kymriah and Yescarta, Luxturna, Zynteglo and Zolgensma) from six countries (France, Germany, Italy, Spain, the UK and the US). See Appendix 2 for a list of all these agreements. Below is a brief description of the agreements for the five products.

Strimvelis

Strimvelis was the first gene therapy to be approved as a nonrecurring treatment with an performance-linked agreement. The treatment involves the use of a viral vector to add a missing gene to the bone marrow of children with ADA-SCID, a disease that impedes the patient's ability to fight infections. The treatment replaces bone marrow transplants. In 2016, Italy signed an agreement with the company, with a money-back guarantee. The company was to reimburse the money if the patient's health deteriorated.[17]

CAR-T pharmaceuticals Kymriah and Yescarta

Kymriah and Yescarta are known as CAR-T cell therapies and are used in the treatment of leukaemia. The treatments involve extracting T cells from a patient, genetically modifying them and then returning them to the patient. The pharmaceuticals were approved by the EMA in 2018, and in 2019 the pharmaceuticals were approved for subsidies in several European countries.

According to information in the database, the US was the first country to establish an agreement for Kymriah (in 2017). Medicare/Medicaid then signed an agreement with the company, whereby payment would only be made if the patient responded to the treatment within the first month. Since then, five European countries have drawn up performance-linked agreements for Kymriah and Yescarta (France, Germany, Italy, Spain and the UK). The list prices are the same for the pharmaceuticals in the different countries. In other respects, the agreements differ between the countries in terms of agreement model, outcome parameters and follow-up periods; see Table 55. (95)

[17] https://www.technologyreview.com/s/602113/gene-therapy-cure-has-money-back-guarantee/

France and the UK use CED models, while Germany, Italy and Spain use performance-linked agreements with discounts or instalments. Below is a more detailed description of the agreements for these countries. (95)

In Germany, free pricing prevails in the first twelve months following market approval, while new pharmaceuticals are assessed and price negotiations take place between manufacturers and health insurance funds. The manufacturers Gilead and Novartis signed performance-linked agreements with the two largest health insurance funds (VDEK and GWO Service Plus) on discounts that apply, in the event of a patient's death following treatment. The outcome period is about twelve months and the discount is below 50 per cent.

In Italy, the pharmaceutical agency AIFA created a web-based platform that has been in use since 2005 to register data on performance-linked agreements. For Kymriah and Yescarta, there are agreements on instalments that are valid provided that of performance targets are attained. For Kymriah, three payments are made: at the time of infusion, six months later and twelve months later. For Yescarta, payments are made after 180 days, 270 days and 365 days. The agreement period is 18 months for both products.

Table 5. Performance-linked agreements for Kymriah and Yescarta in five European countries. Source: Jörgensen et al.

	Germany	Italy	Spain	France	UK
Agreement-model	Performance-linked, with discounts	Performance-linked, instalments	Performance-linked, instalments	CED	CED
Details	Instalments depend on the outcome for individual patients.	Payment in three instalments depending on the outcome for patient levels.	Payment in two instalments depending on the outcome for patient levels.	Annual reviews based on long-term follow-up data from Phase III (pivotal) trials, as well as RWD from French patients	Future price reviews based on long-term follow-up data from Phase III (pivotal) trials, as well as RWD from UK patients
Key factors, outcomes	Survival	No details disclosed	Complete response/Survival	Several (survival, remission status, progression, adverse events)	Survival/Need for post-treatment with stem cell transplantation and/or use of immunoglobulins.
Time for outcome measurement	12 months	Kymriah: 6 months, 12 months. Yescarta: 180 days, 270 days, 365 days	18 months	28 days, 100 days, 6 months, every 6 months thereafter. Annual assessment	Follow-up in 2023.
Contract length	12 months	18 months			4–5 years
List price	Kymriah: EUR 320,000 Yescarta: EUR 327,000	Kymriah: EUR 300,000 Yescarta: EUR 327,000	Kymriah: EUR 320,000 Yescarta: EUR 327,000	Kymriah: EUR 320,000 Yescarta: EUR 327,000	Kymriah: GBP 282,000 (approx. EUR 319,000). Yescarta: GBP 280,451 (approx. EUR 317,000)

Spain has agreements similar to those of Italy. Spain has recently created a platform (Valtermed) for the registration of RWD. Kymriah and Yescarta were pilot products for the platform. Kymriah is paid for by the national health service in two

performance-linked instalments. Just over half is paid upon treatment, and the other half 18 months later, provided that the patient responds 'fully' to the treatment. For Yescarta, a first payment is made for about one-third of the price (EUR 118,000) upon commencement of treatment, and a second payment (EUR 209,000) 18 months later. The criterion for the second payment is survival.

In France, HTA assessments of new pharmaceuticals are performed by the HAS (Haute Autorité de Santé). In the cases of Kymriah and Yescarta, HAS found that they provided superior clinical benefits over the available alternatives, allowing for rapid introduction. Subsidy decisions were conditional on the creation of a special register to assess the benefits of the pharmaceuticals for French patients in clinical practice. The collected outcome parameters are survival, remission status, progression and adverse events. Measurements take place after 28 days, 100 days, 6 months, and every 6 months thereafter. Based on this data and follow-up data from the Phase III trial, HAS will perform an annual assessment of the pharmaceuticals. The agreement is of the CED type, so the payment for previous patients is not adjusted to the results of the follow-up.

In the UK, Kymriah and Yescarta are being replaced through the Cancer Drugs Fund (CDF), to allow for the rapid introduction of pharmaceuticals with great potential alongside considerable uncertainties about their clinical effectiveness. Their subsidy is conditional on the generation of new evidence in clinical practice with respect to clinical effectiveness (*coverage with evidence development*). In 2023, the price will be assessed, where the main source of data will be follow-up data from clinical trials, but which will also include usage of RWE from clinical practice. The criteria are survival and the need for other treatments.

Zynteglo

Zynteglo is a gene therapy for the treatment of beta-thalassemia. Four European countries – Germany, Italy, France and the UK – are said to have negotiated or assessed the introduction and subsidy of the pharmaceutical. The company proposes instalments over five years. An initial payment of € 315,000 is made upon treatment. The same amount is then paid for the following four years, provided that the patient responds to the treatment. The outcome parameter is transfusion independence.

