Market access of a new innovative method for diagnostics of RA in Sweden

Hanna Welander
Abstract

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Rheumatoid Arthritis (RA) is a chronic autoimmune disease that affects 0.5-1% of the general population worldwide. The disease is a complex genetic disease, meaning that several genes, environmental factors and stochastic factors act as players in the development of the disease. RA causes inflammation in the joints typically in the hands and feet. It also can affect surrounding tissue and organs in the body. RA affects mostly women in their middle age, but the disease can occur at every age and in both genders. New research indicates that early treatment can improve quality of life and living conditions for the patients since medical treatment of the disease can cause remission.

Thermo Fischer Scientific ImmunoDiagnostic Division in Uppsala started the development of a new diagnostic tool, ISAC, to provide early diagnosis for RA patients and consequently enable early treatment.

The report will discuss the costs associated with the disease today and in connection to diagnosis, medication, hospital admissions and sick leave in Sweden. This will lead to a discussion and presentation of a market strategy for the first phase of the introducing the product.

The results from the latest study done with ISAC shows that ISAC is “as good as” the present and competitive diagnostic method such as ELISA/CCP2 tests but ISAC has the ability to diagnose 18% more patients.

Early diagnosis allows cost savings and during year 4 and with patient base of 3600 patients the savings are 154 million SEK or more for the healthcare system. From the selected group of patients around 900 new patients will be added annually.

The associated cost savings for the healthcare system can be up to 25% for each patient compared to present methods. In addition, there is a great value for each additional year of working life for the patient. However this added value is extremely difficult to predict.
**Market access of a new innovative method for diagnostics of RA in Sweden.**

An initial investigation of the development of a market access strategy for a new product enabling earlier diagnostic of an autoimmune disease.

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*Kandidatuppsats i Teknik*

Civilingenjörsprogrammet i Molekylär bioteknik

Uppsala Universitet, 2012

**Date for approval: 2012**

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1 Abstract

Rheumatoid Arthritis (RA) is a chronic autoimmune disease that affects 0.5-1% of the general population worldwide\(^1\). The disease is a complex genetic disease, meaning that several genes, environmental factors and stochastic factors act as players in the development of the disease. RA causes inflammation in the joints typically in the hands and feet. It also can affect surrounding tissue and organs in the body.\(^2\) RA affects mostly women in their middle age, but the disease can occur at every age and in both genders.\(^3\) New research indicates that early treatment can improve quality of life and living conditions for the patients since medical treatment of the disease can cause remission.\(^4\)

Thermo Fischer Scientific ImmunoDiagnostic Division in Uppsala started the development of a new diagnostic tool, ISAC, to provide early diagnosis for RA patients and consequently enable early treatment.

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The associated cost savings for the healthcare system can be up to 25% for each patient compared to present methods. In addition, there is a great value for each additional year of working life for the patient. However this added value is extremely difficult to predict.

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\(^3\) Ibid.

\(^4\) Klareskog, L. Rheumatoid arthritis, Lancet 373, (2009), 659-72
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3 Introduction

Rheumatoid Arthritis (RA) is an autoimmune disease that affects about 0.5-1% of the general worldwide population\(^5\). In Sweden this represents around 60,000 patients and the number is increasing annually with approximately 2000 persons. The disease is overrepresented by women in their middle age\(^6\). Today, the disease cannot be cured but with treatments the symptoms can be reduced and patients can live a relatively normal life. Therapy, with the aggressive and effective drug TNF-blockade, is expensive and requires early insertion to get the best results\(^7\).

Lekander\(^8\) states that “The disease has a considerable social and economic impact, and the costs to society associated with RA are substantial, as the disease can rapidly lead to restricted joint mobility, chronic pain, fatigue, and functional disability, with approximately one-third of patients unable to work within 10 years of disease onset.”

Thermo Fisher Scientific ImmunoDiagnostic Division (TFS IDD) has developed a new diagnostic tool that may have the ability for earlier diagnosis and with greater specificity and sensitivity than other methods used today.\(^9\)

3.1 The aim

The aim of this report is a first guideline for a market access strategy for this new product entering an existing market. It is important to understand the impact of the economics to make a reliable market access plan. For this reason a health economic evaluation has been conducted. The study is based on the new technology at TFS IDD and is focused on the factors affecting the costs. The report provides TFS IDD with an overall guideline of behaviour for future promotion.

The concept of health economics has lately been increasingly emphasised and the state demands evaluation of the health economic aspects of new drugs and new diagnostic tools. Health economics is a concept that can evaluate the effects and costs of implementing new technologies/treatments for the healthcare system and individuals.

The desire of TFS IDD is that the new method allows earlier medication for the patients, which increases the number of life quality years for RA patients and reduces the costs for the society. One question to be answered is: how earlier and more specific diagnosis can affect the societal costs associated with RA.

The report will present the costs associated with the disease today and in connection to diagnosis, medication, hospital admissions and sick leave in Sweden. Within the scope of the report a comparison is done between costs “today and “tomorrow” and estimates about what the cost will be due to the introduction of the new technology.

\(^6\) Klareskog, L. Saxne, T. Reumatologi, (2011)
\(^7\) Klareskog, L. Rheumatoid arthritis, Lancet 373, (2009), 659-72
\(^9\) Matsson, P. Oral source, (2012), TFS IDD
These two cases will be presented in the results:

- “Today” Indirect and direct costs associated with the disease.
- “Tomorrow” Indirect and direct costs associated with the disease using the new technology ISAC for diagnosis.

3.1.1 Delimitation
The conclusions and estimates are based on a literature study of existing research results, the facts about the product provided by TFS IDD and a health economic analysis. The present study is limited to women between 35-64 years old with the most common subgroup (ACPA(+)) of the RA disease in Sweden. This is because of the availability of a good patient databases and research results. The result and report provides overall estimations and a first insight in future product profitability.

3.2 Research question
This report aims to provide answers for the following questions:

- What would the first step be for implementation of the product?
- What attribute of ISAC is crucial for the acceptance by the early adaptors in the first step of the implementation?
- Are there any cost-benefits related to early diagnosis of RA
4 Background and theory

4.1 Thermo Fisher Scientific
Thermo Fisher Scientific Inc. formerly Phadia AB, develops and produces tools for diagnosis of allergy, asthma and autoimmune diseases. The headquarters is in Uppsala, Sweden which has a history as the former diagnostic department of former Pharmacia AB. Thermo Fisher is the world leader for diagnostic tools for allergy and one of the top manufacturer of tests for autoimmune diseases. Thermo Fisher Scientific ImmunoDiagnostic Division (TFS IDD) is a division within Thermo Fisher responsible for the research within immune diagnostics.

Thermo Fisher vision is ”to remain focused on excellence as we respond to the diagnostic needs of the world.”

Early diagnosis and treatment have been shown to be favourable and has become increasingly important. TFS IDD therefore started the development of a new version of the CCP2 test, a test to identify auto-antibodies that are markers for autoimmune diseases in the body. It is seen that the presence of anti-CCP antibodies can help physicians to decide which patients need early treatment. Early treatment is believed to be the key for remission. The goal of the research at TFS IDD is to make a diagnostic tool that can increase the number of remissions in patients suffering with all kinds of autoimmune diseases. TFS ISS has selected RA as the start up case and a first area for their development efforts. Remission is the medical term for the state of a chronic disease where symptoms partly have decreased or temporarily have disappeared due to treatment.

4.2 Rheumatoid Arthritis: The disease
Rheumatoid arthritis is an autoimmune chronic disorder with rapid transition. An autoimmune disorder is a disease where the immune system of the body by mistake attacks healthy tissues, especially in the joints. It is a common health disease and approximately 0,5-1% of the population is diagnosed annually. The affected are mostly women in their middle age, but the disease can occur at every age and in both genders. New research indicates that earlier treatment can improve life quality and conditions for these patients since the disease can be reversed. To make remission early treatment is believed to be crucial.