Luxturna

Luxturna is a gene therapy pharmaceutical used to treat vision loss due to inherited retinal degradation caused by mutations of a gene. The mutation leads to loss of vision and ultimately to blindness. The database contains information on an performance-linked agreements for Luxturna in the US, between the manufacturer and an insurance company (Harvard Pilgrim). Discounts apply if the pharmaceutical is not effective after 30 to 90 days, or after 30 months. The outcome parameter is the 'Full-field light sensitivity threshold (FST) testing score', which measures the eye's ability to perceive light of different wavelengths. The scope of the discounts is unknown.

Zolgensma

Since November 2020, Zolgensma has been part of the Italian pharmaceutical benefit system by agreement. The agreement applies to patients under the age of six months. The treatment is paid for, provided that the patient meets the conditions in accordance with a carefully specified questionnaire (96). The payment is not linked to outcome.

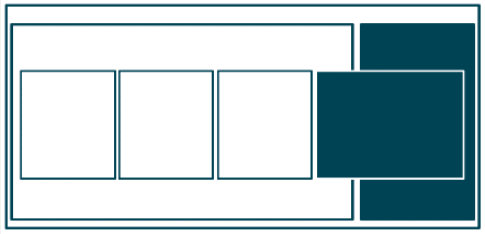
8.7.9 Conclusions from agreements on ATMP-related pharmaceuticals

TLV has arrived at some conclusions based on information in the database. Several European countries appear to have signed performance-linked agreements for ATMPs. However, such performance-linked agreements are relatively new for many countries such as Spain and Germany, and several countries are establishing platforms to record the effects of performance-linked agreements (95). Italy has had such a platform for quite some time. Spain and France are countries where similar systems were recently established.

Furthermore, the window for performance-measurement is small. On average, the contract periods are for up to two years. The UK agreement for Kymriah and Yescarta is an exception: here the contract period extends up to five years. The contract proposals for Zynteglo also extend further into the future, with payments spanning four years after treatment. In this context, four years is still a relatively short time, as the expected effects of the treatment extend far into the future. Uncertainties regarding long-term clinical effects will therefore be difficult to resolve through these agreements.

Finally, TLV can report that there are no examples of agreements that address market uncertainties, such as the introduction of new (superior) treatment alternatives and price fluctuations on comparison alternatives – this, despite the fact that this risk is probably significant for such pharmaceuticals.

9 In-depth study of payment models based on clinical outcomes



In this chapter, we expound on the following:

- In theory, performance-linked payment models are an efficient method of reducing the payer's risk – particularly for highly priced nonrecurring treatments. Companies and payers do not need to have the same opinion about what clinical effectiveness can be expected, but the future will show the extent of the health gain and the payment will then be in proportion to the actual proven effectiveness.
- In accordance with value-based pricing, a performance-linked payment model needs to be based on the *difference* in actual health gain compared to the standard treatment. This can be challenging to determine.
- It is not the contract period that is critical to how much risk reduction an outcome-based model can provide, but the follow-up period: how long after the administration of treatment are outcomes observed and payments adjusted?
- If the follow-up period is significantly shorter than the number of years that the new pharmaceutical is expected to provide health gains – which will often be the case – it is more difficult to cover a significant portion of the uncertainty with a performance-linked payment.
- In order for a limited follow-up period to provide a significant risk reduction for the payer, there needs to be a predictor that can be read at the end of the follow-up period, which clearly indicates what the pharmaceutical's effect on the patient will be in the future. A large part of the payment can then take place at the end of the follow-up period and only if the predictor indicates positive and long-term future effectiveness.

9.1 Performance-linked payment models can be useful for diverging perceptions of effectiveness

In theory, performance-linked payment models are an efficient method of reducing the payer's risk – particularly for highly priced one-time treatments, such as ATMPs. The model can facilitate companies and payers in agreeing on payments,

even if they have widely differing views of the clinical effectiveness that can be expected in the long term. The future will show what the extent of health gains will be, and the payment model means that the payment will be in proportion to the actual effectiveness shown. This reduces the payer's risk, which could in turn provide patients with access to the pharmaceutical and generate revenue for the company.

However, there are a number of practical challenges in applying performance-linked payment models. These challenges set limits on which particular models are applicable and thus, what uncertainties can be addressed. One important aspect is the duration of the follow-up period that an agreement allows for, i.e. how long after treatment has taken place that the patients' outcomes can be observed and the payments adjusted externally. Given that uncertainties about the long-term effectiveness of treatments must be addressed, the follow-up period is crucial to how well the payment model can address such uncertainties. Another important aspect concerns access to data for follow-up: What are the opportunities to identify, collect and analyse data for the outcomes that are important to the patient, and on which the payment should be based? Chapter 8 provides an in-depth account of these aspects. In the following section, we will describe the problem based on an example and show the practical consequences it could have. We also propose solutions for how they can be bridged.

9.2 Challenge when the follow-up period is shorter than the period in which the health gain is expected to occur

9.2.1 The health gain will often not have been realised before the follow-up period ends

We use an example scenario to illustrate the consequences of various paying methods. The focus is on highlighting the importance of the follow-up period's duration in the performance-linked payment model, as well as how much money is paid and when.

As discussed in Chapter 8, there are limitations on the length of the follow-up period in one agreement. Exactly how long the follow-up period may be, depends on the circumstances. In our example, we proceed from a scenario where we have an agreement with a five-year follow-up period.

Description of the example

The example is based on a scenario with two treatments, a new ATMP and the established treatment alternative. Figure 13 shows the expected survival curves for the treatments (blue and yellow curves, respectively) at the time when the ATMP is new. The area between the blue and yellow curves constitutes the expected gain in life years (in this case 10 years), on which the estimated cost per QALY is based. To simplify the presentation, we assume that the quality of life is 1.0 regardless of which of the treatments the patients receive. Thus, it is only a gain in life years that matters for cost per QALY gained.

We assume that the company has set the price for the ATMP at a level that makes the product just on the verge of having a reasonable cost per QALY, provided that actual survival is as expected. For the sake of argument, if we assume that the company deems that the payer will accept a maximum of SEK 1 million per QALY, then the company sets the price at SEK 10 million.

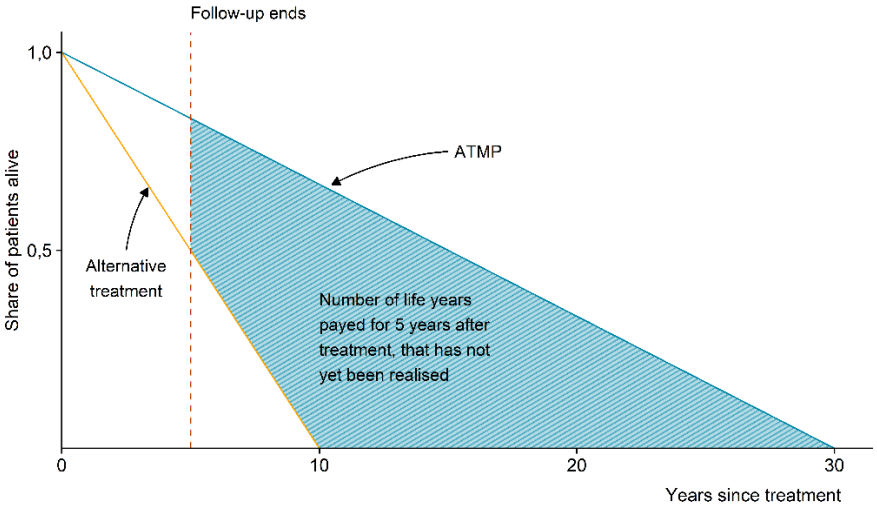


Figure 13. Estimated survival curve with ATMP (blue) and alternative treatment (yellow). The expected survival with the ATMP is 15 years (30/2) and with the alternative treatment it is 5 years (10/2)

However, there is considerable uncertainty as to whether actual survival after treatment with the ATMP will be as indicated by the blue curve. The regions see a risk that the survival gain will be less than expected, which makes them hesitant to utilise the treatment.

In our example, we illustrate three different methods of payment:

1. One-time payment in conjunction with the treatment.
2. Straight 5-year annuity, where the payment is divided into five equal payments and is conditional on the patient's survival.
3. 'Tail-heavy' 5-year annuity, where the bulk of the payment occurs in the fifth year and is conditional on the patient's survival.

Table 6 shows a payment overview of each model.

Table 6. Payment with the three different models for a patient who lives for at least 5 years following treatment.

Years after treatment	Nonrecurring payment SEK millions	Straight 5-year annuity, SEK millions	Tail-heavy 5-year annuity, SEK millions
0	10	2	0.5
1	0	2	0.5
2	0	2	0.5

3	0	2	0.5
4	0	2	8
Total	**10.0**	**10.0**	**10.0**

The inherent fairness of the annuity models (models 2 and 3) are that the full amount does not have to be paid for patients who do not survive during the first five years, which thus results in a slightly lower average cost per treated patient than a nonrecurring payment.

Regardless of which of the three models is chosen, the consequence is that after five years, payment has been made for a health gain that is yet to be realised, the blue-shaded area in Figure 13. The size of the area indicates the extent of the payer's risk and is impacted by the following factors:

- The slope of the blue curve, i.e. the degree of optimism about the predicted survival curve for the ATMP.
- The slope of the yellow curve, i.e. the degree of pessimism about the survival curve for the alternative treatment.
- The location of the dashed vertical line, i.e. the duration of the follow-up period.
- The proportion of the estimated survival gain that falls within the follow-up period, i.e. the first five years. In a scenario with a shorter survival rate, for example that both the blue and the yellow curve reach the horizontal axis 5 years earlier, the expected survival gain will be the same as in our example (10 years), but the shaded area will be smaller.

9.2.2 The models only partially reduce the risk

A payment model aimed reducing the payer's risk must be assessed on the basis of what the consequence will be if the outcome is worse than expected. Figure 14 and Figure 15 show two scenarios when the outcome is worse than expected.

The first, Figure 14, illustrates a scenario when an ATMP loses its effectiveness advantage over the comparison alternative after ten years. It is a fairly foregone conclusion that none of the three payment models discussed here, with five-years of follow-up, will reduce the cost for the payer and ensure that the cost will be proportionate to health gains. With all three payment methods, there has been an overpayment, i.e. payment for a health gain that is yet to be realised, represented by the red shaded area. This is due to the relatively short follow-up period in combination with payment being conditional on an outcome that for many patients is not realised until much later.

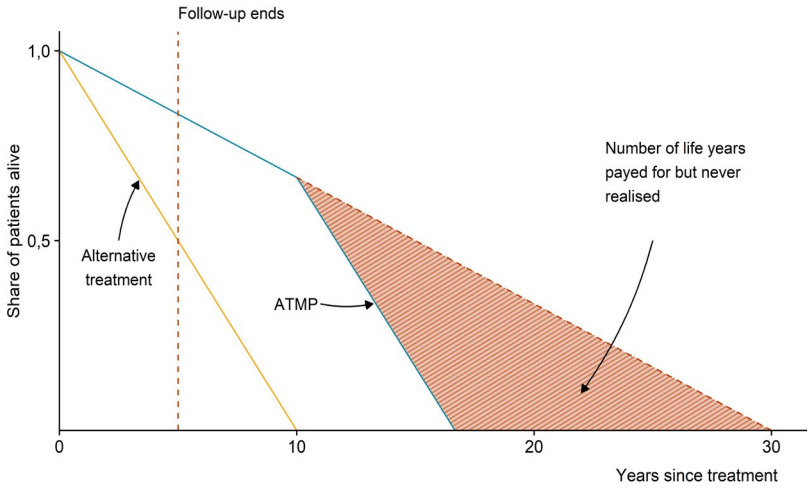


Figure 14. Expected survival for ATMP (blue) and alternative treatment (yellow) in a scenario where effectiveness decreases after 10 years

Figure 15 shows another scenario where the outcome is worse than expected. Here, we assume that the effectiveness advantage of the ATMP disappears as early as one year following treatment: the blue and the yellow curves are parallel after Year 1, and the mortality is the same.

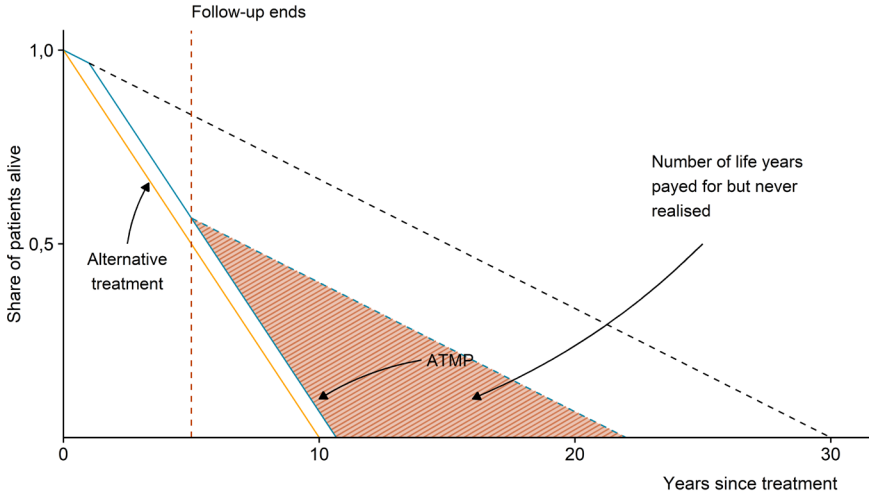


Figure 15. Expected survival for ATMP (blue) and alternative treatment (yellow) in a scenario where effectiveness diminishes after 1 year

The purpose of this example scenario is to demonstrate that even if the ATMP were to prove *not* to have the expected effectiveness within the first five years, payment models limited to five years of follow-up will not address this risk very adequately. An annuity payment manages the risk to some degree, but far from fully, in that full payment does not have to be made for patients who do not survive the first five years.