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10 www.phadia.com 2012-06-21
12 Klareskog, L. Rheumatoid arthritis, Lancet 373, (2009), 659-72
14 Klareskog, L. Rheumatoid arthritis, Lancet 373, (2009), 659-72
The graph above depicts a schematic image of the development of the disease over time. We can see that if diagnosis and treatment can be made early, the treatment with TNF-blockade can reduce the impact on the disease and joint destruction is reduced; full or part remission can be reached. The further the disease has progressed, the more difficult it gets to reduce the destructive process. Researchers have done investigations on early treatment of RA and found that early treatment will delay the progress of the disease and to proved favourable outcome for the patient.

Early diagnosis has been shown to be profitable and generate large savings for the society. Early diagnosis and early treatment is beneficial for the development of the disease, not only in RA but also in other chronic disorders. For example, in a study of the Celiac disease in children, researchers have seen a pattern of better life quality and conditions for children diagnosed before the age of five than in the children diagnosed later in life. It is possible that earlier diagnosis makes a patient adapt to the new living situation easier than a person suffering with the symptoms a longer time before diagnosis.

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15 www.phadia.se 2012-04-22
17 Van Dongen, H. Efficacy of Methotrexate Treatment in Patients With Probable Rheumatoid Arthritis, (2007)
18 Klareskog, L. Rheumatoid arthritis, Lancet 373, (2009), 659-72
20 Byström, I-M. Hollén, E. Health-Related Quality of Life in Children and Adolescents with Celiac Disease, (2012)
In figure 1 above it can be seen that it is important to bring forward the time for diagnosis. The research at TFS IDD shows that earlier diagnosis in RA is possible up to 8 years before symptoms arise but the question is; is this point of diagnosis possible other than in theory? A patient that is diagnosed long before the symptoms appear might not have better quality-adjusted life years (QALY), a measure of a patients disease burden, than for patients diagnosed 4 months prior symptoms. There are also evidence suggesting that patients, before they have received therapy, can misjudge their ability to work and “give up”. Can this misjudgement of ability be changed by earlier diagnosis or is the misjudging a part of the diagnosis regardless the time for diagnosis?

RA is a complex genetic disease, meaning that several genes, environmental factors and stochastic factors act as players in the development of the disease. RA causes joint inflammations usually in the hands and feet. It can also affect surrounding tissues and organs in the body. The genetic factor is responsible for about 50% of all cases of RA. It is therefore important to investigate the cause of disease in all areas. For an example, smoking has been found to be one of the environmental factors that have an important impact of the progress of the disease. Research results show that in 55% of the patients, with normal genetic form of RA, the disease never would have developed if they had not smoked.

The figure below shows the differences in number of incidence patients of RA between male and females. It is clear that RA affects women to a greater extent than men. It is also seen that the disease foremost affects men and women in their middle age. This figure and the incidence numbers are the base for the estimates in this report. The graph shows the number of women that every year are affected and it can be seen that the target group for this study is the largest group i.e. women between 35-64 years. While investigating the cost around the disease the report only focus on the group of working age where the socio-economic impact is the largest.

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21 Lambert, C. M. Medical therapy for Rheumatoid arthritis- value for money? (2001)
23 Klareskog, L. Rheumatoid arthritis, Lancet 373, (2009), 659-72
24 Klareskog, L. Klinisk Utveckling av Register (KUR), PowerPoint presentation (2011)
4.2.1 Molecular background of the disease

Earlier, researchers talked about the Rheumatoid Factor (RF) as the causing agent of the disease. RF is a co-expressed auto-antibody against the Fc-part of the IgG-molecule and can be present as more than one isotype such as IgM and IgA in a patient. The probability for acquiring RA increases with the number of isotypes. Recently, researchers have shown that the RF factor is more likely to be just a biomarker for the disease instead of the disease-causing factor. Results show that the RF factor also can be present in individuals without RA and instead studies have shown a new marker for disease activity, ACPA, Anti Citrullinated Peptide Antibodies for the disease.

The new method for measuring the activity of RA in patients is to investigate the auto-antibodies from the citrullinated peptide. ACPA or anti-citrullinated peptide antibodies are also referred to as Anti-CCP. The ACPA is proven to be more specific for RA and more informative as a diagnostic test for early RA than the RF. Approx. 67% of all RA patients have the ACPA antigen and it is also produced at a significant level early in the disease development. Up to 18 years before the visible symptoms will arrive ACPA-molecules can be founded in the body.

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26 Rantapää-Dahlqvist, S. Antibodies Against Cyclic Citrullinated Peptide and IgA Rheumatoid Factor Predict the Development of Rheumatoid Arthritis, (2003)
27 Klareskog, L. Saxne, T. Enman, Y. Reumatologi, (2011)
28 Klareskog, L. Rheumatoid arthritis, Lancet 373, (2009), 659-72
There are two general types or subgroups of patients with RA, the ones that have the ACPA(+) molecule and the ones with the ACPA(-) molecule. The treatment of the two ACPA-groups of RA may differ and it is therefore important to continue to study the molecules and the development of the disease. It is also important to separate these two types in the diagnosis to understand the progress of disease in the patient and treat the disease with the proper medication. Pruijn writes that “if patients are diagnosed with Anti-CCP(+); 90 % of them will develop disease within 3 years in contrast to only 30% in the group with the ACPA(-) version”\textsuperscript{30}. It has also been shown that the ACPA(+) form of the disease is the most common version representing 75% of the long-term and 61% of the early established RA is ACPA(+). As seen in the picture below in the study that Klareskog, L. et al. made in 2012 the ratio between ACPA(+) and (-) is 72% versus 28%\textsuperscript{31}.

Figure 3. Different patterns of ACPA:s in different RA patients.\textsuperscript{32}

There are (Figure 3) many different subtypes of the ACPA-antigen. This is depending on which peptide that is the base for the citrullination. The picture above shows that the new method ISAC can differentiate the patients by different molecules. It is now up to researcher to study these groups more and hopefully a pattern of disease aggressiveness can be made. This might help future physicians to understand how to treat patients right from start.

\textsuperscript{31} Klareskog, L. Rationale for multiplex antibody testing in autoimmune diseases, PowerPoint presentation, (2012)
\textsuperscript{32} Ibid.
4.2.2 ACPA versus RF-factor for diagnosis

As described in the article “The use of citrullinated peptides and proteins for diagnosis of rheumatoid arthritis” by Pruijn, the RF factor was formerly the only predictor of the disease but today new research shows that the antigens of CCP is a good predictor in most cases. Researchers do not fully agree about RF or ACPA as a tool for diagnosis, but it is certain that a combination will more likely tell the truth. Purijn argues that the prediction should be based only on ACPA test.

“The radiographic progression seen is actually associated with ACPA(+)/RF(+) and ACPA(+)/RF(-) but not with ACPA(-)/RF(+) or ACPA(-)/RF(-) RA.” This shows that the RF factor is not associated with the joint destruction but, as know before, a co-expressed auto-antibody.

This is also something that the Swedish National Board of Health and Welfare (Socialstyrelsen) is discussing and in the guidelines, chapter 4.5, both RA and CCP are taken into account.

4.3 Diagnosis

Diagnostics of RA have historically been done by a couple of classification criteria’s conducted by the rheumatologists at American College of Rheumatology (ACR) in the 1980s. This classification has been the base for diagnosis but has only contained criteria’s that are based on pain and stiffness in the joints felt by the patient. However, later research have shown that biomarkers, as explained before, can show the progress of disease and new classification criteria was established in 2010. The new criteria contain one laboratory test on the citrullinated peptide, ACPA.