The reason is that the amount paid in the first five years is based on a high survival rate after this point in time (the blue dashed curve), which is ultimately not realised.

Table 7 shows what the average cost per treated patient will be with the different payment methods in the scenario shown in Figure 15.

Table 7. Costs if effectiveness decreases after 1 year.

Years after treatment	Proportion of surviving patients with AMTPs, %	Nonrecurring payment	**Straight 5-year annuity**, SEK millions		**Tail-heavy 5-year annuity**, SEK millions	
			Payment per patient who lives for at least 5 years	*Average-cost per treated patient*	*Payment per patient who lives for at least 5 years*	*Average-cost per treated patient*
0	100	10	2	2	0.5	0.50
1	97	0	2	1.94	0.5	0.48
2	87	0	2	1.74	0.5	0.43
3	77	0	2	1.54	0.5	0.38
4	67	0	2	1.34	8	5.36
	Total:	**10**	**10**	**8.56**	**10**	**7.15**

With the two annuity payments, the average cost per treated patient is SEK 8.6 million and SEK 7.1 million, respectively, compared with SEK 10 million for a nonrecurring payment (disregarding any discounts). However, the actual realised survival gain can be calculated to be only 1.17 years (the area between the solid blue and the yellow line in Figure 15. The payment is thus much larger than what is justifiable by the health gain.

9.2.3 Opportunities for more efficient risk reduction

One method of creating a payment model to further reduce the payer's risk is to use a surrogate endpoint as an outcome parameter, instead of making the payment conditional on whether the patient is alive. The surrogate endpoint can be useful if, within the follow-up period, it can predict the extent of long-term effectiveness a patient will derive, and therefore function as a measure of how much payment should be made. We elaborate on this argument in section 9.3.

Regarding the situation in Figure 15, a potential theoretical solution would be to perform a new analysis after Year 5, to obtain a better estimate of what the survival curve will look like in the future, and then adjust the payment based on this. Such an adjustment must then be written into the agreement between the company and the payer from the onset, i.e. that the payment for already treated patients be adjusted on the basis of data that is not available when the treatment occurs. However, the challenge with such an approach, is for the agreement to specify the method to be used to perform a new survival analysis and for the extrapolation to be sufficiently accurate, failing which there will be a risk of numerous discussions between companies and regions when the analysis is to be performed. Therefore, TLV is of the opinion that it will frequently be difficult to apply this method in practice.

9.2.4 The payer's risk depends on the probability of effectiveness receding over time

In connection with the situation in Figure 13, we described that the blue-shaded surface is a measure of the payer's risk: the amount of payment made for health gains at the end of the follow-up period, for gains that are yet to be realised. However, the extent of risk to the payer is not determined solely by this, but also by the probability of the effectiveness diminishing over time.

Figure 16 illustrates two possibilities. In one case (blue line), the probability that the treatment will *not* work is initially high, but then falls. Short follow-up periods do not have to be a problem because after five years, there is little probability that effectiveness will disappear. In the second case (black line), the probability increases that effectiveness will recede over time. In such a scenario, an agreement with a short follow-up period provides poor risk reduction for the payer. As ATMPs are used in clinical practice, we will gain better knowledge of which of these scenarios is most likely to occur.

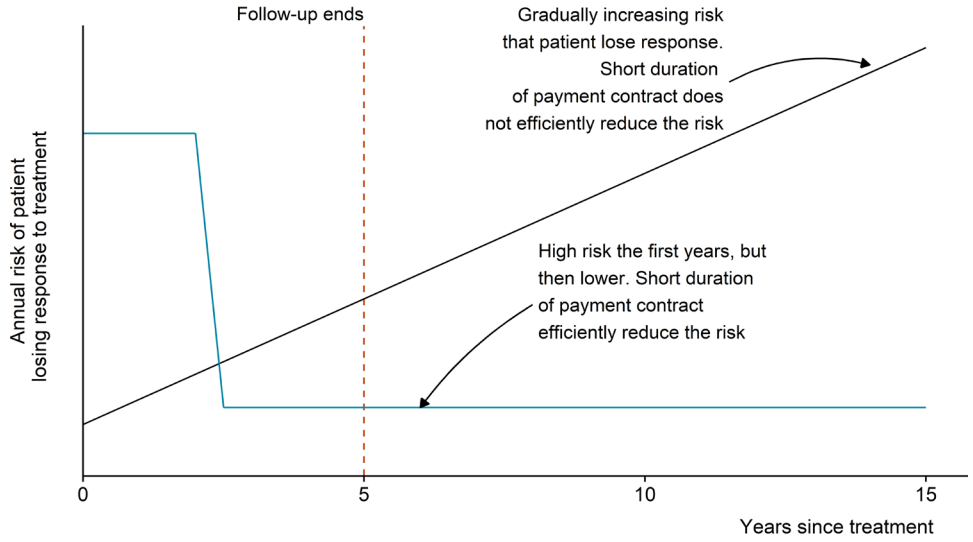


Figure 16. Schematic diagram of possibilities for how probable effectiveness will recede over time

9.3 Payment based on surrogate endpoints could entail greater risk reduction

9.3.1 Surrogate endpoints may be useful if they provide early information about a future outcome

The situation described in Figure 14 serves as a basis for the following reasoning. Here, we assume that effectiveness recedes after ten years only for certain patients. We also assume that there is a surrogate endpoint – an indicator – that can be read during the follow-up period and which provides a prediction of the duration of effect that can be expected for that particular patient. An example of a surrogate endpoint for a cancer disease could be if the disease has progressed or if the treatment has yielded a deep response. A payment model where the greatest part of

the payment occurs towards the end of the follow-up period and only for patients whose surrogate endpoint indicates long-term effectiveness, could then provide a significant risk reduction.