These criterias will make it possible for physicians to diagnose the disease before the patient have gone to far in the progress of joint destruction. The new criteria becomes crucial due to the studies showing that early RA cannot be diagnosed during the first visit and it is during the first months of symptoms that we have the possibility to make

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34 Rantapää-Dahlqvist, S. Antibodies Against Cyclic Citrullinated Peptide and IgA Rheumatoid Factor Predict the Development of Rheumatoid Arthritis, (2003)
35 Nishimura, K. Meta-analysis: Diagnostic Accuracy of Anti-Cyclic Citrullinated Peptide Antibody and Rheumatoid Factor for Rheumatoid Arthritis, (2007)
remission. Klareskog writes that 2 of 7 of the old criteria are never fulfilled when it is the best time for diagnosis.

**ACR criteria for diagnosis of RA 1987**

At least 4 of the following 7 criteria’s must be met (criteria 1 through 4 must have been present for at least 6 weeks)

- Morning stiffness for at least 1 hour
- At least 3 joint areas simultaneously had soft-tissue swelling of fluid
- At least 1 area swollen in a wrist
- Simultaneously involvement of the same joint areas on both sides of the body
- Subcutaneous nodules observed by a physician
- Demonstration of abnormal amounts of positive serum RF
- Radiographic changes typical of RA on hand and wrist radiographs.

These criteria’s from 1987 are not good enough with the new studies showing the ACCP factor is an early identifier of the disease. The ACR have therefore published new criteria’s and the new ones contain one criteria of a positive anti-CCP test.

**ACR criteria for diagnosis of RA 2010**

Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)

**A. Joint involvement**
- a. 1 large joint 0
- b. 2-10 large joints 1
- c. 1-3 small joints (with or without involvement of large joints) 2
- d. 4-10 small joints (with or without involvement of large joints) 3
- e. >10 joints (at least 1 small) 5

**B. Serology (at least 1 test result is needed for classification)**
- a. Negative RF and negative ACPA 0
- b. Low-positive RF or low-positive ACPA 2
- c. High-positive RF or high-positive ACPA 3

**C. Acute-phase reactants (at least 1 test result is needed for classification)**
- a. Normal CRP and Normal ESR 0
- b. Abnormal CRP or Abnormal ESR 1

**D. Duration of symptoms**
- a. <6 weeks 0
- b. ≥6 weeks 1

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The new criteria makes it easier for both the patients and the physicians to find the cause of the symptoms and the therapy can start earlier. As written in the criteria above, physicians are still measuring the presence of the RF factor and it is, as explained before, a good complement to the other criteria.

Today, the ACPA test is done by one of the two following techniques; CCP2 or CCP3. In 2002, the CCP2 test was launched and according to Purijn it soon became the standard at many clinics. There are at least 6 companies offering the peptides/antigen for the test and TFS IDD is one of them.  

### 4.4 Treatment and Therapy

The treatment of RA has been studied from a health economical perspective many times on the occasion of the cost associated with the expensive medications, Methotrexate and the TNF–blockade. The medications has been proven to be highly beneficial for controlling the disease, lower the activity and also in some cases cause remission, especially in ACPA(+) patients. Von Dongen describes in an article from 2007 that "ACPA(+) patients responded well to Methotrexate treatment while parallel ACPA (-) did not. It was also shown that Methotrexate treatment resulted in a more favourable response in patients with low or intermediate pre-treatment levels."

The positive results, both long term and short term, from medication of RA significantly increases if the diagnosis and the therapy is started in an early stage. It is crucial to periodically have careful follow-ups in order to evaluate the therapeutic results. If the therapy is efficient it can lower the infection and increase the QALY for the patient. The choice of medication is based on the disease activity and how long in progress the patient has become.

The Swedish Research-based Pharmaceutical industry (LIF) published, in 2012, a list with a ranking of the top expensive medications in Sweden (figure 4). Enbrel (TNF-blockade), Humira (TNF-blockade) and Remicade (TNF-blockade) are among the top 4 (marked in yellow below). Together they represented approximately 6.8% of the total pharmaceutical sales during 2011. This image shows the economic impact that these medications has and the importance to medicate “right” to reduce costs for society.

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45 Klareskog, L. Rheumatoid arthritis, Lancet 373, (2009), 659-72
Sales of the largest medications in Sweden 2011

<table>
<thead>
<tr>
<th>Rank 2011</th>
<th>Rank 2010</th>
<th>Medication</th>
<th>MESK 2011</th>
<th>% of part of total 2011</th>
</tr>
</thead>
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<td>1</td>
<td>ENBREL</td>
<td>776,5</td>
<td>2,5</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>HUMIRA</td>
<td>742,3</td>
<td>2,4</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>SYMBICORT</td>
<td>656,3</td>
<td>2,1</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>REMICADE</td>
<td>574,3</td>
<td>1,9</td>
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<tr>
<td>5</td>
<td>6</td>
<td>LIPITOR</td>
<td>379,5</td>
<td>1,2</td>
</tr>
</tbody>
</table>

Figure 4: The first part of the list of the top 50 medications in Sweden in 2011. The 1, 2 and 4th are medications related to RA.

4.4.1 Medications

Disease-modifying anti-rheumatic drugs (DMARDS) is a group of medications that have a defined use in treatment of RA patients, for an example TNF-blockade and Methotrexate. The DMARDS lowers the inflammatory processes. According to the author of the article “Disease Modifying Anti-rheumatic drugs” all patients with RA should receive one or more of the DMARDS as soon as possible after diagnosis because evidence suggest that the long-term outcome is improved when the treatment is started within the first 3 months of disease.\(^5^0\) Today, in clinics the biologics are not used until a failure to treat with other medications. The insertion of biologics is therefore in many cases not done within the first 6-12 months where the chance of remission is the highest.\(^5^1\)

**Methotrexate** is the most common medication for RA and is “generally considered as the DMARD of choice”. Methotrexate is a cytostatic with methotrexate as the active substance. The growth of the cells is inhibited and in RA the immune system is the one that is affected and attenuated.\(^5^2\)

- **Methotrexate Teva, 100 pcs (2,5 mg), 122 SEK.**

  This makes with the recommendation of 3-6 tablets per week an approximately annually cost of **380 SEK/year**. For maximum of 6 tablets and 52 weeks.

**TNF-blockade** (Tumour necrosis factor-blockade) is a biological treatment, meaning that the active substance has biological origin. In a RA patient the level of TNF is high. The TNF is produced by the white blood cells that are a part of the immune system and is participating in an inflammation. The TNF-blockade lowers the effect of the TNF and can therefore also lower the inflammation.\(^5^3\) TNF blockade that are approved and used at

\(^5^0\) Brasington, R. Disease-Modifying Antirheumatic Drugs, (2009)

\(^5^1\) Kobelt, G. Lekander, I. Cost Effectiveness of etanercept treatment in early active rheumatoid arthritis followed by dose adjustment, (2011)

\(^5^2\) http://www.1177.se/Fakta-och-rad/Lakemedel-A-O/Methotrexate-Wyeth/ 2012-07-22

\(^5^3\) Socialstyrelsen, Nationella riktlinjer för rörelseorganens sjukdomar 2010, (2010)
clinics today are Infliximab (Remicade), Etanrecept (Enbrel) and Adalimumab (Humira).\textsuperscript{54}

The TNF-blockade treatment is very expensive. The costs is:

- **Enbrel (TNF-blockade), 4 * 1 injection (50 mg), 10 426 SEK**

This makes with the recommendation of 1 injection per week an approximately annually cost of **135 538 SEK/year**.