Surrogate endpoints occur in both clinical practice and clinical trials. A surrogate endpoint may be a laboratory result, such as cholesterol, which is a predictor of the likelihood of a future cardiovascular event. As mentioned above, it may also be the progression of cancer as an indicator of survival. Surrogate endpoints are often used in an earlier phase of the clinical development program (Phase II), but to obtain regulatory approval, verification with a 'hard' outcome parameter is required, due to the uncertainty in how the surrogate endpoint relates to the expected health gain. An example of a hard outcome parameter is survival. Outcome parameters are usually verified in Phase III of a trial. Since it takes longer for a hard outcome parameter such as survival to be realised, these studies require a longer follow-up period than a study with a surrogate endpoint.

However, that it takes less time to assess the surrogate endpoint is precisely the feature that is usable for a performance-linked payment model with a limited follow-up period.

9.3.2 One prerequisite is that knowledge is available about how the surrogate endpoint relates to the outcome parameter

If the surrogate endpoint is to be used in a payment model, it is crucial to have reasonable certainty about how the parameter relates to what is essential to the patient's health gains, i.e. the hard outcome data. Figure 17 shows the relationship between different types of outcome parameters in two different scenarios. In Scenario A, the surrogate endpoint is causally linked directly with the hard outcome data at the individual level, while in Scenario B, there is only one correlation between the surrogate endpoint and the hard outcome *at the group level*.

TLV is of the opinion that surrogate endpoints are causally linked at the individual level to the hard outcome that will often be the best option for conditional payment, i.e. as in scenario A. Why? It is true that in scenario B, if you have an overview of the correlation between surrogate endpoints and hard outcomes, the payment will be correct on average – which is important. However, a significant challenge is that there will often be a lack of strong evidence for the nature of the connection between the surrogate endpoint and long-term health gain (the hard outcome). In TLV's opinion, the potential is greater that there is knowledge about surrogate endpoints that are causally linked to the hard outcome at the individual level, as in scenario A.

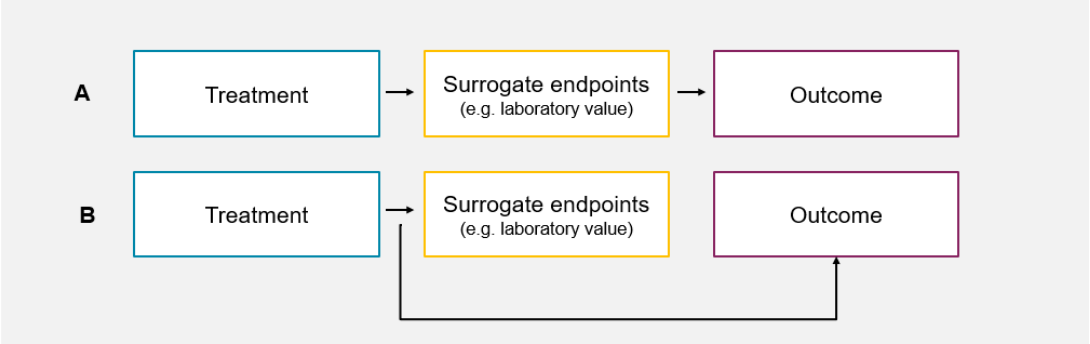


Figure 17. Schematic diagram of correlation between different outcome parameters

Example: use of surrogate endpoint as a predictor of a future outcome

In section 8.6.2, we described the conditions for follow-up – both in terms of access to data and the analysis of such data. There, we reported, among other things, on the benefits of leveraging secondary data from existing health data registers when choosing outcome parameters for a payment model.

When treated with a cholesterol-lowering pharmaceutical, the laboratory value, LDL cholesterol, is a surrogate endpoint that can be read quickly, as we mentioned above. If LDL cholesterol is to be used as an outcome in a payment model, a prerequisite – in addition to companies and payers having to agree on how LDL correlates to hard outcome data – is that data on lab values for LDL be available for follow-up. Currently, there is no national health data register that collects the lab values of this parameter. This is discussed in more depth in TLV's forthcoming report on government assignments.[18] This type of test result can also be burdened with both uncertainty and data dropouts. What happens if one of the parties questions a test result – should a new measurement then be made? If so, is an average of these two measurements to be used? What happens if different regions use different measurement methods for the laboratory results? If an agreement is designed to make the payer pay until a pre-determined change in a lab value occurs, how would a scenario where the patient does not show up for a sampling be managed? Such challenges can be solved, but must be carefully specified in an agreement.

Instead of using a lab value as a surrogate endpoint, another diagnosis that is assumed to be linked to the hard outcome data could be used. Such a diagnosis could be defined according to ICD-10 codes, and the information could be made available in the National Board of Health and Welfare's Patient Register. In the cholesterol-lowering scenario for example, it may be that a cardiovascular event has occurred. To illustrate this with an example, data from the patient register is used for patients who commenced treatment with a pharmaceutical of the type PCSK9 inhibitor (Figure 18). The image shows that about 50 per cent of the patient population has had a cardiovascular event within four years, while almost all are alive. A payment model based on whether the patient is alive would mean full

[18]Developed follow-ups with data from sources such as the National Service Platform; ref no. 1694/2020

payment for nearly all patients, but only for half of the patients, if the outcome was a cardiovascular event.

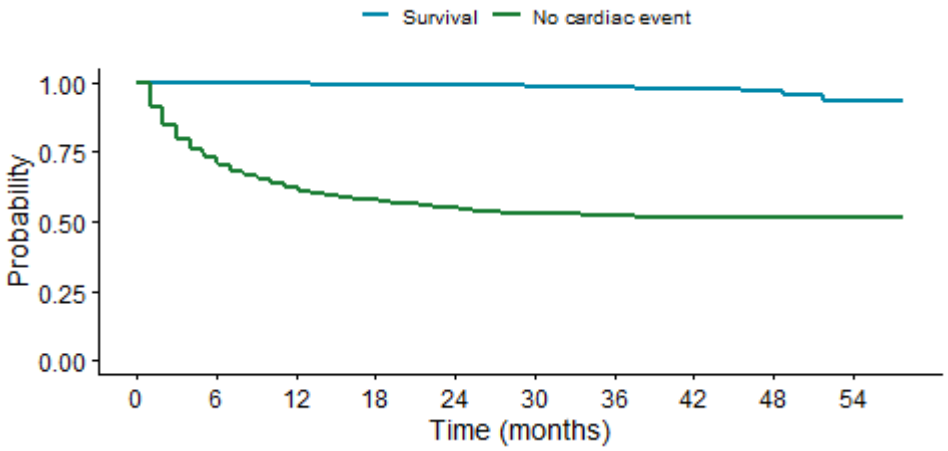


Figure 18. Probability of survival or of not having a cardiovascular event against time, following treatment with PCSK9 inhibitor. Data from the National Board of Health and Welfare.

9.4 Performance-linked payment models – what is important to consider?

As a summary of this chapter, we list below several questions that should be answered in connection with payers and companies assessing agreements on a payment model based on clinical outcome:

1. What risk is to be reduced?
2. How many QALYs must be realised in clinical practice after the end of the follow-up period, for the pharmaceutical to have a reasonable cost per QALY?
3. What do we know about the probability of effectiveness receding and how it may change over time?
4. Surrogate endpoints:
   a) Is there any surrogate endpoint that serves as a good predictor of long-term effectiveness on the hard outcome data that determines the patient's health gains?
   b) Is the effectiveness or the absence of effectiveness realisable through the surrogate endpoint within the follow-up period?
   c) Are measurements of the surrogate endpoint made routinely or are special examinations required?
   d) Is data on the surrogate endpoint available in publicly accessible health registers?
5. If there are no suitable surrogate endpoints, can a patient's need for other treatments or the existence of another diagnosis be used as an outcome that governs payment?
6. Based on the given conditions, does an agreement have the opportunity to gain acceptance and a high level of compliance in the regions?

Regarding the first question, it is important to first clarify which risk is to be reduced, i.e. what factors are decisive for the ATMP treatment's long-term health gain and what is to be regarded as a successful treatment: Is it the patient's survival? Is it being symptom free? Or is it that the patient does not require follow-ups with other expensive treatments?

The second question pertains to the extent of the risk. The more QALY that payment has been made for at the end of the follow-up period, but which has not yet been realised, the greater the payer's risk. The third question is also related to this, because the trend in the probability of effectiveness receding over time also has an impact on the payer's risk.

The fourth question becomes relevant if payment based on hard outcome data, such as whether the patient is alive, is not deemed to reduce the risk sufficiently. Are there surrogate endpoints that could be assessed within the follow-up period, which could serve as a reliable predictor of long-term health gains and therefore also be used for conditional payments?

The health-economics model can be leveraged to provide part of the answer to the first three questions, by simulating the consequences of costs and health gains for different clinical outcomes and payment models. On the questions of follow-up, knowledge is required about the conditions for such in the particular situation concerned. Examples of questions to ask here, are whether the parameter is measured routinely or whether special examinations or measurements are required? In which registers will the data be available? What are the administrative requirements for acquiring the data? The conditions for compliance with the agreement in the regions are partly associated with the opportunities for follow-up. In addition, there are aspects such as the predictability of outcome and transparency of the terms and conditions.

10 Some parting reflections and proposals for the next step

The availability of precision medicines and ATMPs could entail major health gains and improved quality of life for patients with serious diseases. At the same time, these therapies are challenging the current system for health-economic assessments, payments and financing. In this assignment, TLV has described its perspective of these challenges and analysed a number of issues associated with them, and arrived at several conclusions. TLV also deems that there is a need for the continued development of health-economic methods and for stronger prerequisites for new types of payment models. Below is our assessment of what future development work should focus on, along with our proposals on how it can be achieved.

Continued development of health-economic methods for the assessment of precision medicines and ATMPs

What does TLV consider to be a priority to further develop?

A distinguishing feature of precision medicine is molecularly-based tests – diagnostic, prognostic and treatment predictive – and that these are now more defined than before as being integral to the treatment chain. In this report, TLV presents several conclusions about how and when the cost of tests should be included in the health-economic assessment of a treatment, and how the cost-effectiveness of the test itself should be evaluated. TLV is of the opinion that the value of a treatment-predictive test depends on how cost-effective the subsequent treatments are. This makes it challenging to perform complete assessments, as it requires considerable amounts of data. The continuous development of new tests also contributes to further complexity. TLV sees a need for further investigation into how simpler, yet informative, assessments of various types of tests could be performed.

The greatest challenge to conducting health-economic assessments of precision medicines and ATMPs will be the lack of evidence. While it is usually clear that the treatments and tests benefit patients, the extent of the benefit relative to the alternative is often uncertain – particularly for new treatments. Consequently, an important question is how the uncertainty in the estimated health gain can be reflected in the health-economic analysis. This is particularly true for ATMPs. TLV offers some suggestions on how to proceed. One approach in these situations, is to let the base-case scenario reflect that there is a probability of several different outcomes. This means, for example, not allowing the basic scenario to represent a fixed number of years for the duration of effect, but basing it on a probability-weighted average of calculations, where different durations of effectiveness have been assumed. The calculation then better reflects the genuine uncertainty that exists with the different possible outcomes. These probabilities can then be

standardised to some degree, to create transparency and facilitate consistent assessments. However, the usefulness of this and the details of how it should be implemented require further investigation.

TLV is of the opinion that there is reason to consider whether greater uncertainty should be accepted, if the consequence of holding off treatment is very serious for the patient. For a serious condition that is progressive and irreversible, which an ATMP treatment could halt or impede, greater uncertainty should be acceptable. However, how this factor should be systematically incorporated with other assessment criteria must be investigated further. Part of the solution may be to develop a parameter that captures the patient's long-term health loss from holding off on treatment. One possible parameter is QALY loss from holding off on treatment for five years.

What are our suggestions on how to achieve this?

TLV does not claim to offer any complete answers to the questions in this report, but deems that they need to be resolved gradually, due to the emergence of various situations.
TLV will continue to develop it working practices and methods within the scope of its core operations, based on the conclusions of this assignment. In the performance of analyses to evaluate tests, we see the need for collaboration with academia and the pharmaceutical industry. With regard to the idea of a weighted base-case calculation of cost per QALY, methods need to be developed and agreed upon with the actors concerned. The same applies to the proposal to calculate the QALY loss from holding off on treatment.

TLV is also requesting increased resources that could enable in-depth forward-looking analyses and the above-proposed further development, such as through a supplementary government assignment.

Continued development of pricing and payment methods for pharmaceuticals used in combination therapies

What does TLV consider to be a priority to further develop?

It has become increasingly common for high-priced pharmaceuticals to be combined with each other. The fact that products are more often included as part of a whole entails challenges in terms of the valuation and payment of these products. TLV deems that part of the solution is for the pricing to reflect that the pharmaceuticals are used in different situations.

This work should be developed in collaboration between TLV and the regions, as well as with the pharmaceutical industry. Combined pharmaceuticals are also frequently prescribed under benefits schemes, for which TLV makes decisions on subsidies, involving requisitioned hospital pharmaceuticals for which the regions have financial responsibility. One important prerequisite for flexible pricing is the possibility for following up which patients receive what treatment; the regions also have a key role in this development (see below).