The total cost is approximately **135 918 SEK annually** for a patient treated with Methotrexate and TNF-blockade.

Results from research shows that a combined treatment with the two types above is the best way to reach remission and results in patients QALY. Klareskog writes in an article from 2004 that a combination of treatment between TNF and Methotrexate is to recommend and gives better results than the medications alone. The results presented in the article shows that 1/3 of the patients treated with both drugs ended up having a remission in their disease activity within a year compared to 1/8 and 1/6 only using one of the above mentioned drugs.\textsuperscript{55} This hypothesis of Klareskog, L. has also been investigated by Lekander and Kobelt and has shown similar results using the combination treatment.\textsuperscript{56} It also aligns with the guidelines from Socialstyrelsen. This is the reason why, in this report, the calculations have been chosen for both medications as the cost of therapy.

About 22-27\% of all patients (in working age) diagnosed with RA today will receive the expensive combination of treatment.\textsuperscript{57}

In 2011, “Tandvårds- och läkemedelsförmånsverket” (TLV) made an investigation about TNF-treatments and the associated costs. The research shows that there are no differences in effect between the different brands of TNF-blockade and that it is important for clinicians to consider the differences in cost between them when recommending the treatment. Due to the TLV analysis the cost for some of the treatments in January 2012 the price was lowered with approximately 5\%. This will make saving of approximately 80 million SEK annually for the Swedish healthcare system.\textsuperscript{58, 59}

\begin{footnotesize}
\begin{itemize}
  \item 54 http://www.fass.se/LIF/produktfakta/artikel_produkt.jsp?NplID=19880318000088&DocTypeID=7&UserTypeID=2 2012-06-24
  \item 55Klareskog, L. Van der Heijde, D. Therapeutic effect of the combination of etanercept and methotrexate compared with ach treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial, (2004)
  \item 56 Kobelt, G. Lekander, I. Cost Effectiveness of etanercept treatment in early active rheumatoid arthritis followed by dose adjustment, (2011)
  \item 57Neovius, M. Simard, J. How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? (2011)
  \item 58 TLV, TNF-hämmare kvar i högkostnadsskyddet, (2011)
  \item 59 http://www.dagensmedicin.se/nyheter/lagre-pris-pa-tnf-hammare-nasta-ar/ 2012-06-24
\end{itemize}
\end{footnotesize}
4.5 Guidelines for diagnosis and medication

The Swedish health government Socialstyrelsen has developed guidelines for diagnosis and treatment for RA. These guidelines are written as a consequence of the government decision about priorities in the health department and will be guidelines for the clinics in these kinds of questions. The priorities are written with consideration of three ethical principals: “human value principle, need and solidarity principle and cost efficiency principle.”

4.5.1 Guidelines for diagnosis

Socialstyrelsen highlights the importance of early diagnosis for the patients with RA. Early treatment can lower the risks for joint destruction. It is also important to have the chance of judge the prognosis of the outcome of the disease to be able to treat with the right medications.

The recommendations:

- Analysis of antibodies against CCP while suspecting undifferentiated arthritis*.
- Analysis of antibodies against CCP and RF while suspecting polyarthritis (at least 3 swollen joints for a longer time)
- Analysis of antibodies against CCP and RF to predict the outcome of the disease in early RA.

Advantages:

- Undifferentiated arthritis: A positive test of CCP is better than a RF test.
- Polyarthritis (at least 3 swollen joints for a longer time): Analysis of both CCP and RF can predict the outcome better than only an analysis of CCP.
- Early RA: Analysis of both CCP and RF can predict the outcome better than only analysis of CCP

Disadvantages:

- Undifferentiated arthritis: Analysis with both CCP and RF will NOT predict the outcome to RA better than only an analysis of CCP

4.5.2 Guidelines for therapy

The healthcare system (Clinics and Physicians) should in cases of:

Early RA:

- Early start a combination treatment with methotrexate and the biological treatment TNF-blockade for a RA patient with high disease activity.

Insufficient effect from treatment with methotrexate (only):

- Combination treatment with methotrexate and TNF blockade for a patient with

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medium or high disease activity

Insufficient effect from treatment with methotrexate and TNF-blockade:
• Combination treatment with methotrexate and another TNF-blockade than earlier (example: rituximab, abatacept or tocilizumab)

*The definition of Undifferentiated Arthritis is early arthritis that has not yet been classified as a rheumatic disorder.

To summarize the guidelines for treatments, Socialstyrelsen recommends a combination therapy between Methotrexate and TNF-blockade for patients with early RA and an early diagnosis with CCP technique for all patients with pain in their joints.

4.6 Technical report of the product; ISAC

TFS IDD has developed a new method for diagnosis of autoimmune diseases. The new product, ImmunoCAP ISAC for Rheumatoid Arthritis, is a microarray chip and has correlations with ELISA methods. The differences in a wide perspective are the number of antigens the method can detect.

“The multiplexed array for detection of multiple auto antibodies against citrullinated epitopes in candidate RA auto antigens will be of benefit in studies of RA pathogenesis, diagnosis and potentially as a guide to individualised treatment.”

The CCP2 test (method also called ELISA) uses one synthetic peptide antigen as the sources for analysis and ISAC uses up to 100 identified citrullinated peptides. Another difference is the amount of patients the different methods have the ability to diagnose at the same time and the amount of serum that is needed. ISAC can diagnosis more patients and is using a lower amount of serum. The number of patients and the lower amount of serum makes ISAC a cheaper method than ELISA.

The results from the last study done with ISAC shows that ISAC is “as good as” the CCP2 test but has the ability to diagnose 18% more patients than the CCP2 or ELISA method. The results are from an examination of the same patient group using the two different methods. The testing of the products ability to diagnose RA has been done in cooperation with Karolinska Institutet (KI) in Stockholm and Prof Klareskog in Rheumatology. Prof Klareskog has also been part in the discussion for development.

One other feature that differentiates the methods from each other is that ISAC has the ability to sub-differentiate the patient into sub-groups with different variations of the ACPA i.e. the name of the group of anti-citrullinated peptides that has its outcome from different antigens, see figure 3. For feature investigations and development of ISAC this

61 Rönnelid, J. Validation of a chip-based microarray for the detection of autoantibodies against 12 citrullinated peptides, (2012)
63 Klareskog. L. Rationale for multiplex antibody testing in autoimmune diseases, PowerPoint presentation, (2012)
can be important for the understanding of the disease and may help physicians to treat the patient with the right individual treatment from the beginning. It may also show physicians how the disease will develop for the patient.

Today this method is only for researchers and laboratories at hospitals thus it can be used to diagnose a large amount of patients at the same time. For the future it will be crucial for the survival of the method that it also can be marketed as a quick test. Hospital and clinics need a test that they us in-house and without sending the serum to a laboratory. The test shall be easy to use and easily analysed with a computer. This is one of the critical criterias for market acceptance.

Assay principle

Figure 5: Assay principle, Solid phase- antigen- serum IgX- fluorescence anti IgX.64

The picture above (Figure 5) is a picture of the assay principle of the method. The chip contains of a solid phase where the various target antigens are attached. The serum is added and a fluorescence anti-IgX is fixed which enables analysis with fluorescence light. The pieces of serum that are attached to the antigens will be seen in the analysis and as seen in Figure 6 the sample is analysed and a report of the outcome is created.

64 Harwanegg, C. (Matsson, P.) ImmunoCAP ISAC Kick-off meeting, PowerPoint presentation (2010)
4.6.1 Sensitivity and specificity

One important thing around the diagnosis methods is that the results need to have a level that is properly stratified. According to Ger JM Purijn stratification means that sensitivity values have to be calculated at a predefined specificity (mostly 98% or more) using the same cohort of RA patients and disease control sera.\(^6^6\)

The specificity and sensitivity of ISAC is not fully investigated but as far as the research has been made able to prove the sensitivity and sensitivity for ISAC is as good as for ELISA. ISAC can predict RA in 18% more patients compared to ELISA, which is a first prediction that ISAC may have better sensitivity and specificity than the CCP2 methods.\(^6^7\)

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\(^{6^5}\) Harwanegg, C. (Matsson, P.) ImmunoCAP ISAC Kick-off meeting, PowerPoint presentation (2010)


\(^{6^7}\) Klareskog. L. Rationale for multiplex antibody testing in autoimmune diseases, PowerPoint presentation, (2012)
First pilot study (n=90), results on anti-CEP-1

<table>
<thead>
<tr>
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<td>+</td>
<td>38</td>
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Sensitivity 0.97
Specificity 0.87

Linear correlation
\[ r=0.35, r_s = 0.66 \]

Figure 7: First pilot study of the differences between ISAC and ELISA. As seen sensitivity and specificity for ELISA is good and it is proven that ISAC has a slightly better prediction.

4.7 Customers and relationships between important actors in the implementation of the product

In the case of implementation of the new product, it becomes important to understand the different customer relations. In this case, TFS IDD is the manufacture of the product and the research and development efforts behind it, has been conducted by TFS IDD.

The primary customer for the product is the healthcare system, hospitals and especially the physicians and specialists in RA.

The secondary customers will be the individuals diagnosed and the health care provider, often the government but also insurance companies. The individual will have an indirect impact on the costs and saving. The patient will benefit from an earlier diagnosis and gain QALYs.

The biggest saver of the customers will be the state and healthcare system; the budget of the politicians. The new investment will in the long run make lower costs due to sick leave and disability pension.

In this report physicians are the primary customer group. The reason is the market access plan to use this early adaptors the focus in the first implementation phase. See chapter 4.7.2 for more information about early adaptors.

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68 Klareskog, L. PowerPoint presentation, ImmunoCap ISAC, (2011)
TFS IDD is the manufacture and will provide the product seeking to that hopefully get a return of investment (ROI) and improve the life quality of the RA patients

The hospitals and physicians will in the first phase increase their cost due to both diagnosis and medication. In the second phase, the product will be funded by the health care system and long-term the costs for medications will be lowered as patients enter remission.

The state and healthcare system will, as an impact form the increased cost in the health care, long term lower the cost due to sick leave and disability pension. Funding schemes will be implemented for covering the healthcare expenses for the RA patients.

The patient will gain health and QALY and it will be his/her win in the case. In addition, the patient may extend his/her period as employee, which will also contribute both in terms of generating taxes, but also increase the total life income of the patient. These later effects have not been added in the model in this report.

Figure 8: The relationship between the actors in the case, TFS IDD, society, health care system and the individual.

This is the relation in Sweden and the relationships and actors will differ between different countries. In the USA the insurance system will play both the role of “the health care system” and “the physicians” roll in the relation and will direct get the savings that the investment will create. This aspect of the problem is left for future studies.

The above discussion leads to additional questions such as how will intricate systems have an effect on the market implementation of the product? Do the various relations and agents have a impact on the market access strategy? What is key for a hospital to accept a cost that does not directly impact the hospital economics but instead generate savings for a third party i.e. the healthcare system? Understanding of the players, what their interest in the product is and how they are affected is fundamental for the implementation. In the next sections of this report, this will be discussed.
4.7.1 Ansoff-matrix

To understand the customers and their behaviour the Ansoff-matrix (Figure 9) has been used including the theories behind early adaptors of new or current products. The Ansoff-matrix describes the relationship between a product and the market and is a tool for developing a marketing strategy for a product. The model is a tool for looking at growth opportunities for a company and is combining products with markets to make 4 strategies. The matrix although has not the ability to tell when to implement the strategies. The matrix is divided into 4 different strategies; Market penetration, Market development, Product development and Diversification.

![Figure 9: Ansoff matrix](image)

The Market penetration or expansion is a strategy for existing products to grow on an existing market. This can be done by “winning competitors customers” or by making moves to streamline the organisation, distribution, promotion or cut the price. Expansion can also be made by turning non-users to users. The expansion requires some creativity to found the new possibilities and new users for the product.

Market development is the strategy to promote an existing product to new users. The new markets could be another gender, age division or a new geographic location for the new product to be implemented on. A market development strategy is the choice if launching a product at new locations. This will, as described more in the discussion, be the case for ISAC in later steps of the implementation when TFS IDD of ready to go world wide with the product.

The fourth square is the Diversification, which is a strategy for entering a new product and creating a new market. This is the most risky strategy but also the one that can be the most rewarding.

In this report, the product is new and aims to be implemented on a current and already existing market. This is the third quarter of the matrix: the product development strategy. There are three kinds of product development: Product line extension, Product development, and Diversification.

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replacement and Innovation. Product line extension is when a company with new products diversifies and increases its product portfolio giving its customers a greater choice. There could be different variations of the same product that suits different customer groups.

In the strategy for product replacement, old products are replaced with new ones. The new products are often upgrades. Cars are a good example of product replacement. The last strategy Innovation is also replacement but the new product is increasingly better and is often based on a change of technology.

ISAC is a product that replaces an already existing product on an existing market. ISAC is replacing ELISA/CCP2s with a new technology. It is important in the implementation of ISAC to continue to be a manufacture of ELISA, which TFS IDD is. They have a steady and large customer base that can be leveraged upon. This reduces the risk of loosing market shares and allows TFS IDD to switch the market over time to the new product.

A product development process can also be seen as 8 steps: new product strategy, idea generation, screening, concept testing, business analysis, product development, market testing and commercialization. This report is a part of the business analysis in order to identify target markets, market size, and projected product acceptance. This is a phase, which includes price discussions and estimates of the products profitability. A next important step for TFS IDD is market testing and evaluation where the customer’s willingness to buy the product is evaluated. Important in this marketing phase is the evaluation and listening to the customer’s response, thoughts and needs for improving the product and is market packaging. The later includes branding of the product, sales message and generating customer and patient awareness. More about the market and implementation will be described and discussed in chapter 7.1.

4.7.2 The diffusion of innovation process

The picture (figure 10) is a schematic image of the different customer groups and their behaviour, a diffusion of the innovation process. There are 5 types of customers. Innovators, Early adaptors, Early majority, Late majority and Laggards. Before launching of a new product it is vital to decide which group to focus in the first step. Any new technique is complicated and needs innovators and early adaptors that are interested in the new technology to make it spread to the other customer groups. When a new product is accepted and approved by these two first groups the willingness to buy increases in the other groups.

The first customers (markets) for TFS IDD are probably physicians and specialist in RA, at major research hospitals in Sweden. This constitutes a relative small group that is easy to identify. This group of innovators and early adaptors are curious, venturesome and usually willing to provide feedback about the product. Their return is a close relationship with the company providing them knowledge and the possibility to do presentations at international conferences. The early adopters help the company to understand the need of the next groups, early majority and late majority. In terms of sales and profit, it is this group that increases and makes the return of investment (ROI) possible. The early adaptors are instrumental during launching and marketing of the product and spreading information.

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75 Lindström, G. Oral Source (2011)
77 Ibid.
The demands that the early adaptors have for the acceptance the product in the first step is:

- Does the product work? How does it differ from other similar products? Specificity and Sensitivity?
- Will the product change the behaviour in our clinics? What impact will there be in our daily work? Harder, easier?
- How is the patients effected? Will there be a difference for the patient?