What are our suggestions on how to achieve this?

Today, TLV has an ongoing dialogue with the regions about working methods for identifying the most important areas and the potential solutions. To enable focused work with collaboration between TLV, the regions and the pharmaceutical industry, we propose development efforts within this area, such as through a government assignment.

Strengthened conditions for implementation of performance-linked payment models for ATMPs, including further investigation of specific key issues

What does TLV consider to be a priority to further develop?

TLV considers it important to develop methods for reducing the payer's risk for nonrecurring treatments that are priced based on an assumption of very positive and long-lasting effectiveness: How do we ensure that the cost is not higher than what is justifiable by the health gain realised in clinical practice? If the payer's risk cannot be reduced, it may lead to patients being unable to access the treatments.

In this report, TLV describes the potential of and conditions for different payment models, with a focus on ATMPs. What we consider to be particularly relevant to ATMPs are performance-linked payment models with partial payments and a relatively long follow-up period, where the bulk of the payment occurs towards the end. It will be easier for the payer and the company to sign an agreement if they are not required to have an identical picture of what health gains can be expected in order to do so. Instead, payments are made gradually as health gains are realised.

However, there are currently several challenges associated with the development and implementation of performance-linked payment models. TLV highlights some key areas that must be strengthened for implementation to be possible:

- Follow-up of relevant outcome parameters
- Prerequisites in place for the public sector to sign agreements based on more complex payment models
- Regional collaboration on the negotiation, signing of agreements and follow-up of payment models

Opportunities for follow-up must be improved, both in terms of data sources and data-acquisition infrastructure. Today, for example, there are no national health data registers that are collecting information about which patients are receiving what pharmaceuticals that are administered in hospitals. This needs to be addressed in order for the prerequisites to be in place for payment models based on outcomes. In previous reports, TLV has highlighted the need to strengthen the development of national health data registers (90).

The possibilities for implementing payment models will also depend on creating conditions conducive to the payer and the pharmaceutical companies negotiating sufficiently well-defined agreements that take into account all aspects of uncertainties, including the long-term conditions, so that there is no doubt about what the parties have agreed on. The opportunities for the public sector to sign national agreements based on payment models must also be investigated.

TLV wishes to emphasise the value of the regions' ongoing collaborations to develop new payment models and recommends that this collaboration be increased. A consensus between the regions on key issues, including the signing of agreements and follow-up, is requisite to the work's progress. During ongoing government assignments, new working methods were tested within the scope of a pilot project aimed at investigating the possibilities of utilising developed payment model(s) for specific products and analysing their consequences. TLV sees great value in the continuation and development of such collaboration. The responsibilities of the various actors need to be further clarified.

Finally, TLV sees a several risks for the irrational use of ATMPs, which the Swedish financing structure for pharmaceuticals could lead to. TLV is of the opinion that ATMPs have certain characteristics that necessitate the consideration of alternative financing solutions.

What are our suggestions on how to achieve this?

As we have noted, the implementation of payment models is associated with a number of challenges. Although the conditions have not been fully investigated, TLV is of the opinion that the next step should be to draft proposals for payment models and to design contracts for a number of concrete situations that have the potential to address the challenges of ATMPs. Based on this, the regions and TLV could garner important experiences for the future. TLV therefore intends to continue to develop working methods for collaboration between TLV and the regions in this regard, including within the framework of the established collaboration with the regions under the hospital pharmaceuticals assignment.

The investigation and development of opportunities for follow-up is key. TLV is engaged in in-depth work in this area, within the scope of ongoing government assignments for the development of Real World Data (RWD) (97).

TLV wishes to highlight the need for TLV to be assigned to further investigate opportunities for the public sector to sign national agreements, such as through a renewed government assignment.

TLV also sees reason for the government to consider the following measures:

- To investigate the possibilities for the state (co-)financing of ATMPs, designed so that rational utilisation can be achieved.
- To clarify – by means of the agreement with the regions on state subsidies for pharmaceuticals under benefit schemes – the regions' responsibility to drive development through the automated reporting of data, so as to enable the follow-up of pharmaceuticals.

New value aspects: the quality of life of next-of-kin caregivers has the greatest potential to be captured with data

In this assignment, TLV does reach any definitive conclusions as to whether the authority should, in future decision-making, factor in any of the four value aspects discussed in this report. However, one conclusion we do draw, is that if a value

aspect is important and ethically reasonable to take into account, it should be included regardless of whether it concerns a precision medicine, ATMP or other type of technology. While TLV deems that there is a need to continue discussing these issues, it is of the opinion that the focus should first be on the question of how the quality of life of next-of-kin caregivers should be factored in. This aspect is not discussed in this report, because it does not have such a clear connection to precision medicines and ATMPs. However, it is a value aspect that is taken into consideration by the government agencies of some other countries. This represents a greater opportunity to acquire data that could capture the value of this aspect. Cooperation with relevant authorities in other countries on this issue will be important.

Leveraging and benefiting from experiences at the international level and from existing structures for cooperation and collaboration

Within the framework of this government assignment, TLV has collaborated with a large number of actors from the pharmaceutical industry, the regions, academia, other government agencies, and with patients and user representatives. We have also discussed the challenges and opportunities associated with precision medicines and ATMPs in a number of contexts. In these conversations, there is a consistent desire for coordination of efforts and the importance of the system being connected, regardless of the responsible principal or financier. Based on this, TLV wishes to emphasise the value of strengthening the work within already-established national collaboration structures; including work within the scope of the Life Sciences Strategy, interagency partnership in the field of health care and the regions' national knowledge-management systems.

The challenges of assessing, pricing and paying for precision medicines and ATMPs are not unique to Sweden. Most countries struggle with the same issues, and we therefore see the need for and value of drawing lessons and experiences from what is implemented beyond Sweden's borders. As a government agency, we also see the value of participating in and strengthening the Nordic and European cooperation that is taking place in health-economic assessment and negotiation. There are many international joint initiatives, some concrete and others more informal. Typically, we can see that the initiatives at the early phase of a product's life cycle, such as horizon scanning and scientific advice, are easier to agree on and can be achieved between more countries. TLV deems that early scientific advice can contribute to the more appropriate development of new pharmaceuticals. Joint evaluations of clinical effectiveness have the potential to save major investigative resources. Joint price negotiations can provide small and medium-sized buyers with a better negotiating position in relation to pharmaceutical companies.

How should we perform an assessment and how should we pay?