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5 Method

5.1 Health economic research
There are 5 traditional types of health economic evaluations i.e. cost-minimization analysis, cost-benefit analysis, cost-effectiveness analysis and cost-utility analysis. The fifth one is cost-illness. The cost-illness method is not yet classified as a real economic tool but it is an important tool since it provides a foundation for the evaluation of costs associated with specific diseases. All of these methods are used for different health economic estimates and in this study two of them are used to make estimates.

5.1.1 Cost of Illness
The cost of illness analysis (COI) is an evaluation of the costs for a specific disorder. The method counts the direct, indirect and the intangible costs due to a specific disease. The method is criticized but is a good guideline for future studies. The reason why it is criticized is because of the lack of completeness. The purpose for this thesis is to provide a guideline and for that purpose the cost-illness method has been used with some adjustments.

There are four questions to consider while putting up a COI study, whose costs are counted? Which are the costs? When are the costs supposed to be counted? How will the costs be presented?

All estimates and simulations in this thesis have been done in Excel.

The first question will explain from whose perspective we are studying the costs. It can be from the individual, the corporation (TFS IDD), the hospital or the perspective of the healthcare system (See also the chapter for relationships, 4.7). In this study the calculations are from the perspective of the health care system since it has the overall view of all the costs due to all involved agents (patient, manufacturer, hospital, government spending etc.).

The answer to the second questions regarding costs take into account the direct and indirect costs. The direct and indirect cost where in the 1960's explained by Dorothy Rice as: “The direct costs are those for which payment are made and indirect costs are those for which resources are lost”. The intangible costs are described as the impact of the quality of life of patients and their families. The intangible costs are not studied in this report, because of the difficulties to quantify the actual cost per patient associated with the disease. Another cost that is not taken into account in this case is the secondary diagnosis that could appear after the first diagnosis or treatment. These cost are not counted for the same reason as above, the difficulties to quantify to real cost and not make an under or over estimation.

79 Olofsson, S. Cost of Illness- teoretisk genomgång, (2008)
80 Ibid.
The direct costs that are included in this study are costs of diagnosis, therapy, hospital admissions and outpatient visits. Not include are trips to and from the hospital and home care etc. The indirect costs that are included are sick leave and disability pension.

The “when” question is explained as the perspective of time. Are the costs in the study the result of a retrospective (when they have arrived) or a prospective (before the will arrive) view? In this case both perspectives are discussed but based on two different methods. The retrospective view is done by the COI and the prospective is done with the cost of minimization analysis method. The costs will be estimated from statistics and studies done in the last decade in Sweden.

The last question to discuss concerns the impact on how the costs are presented for the reliability of the results. For a study to be countable, an analysis of the sensitivity is needed. The analysis below is a systematic examination of the different variables having an impact on the results.82 This study is a guideline for early marketing and entrance of a new product for TFS IDD and to help them to make a decision about the progress of the method. The limited scope of this thesis only allows a short discussion and variable sensitivity analysis. The discussion is included in the discussion section and no estimates are presented.

5.1.2 Cost of Minimization

The costs in the report are first counted by a Cost of Illness analysis to get an overall picture of the economic advantages and disadvantages of the case. To complement the analysis estimation of the future costs are made using a cost of minimization method. This allows a comparison between “today” and “tomorrow”.

In a cost of minimization analysis the cost from different alternatives with the same effect is counted. Socialstyrelsen writes that “costs are measured from all alternatives and that the outcome with the lowest cost is the one that is recommended”.83 In this case the costs taken into account is the direct and indirect cost associated with the disease and the argument for which ones that are involved are the same as for the cost of illness analysis.

While making a cost of minimization analysis it is crucial that clinical equivalence is achieved and proven by clinical evidence. While comparing different treatments the measured outcomes need to be equivalent using this technique.84 In this study the outcome of the diagnosis is known to be equivalent and the comparison can therefore be done.

Many different mathematical estimates can be done in the cost of minimization analysis. The method is discussed and included based on its merits as a theory. However, it is recommend that a thorough cost of minimizations analysis is conducted.

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82 Olofsson, S. Cost of Illness- teoretisk genomgång, Karlstad universitet, (2008)
84 Haycox. A. What is cost minimization analysis? (2009)
5.2 Literature study
Scientific papers and available articles of health economic studies are the base for the calculations and the data used. The results and in the articles have been critical reviewed for the reliability of the results in this report. The articles are taken from well-known and reliable publications. The literature is also used to give the author an overall picture about the background and the research behind the disease.

5.3 SWOT-Analysis
A SWOT-analysis is a general and widely accepted international economic tool used to help out putting up a strategy for a company, a new product etc. The SWOT is a short form of the 4 different parts of the analysis; Strengths, Weaknesses, Opportunities and Threats.\(^{85}\) The factors can be grouped into internal and external, while you can see strengths and weaknesses as internal and opportunities and threats as the external factors. A SWOT-analysis is simple but it is important to use the tool right.\(^{86}\) The strengths and weaknesses should be viewed from the customer perspective and not the company perspective. Once the SWOT-analysis is done you can develop a strategy and ideas around how to turn weaknesses into strengths.\(^{87}\) The SWOT- analysis for this case is presented in chapter 6.3.

This report uses SWOT analysis instead of Porters Five Forces analysis. The Porter analysis focuses more on the competitive environment than the analysis. The four aspects of SWOT will in this case provide a better overall picture for market approval, product introduction and early phase marketing than Porter Five Forces. For future studies a Porter analysis should be done.

5.4 Interviews
The following scientists and experts have been interviewed in order to increase the background for the report but has not been documented and minutes of meetings are not attached to the report. However, some of the persons have been quoted in the report.

Per Matsson, Chief Technology Officer, Thermo Fisher Scientific ImmunoDiagnostics

Lisse-Lotte Hermansson, Director Health Economics for Global Marketing, Thermo Fisher Scientific ImmunoDiagnostics

Lars Klareskog, Professor in Rheumatology, Karolinska Institutet

Martin Neovius, Associate Professor, Department of health, Karolinska Institutet

\(^{86}\) Ferrel, O C. Hartline, M. Marketing strategy, (2011)
\(^{87}\) Jobber, D. Principles and Practice of Marketing, (2007)
5.5 Validity and Reliability

The validity and reliability notions are used to describe how well an investigation or a collection of data are relevant for the study at hand. Validity is an index of the relevance of the measurement and reliability is a measure of the trustworthiness of the method. Any investigation should always have high reliability and high validity.

Reliability can also be viewed as a measure of dependability. High reliability is not a warranty for the investigation’s validity. But high validity requires high reliability. This means that results need to be consistent with other researchers’ results and with other methods used. Sensitivity and specificity are important key words that are supposed to be measured. 88 Validity and reliability will be discussed in chapter 7.3.

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6 Results

6.1 Cost of Illness and Minimization estimates

The results from the calculations can be seen below in chapter 6.1.7. The calculations are made in Excel and in the following there will be an explanation of the attributes and the number that the calculations are based on. The costs are based on the number of new RA patients in Sweden within the target group, and will give a value for what the new diagnostic method is “worth” for the market to make cost savings. The case is based on an analysis period of 4 years. This is because of the political mandate period and budget period for decision makers. It is a normal timeframe to use and to see the health economic impact from a budget change and makes a reliable argument for implementation. No estimations are done for the cost before the diagnosis or after the 4 years. Extending the timeframe will change the economic impact substantially for all agents involved. Four years timeframe is short in comparison with lifelong treatment, disability retirement and more based on a disease emanating early (40+ years) in life.

From the result we can see that the mean cost for one patient “today” at the year for diagnosis is: 170 594 SEK. In the hypothetical case, “tomorrow” the cost is 135 980 SEK.

Conclusion

This makes the cost saving calculated during year 4 and with patient base of 3600 patients 154 million SEK or more, a annually saving of 23% per patient. From the selected group of patients around 900 new patients will be added annually. More about the results of the costs is presented in 6.1.7.

6.1.1 Incidence and Prevalence

Prevalence

According to Neovius the prevalence for RA is in general 0.77% for men and 1.11% for women. In 2008 the total number of patients where 58 102 ≥ 16 years and of them 73% are women.89

Statistics Sweden (Statistiska centralbyrån) provides populations statistics in Sweden for different age divisions. There are 1 888 743 women between 35-64 years of age.90 This gives us the estimate for prevalence RA patients (women) to be 20 965 in our target group.

The average cost for a prevalent patient, year 4, is in the first case 186 273 SEK. This makes the total estimated cost approximately 3,9 billion SEK for the prevalent patients in

90 www.ssd.seb.se/databaser/makro/start.asp, 2012-05-20
the target group of 20 965 women. In the second case with ISAC the cost is 143 428 SEK, which makes a total cost for of approximately 3 billion SEK.

The calculation of the number of prevalent patients is not used in the other calculations but for the understanding of the cost associated with RA they are presented in this chapter.

The number of prevalent patients is increasing every year with the number of new patients (incidence, see below). If the prevalence of patients from 2008 is still the same percentage, the number of patient today would be 60 025, which makes a total cost for all RA patients of above 11 billion SEK annually.

**Incidence**

From the incidence figure in chapter 4.3 the following incidence quotes are selected for women:

- Year 35-44 36/100 000 inhabitants
- Year 45-54 53/100 000 inhabitants
- Year 55-64 59/100 000 inhabitants

Thus the mean incidence is about 49/100 000 for women in the age division.

From Statistics Sweden the numbers of women inhabitants in every age division is counted and the incidence number for each division is counted.\(^9\)

**Incidence calculation:**

\[
\text{Number of patients} = \frac{\text{Incidence}}{100 000} \times \text{Numbers of inhabitants}
\]

- Year 35-44 625 955 persons => 225 persons
- Year 45-54 614 383 persons => 325 persons
- Year 55-64 585 686 persons => 345 persons

The total incidence of patients is 896 persons annually. Thus the estimate used in the following calculations is 900 new patients every year. Note, this is not the same as the total number of new patients annually.

\(^9\) www.ssd.seb.se/databaser/makro/start.asp, 2012-05-20
6.1.2 Diagnosis
Diagnosis today is done, as described before, with the ACR 2010 guidelines and the CCP2 test. The hypothesis contains the idea that ISAC could replace the CCP2 test and the cost associated with diagnosis is therefore just counted on the cost for the test.

- CCP2 test
  - approximate cost per test 100 SEK per test 92

- ISAC test
  - approximate cost per test 300 €
    2636 SEK per test 93

Calculated using exchange rate 8.80SEK/Euro

The cost for ISAC is an estimated hypothetical cost and not yet decided by TFS IDD. It is assumed that every patient is tested with one of the two available methods one time.

6.1.3 Out patient visits
The average cost for one out patient visit was 4053 SEK at region hospital in Sweden during 201094 and according to a study by Eriksson, J. 81% of the prevalent patients has one or more visit annually to a RA specialist physician.95 In the following calculations it is assumed that all incidence patients during the year of diagnosis have one RA specialist visit. It is probable that this assumption is low and that most patients visit a RA specialist more than once during the first year. This is further discussed below.

According to the “TIRA” report from 2007, an average patient during the first year of diagnosis has three out patient visits. These visits include visit to a physician, nurse and physiotherapists. The second year the patient has two visits and the third year only one visit. Due to the uncertainness of what kind of visit this is the focus in this study is only on the specialist visits and we are leaving the cost estimation for the others for further investigation. Most of the visits above are likely related to the therapy and treatment and is not directly related to the diagnosis.96 In the calculations this can create an error and lead to uncertainness. However, the effect of omitting this discussion is an underestimation of the results presented not an overestimation. If the hypothesis of ISAC making the diagnosis earlier and with better specificity will become reality this will lead to substantial cost saving since the number of visits needed can be lowered and hopefully even with good medication prevent the visits related to physiotherapy.

92 Matsson, P. Oral source, (2011)
93 Matsson, P. Oral source, (2011)
95 Eriksson, J. Burden of Hospital Admissions in Prevalent Patients with RA in Sweden in relation ro RA Diagnosis, (2011)
96 Hallert, E. Schmidt, A. Sjukdomsförlopp, kostander och livskvalité vid nydebuterad Reumatoid artrit (TIRA), (2007)
The percentage of outpatient visits has been increasing over the last decade but at the same time the percentage of hospital admissions has decreased. This is a positive sign and can be an effect of the earlier diagnosis and insertion of therapy we have seen in the same period.

6.1.4 Hospitals admission
Cost of hospital admission where during 2012 approximately 53,840 SEK per treatment time. In general for RA patients one hospital admission is 6.6 days. In 2007, 27% of all prevalent patients with RA had at least one hospital admission. The year before diagnosis the hospitals admissions increased from 10% to 21% and rebounded to around 15% from two to four years after diagnosis. These numbers are used to estimate the cost associated with hospital admission.

6.1.5 Sick leave and disability pension
Martin Neovius et al. at Karolinska Institutet in Stockholm have investigated the mean days of disability pension and sick leave in Sweden related to the RA disease in 2011. Their results indicates that the numbers of days of sick leave and disability pension increases one year prior diagnosis, peaks one month after diagnosis and then is stabilised the next coming years. The same pattern is seen for the initiation of treatment, the days are peaking one year after initiation.

“The percentage of patients with RA with no sick leave episodes >14 days or any disability pension decreased from 74% 2 years before to 36% 1 year before and 30% 1 year after the RA diagnosis, but thereafter increased again”

The results above shows the pattern of sick leave days and disability pension and also shows how important right diagnosis and treatment are for the ability to work.

Sick leave: Days off from work caused by illness. Sick days <14 days is paid by the employer and sick days >14 is reported to Social Insurance Office.

Disability pension: Time limited or permanent reduction of working hours in relation to disease. The reduction is at least 25%.

97 Ibid.
99 Eriksson, J. Burden of Hospital Admissions in Prevalent Patients with RA in Sweden in relation to RA Diagnosis, (2011)
100 Neovius, M. Simard, J. How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? (2011)
102 Neovius, M. Simard, J. How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? (2011)
Figure 11; Sick leave and disability pension in relation to diagnosis, where the green curve is the hypothesis. Diagnosis at 1-year prior of today makes the peak yield a lower number of days.

The image above shows the mean number of sick leave and disability pension days in relation to diagnosis. The hypothesis is what would happen if the diagnosis were made earlier. A 1-year earlier prediction has been used for the current report compared to today later diagnosis. Many researchers showed results that diagnosis is possible even earlier but as discussed shortly above: What impact will too early diagnosis have on the patients QALY? One year prior today’s diagnosis symptoms have appeared and the patient have started to have sick leave days associated with the disease. The green line has the same pattern as the blue one but with earlier therapy the days of sick leave can be lowered.

Diagnosis one year earlier gives a pattern as seen with the diagnosis at 77 days and the peak on 112 days. The days are then lowered and stabilised to a level higher than the general population but lower than the RA where diagnosis where done later. (This is just a schematic picture of what the reality could be but is only a hypothesis)

In the calculations of costs the numbers of days in the picture is used. For the case of “Today”: 112, 147, 124, 118, and the case of “Tomorrow”: 77, 112, 94, 89 days.

103 Neovius, M. Simard, J. How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? (2011)
The average patient annually cost for RA patients associated with the disease was during 2007 92 000 SEK. The total cost associated with sick leave and disability pension was 168 000 SEK/patient annually but compared to the cost for the general population the cost of 92 000 SEK above is the cost attributable only to RA. Thus, 92 000 SEK is associated with the additional cost due to the RA disease and has been used in the following estimates.