In conclusion, TLV would like to point out that many of the challenges and issues that are analysed and answered in this report are already being worked on by TLV in various ways. We therefore do not regard most of these challenges as entirely new phenomena. This also means that the conclusions we have arrived at regarding developed health-economic analyses will also be supported by the assessment of treatments that are not within precision medicines and ATMPs. The work that has

been undertaken within the scope of this assignment has meant an opportunity to reflect on how the methods and approaches need to be developed – a development that we deem needs to continue. TLV also wishes to emphasise that a prerequisite for making progress in this work is for all parties, including the companies responsible for pricing the products, to take their responsibility for finding solutions that sustainable in the long term.

How should we perform assessments and how should we pay? Our belief and hope is that through this work, we have helped to enhance the knowledge and understanding of what we consider to be the most important challenges, and how some of them should be managed. TLV will continue to it work to further develop knowledge in this area. The goal is for efficacious and reliable treatments to be made available to Swedish patients – at a reasonable cost to the public sector.

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Appendices

Appendix 1 Analysis of the significance of a test's sensitivity and specificity

Section 4.3.1

Here, we show the expression of the *incremental net monetary benefit* (INMB).[19]

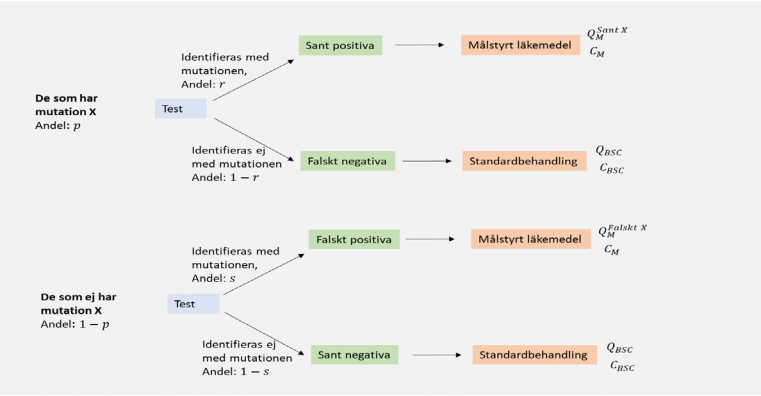
It is easiest to set up the expression for our example if we start from the figure below. Consequently, we are of the opinion that there are two different tests, *New* and *Established*, where r and s are different.

Sensitivity is defined as the probability of a positive outcome (that the mutation exists) for an individual who has the mutation. This is r.

The specificity is defined as the probability of a negative outcome (that the mutation does not exist) for an individual who does not have the mutation. This is 1-s.

We therefore assume that the *New* test has both better sensitivity and specificity than the *Established* test, but that the *New* test also costs more, i.e.

$r^{New} > r^{Established}$, $1 - s^{New} > s^{Established}$ as well as $C_{test}^{New} > C_{test}^{Established}$.



[19] The relationship between INMB and ICER is as follows, if treatment A and B are to be compared:

$$ICER = \frac{C_A - C_B}{Q_A - Q_B} < k$$

where K is willingness to pay per QALY gained.

$$INMB = k(Q_A - Q_B) - (C_A - C_B)$$

$$INMB = C_{test}^{New} - C_{test}^{Established} + p\left(r^{New} - r^{Established}\right)\underbrace{\left[k\left(Q_M^{SantX} - Q_{BSC}\right) - \left(C_M - C_{BSC}\right)\right]}_{\substack{Net\ monetary\ benefit\ for\ true\ positives,\\ assumed\ to\ be\ >0}} +$$

$$(1-p)\left[(1-s^{New}) - (1-s^{Established})\right]\left[\underbrace{k\left(Q_M^{False\ X} - Q_{BSC}\right)}_{\substack{Net\ monetary\ benefit\ for\ true\ positives,\\ assumed\ to\ be\ <0}} - \left(C_M - C_{BSC}\right)\right]$$

where k is willingness to pay per QALY, Q is QALY and C is cost.

We then see that

- the greater the difference in test cost, the greater the INMB$C_{test}^{New} - C_{test}^{Established}$
- the greater the difference in sensitivity, the greater the INMB:

$$\frac{dINMB}{d\left(r^{New} - r^{Established}\right)} > 0$$

- the greater the difference in specificity, the greater the INMB:

$$\frac{dINMB}{d\left[(1-s^{New}) - (1-s^{Established})\right]} > 0$$

- the greater the “net monetary benefit” for true positives, the greater the INMB
- the greater the “net monetary benefit” for false negatives, the greater the INMB.

Appendix 2 Summary: Countries with performance-linked agreements for ATMP products

Pharmaceuticals (ATMPs)	Countries that have or have negotiated performance-linked agreements for this product	Year	Contract length	Type of agreement	Summary
Strimvelis	Italy	2016		PLR	Agreement with money-back guarantee if the patient's health deteriorates following treatment.
Luxturna	USA	2018			Discounts if Luxturna is not efficacious within 30 to 90 days, or after 30 months. Outcome parameter: 'Full-field light sensitivity threshold (FST) testing scores'.
Kymriah	France	2019		CED	Market access contingent on annual follow-ups of clinical trials and data generated following access.
Kymriah	Germany	2019		PLR	Discounts depending on outcome. Outcome parameter: the patient is deceased by a certain time.
Kymriah	UK	2019	4 years	CED	Future revaluations of price depending on follow-up of clinical trials and data generated after market access.
Kymriah	Italy	2019		PLR	Three instalments depending on outcome.
Kymriah	Spain	2019		PLR	Two instalments depending on the outcome of individual patients.
Kymriah	USA	2017		PLR	Payment only for patients who respond within the first month of treatment.
Yescarta	France	2019		CED	Time-limited access contingent on follow-up of clinical trials and generation and follow-up of RWD after access.
Yescarta	UK	2019	3 years	CED	Access with follow-up of clinical trials (ZUMA-1) and data generated after access.
Yescarta	Germany	2019		PLR	Discounts depending on outcome of individual patients.
Yescarta	Italy	2019		PLR	Three instalments depending on the outcome of individual patients.
Yescarta	Spain	2019		PLR	Two instalments depending on the outcome of individual patients.
Zynteglo	Germany ** France ** United Kingdom ** Italy**	2020	5 years	PLR	Instalments over five years. Following an initial payment of EUR 315,000, the same amount is paid only if the patient continues to respond to the treatment.
Zolgensma	Italy	2020		AAP*	

* 'Accordo appropriatezza prescrittiva'. ** Negotiations/evaluation of entry into benefits scheme.