The average total number of days on sick leave and disability pension annually for RA patients is 158 days for both men and women. For the general population the value is 71 days. The difference (days attributable to the RA disease) is 87 days. This makes a total cost attributable to RA of 1057 SEK/day on sick leave and disability pension. The cost attributable to RA is measured for both women and men and the mean number of days for both sexes has been used in the below calculations.

6.1.6 Treatment and Therapy

The total cost for a patient treated with TNF-blockade and DMARD is 135 918 SEK annually. See chapter of Medication for the specification of costs.

According to researchers a combination treatment with both TNF-blockade and Methotrexate is recommended. Van Dongen have investigated the impact of Methotrexate in early treatment for RA patients and his results showed that Methotrexate treatment have the ability to postpone the diagnosis of RA and retarding joint destruction.\textsuperscript{105}

\textit{“For a number of autoimmune diseases, such as Diabetes Mellitus, it has been suggested that a critical period exists during which intervention may reverse the disease process. For RA such a window of opportunity may also exist.”}\textsuperscript{106}

The results of the Van Dongen investigation showed that 17\% of the ACPA(+) patients received sustained remission after 30 months. 83\% of the patients with methotrexate treatment eventually developed RA but the treatment postponed the disease development. For comparison and estimation purposes this study focus methotrexate treatment and does not investigate the impact of TNF-blockade. Klareskog on the other hand have made a calculation of the number receiving remission with a combination of treatments and 33\% of the patients received remission after one year.

This report uses 33\% remission during the calculating of the cost of the combination treatment. It is important to know both investigations impact on the result, early treatment or a combination of treatment. A combination of both investigations in future new research study will likely revile new data and possibly improve the numbers for remission in RA patients.

\textsuperscript{104} Ibid
\textsuperscript{105} Van Dongen, H. Van Aken, J. Efficacy of Methotrexate Treatment in Patients With Probable Rheumatoid Arthritis, (2007)
\textsuperscript{106} Ibid.
Today 22-27% of all patients, in working age, receive a combination of TNF-blockade and MTX.\textsuperscript{107} For the below estimates 27% have been used in the calculations.

Attributes for the calculation:

- Year 1 or the year of diagnosis:
  27% of the patients will receive a combination of treatment, other than NSAID (non-steroidal anti-inflammatory drugs)
- After 12 months:
  The medication will be taken out for the 33% of the patients receiving remission. That means 33% of the cost attributable to the 27% of the patients will be the saving. In the calculation the cost of NSAIDs are not taken into account.

\textsuperscript{107} Neovius, M. Simard, J. How large are the productivity losses in contemporary patients with RA, and how soon in relation to diagnosis do they develop? (2011)
6.1.7 Estimates

Today

The estimates below are based on the numbers presented above and in the former discussion.

<table>
<thead>
<tr>
<th>&quot;Today&quot;</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (Total)</td>
<td>900</td>
<td>1 800</td>
<td>2 700</td>
<td>3 600</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>900</td>
<td>1 800</td>
<td>2 700</td>
</tr>
<tr>
<td>Incidence</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td>900</td>
</tr>
<tr>
<td>Diagnosis (CCP2 test)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>90 000</td>
<td>90 000</td>
<td>90 000</td>
<td>90 000</td>
</tr>
<tr>
<td>Prevalence</td>
<td>-</td>
<td>900</td>
<td>900</td>
<td>900</td>
</tr>
<tr>
<td>Incidence</td>
<td>90 000</td>
<td>90 000</td>
<td>90 000</td>
<td>90 000</td>
</tr>
<tr>
<td>Out Patient</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3 647 700</td>
<td>6 602 337</td>
<td>9 556 974</td>
<td>12 511 611</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>2 954 637</td>
<td>5 909 274</td>
<td>8 863 911</td>
</tr>
<tr>
<td>Incidence</td>
<td>3 647 700</td>
<td>3 647 700</td>
<td>3 647 700</td>
<td>3 647 700</td>
</tr>
<tr>
<td>Hospital admission</td>
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<td></td>
</tr>
<tr>
<td>Total</td>
<td>10 175 760</td>
<td>23 258 880</td>
<td>36 342 000</td>
<td>49 425 120</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>13 083 120</td>
<td>26 166 240</td>
<td>39 249 360</td>
</tr>
<tr>
<td>Incidence</td>
<td>10 175 760</td>
<td>10 175 760</td>
<td>10 175 760</td>
<td>10 175 760</td>
</tr>
<tr>
<td>Sick leave/Disability pension</td>
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<tr>
<td>Total</td>
<td>106 593 103</td>
<td>246 496 552</td>
<td>364 510 345</td>
<td>476 813 793</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>139 903 448</td>
<td>257 917 241</td>
<td>370 220 690</td>
</tr>
<tr>
<td>Incidence</td>
<td>106 593 103</td>
<td>106 593 103</td>
<td>106 593 103</td>
<td>106 593 103</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>33 028 074</td>
<td>66 056 148</td>
<td>99 084 222</td>
<td>132 112 296</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>33 028 074</td>
<td>66 056 148</td>
<td>99 084 222</td>
</tr>
<tr>
<td>Incidence</td>
<td>33 028 074</td>
<td>33 028 074</td>
<td>33 028 074</td>
<td>33 028 074</td>
</tr>
</tbody>
</table>

Per patient (mean):

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>170 594</td>
<td>year 1</td>
</tr>
<tr>
<td>186 376</td>
<td>year 4</td>
</tr>
</tbody>
</table>

Figure 12: Cost associated with RA today with the CCP2 technique for diagnosis
Tomorrow

The estimates below are based on the numbers presented above and in the former discussion.

<table>
<thead>
<tr>
<th>&quot;Tomorrow&quot;</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients (total)</td>
<td>900</td>
<td>1 800</td>
<td>2 700</td>
<td>3 600</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>900</td>
<td>1 800</td>
<td>2 700</td>
</tr>
<tr>
<td>Incidence</td>
<td>900</td>
<td>900</td>
<td>900</td>
<td>900</td>
</tr>
<tr>
<td><strong>Diagnosis (ISAC)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2 372 400</td>
<td>2 372 400</td>
<td>2 372 400</td>
<td>2 372 400</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Incidence</td>
<td>2 372 400</td>
<td>2 372 400</td>
<td>2 372 400</td>
<td>2 372 400</td>
</tr>
<tr>
<td><strong>Out Patient</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3 647 700</td>
<td>6 602 337</td>
<td>9 556 974</td>
<td>12 511 611</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>2 954 637</td>
<td>5 909 274</td>
<td>8 863 911</td>
</tr>
<tr>
<td>Incidence</td>
<td>3 647 700</td>
<td>3 647 700</td>
<td>3 647 700</td>
<td>3 647 700</td>
</tr>
<tr>
<td><strong>Hospital admission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>10 175 760</td>
<td>23 258 880</td>
<td>36 342 000</td>
<td>49 425 120</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>13 083 120</td>
<td>26 166 240</td>
<td>39 249 360</td>
</tr>
<tr>
<td>Incidence</td>
<td>10 175 760</td>
<td>10 175 760</td>
<td>10 175 760</td>
<td>10 175 760</td>
</tr>
<tr>
<td><strong>Sick leave/Disability pension</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>73 250 100</td>
<td>179 795 700</td>
<td>269 217 900</td>
<td>353 883 600</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>106 545 600</td>
<td>195 967 800</td>
<td>280 633 500</td>
</tr>
<tr>
<td>Incidence</td>
<td>73 250 100</td>
<td>73 250 100</td>
<td>73 250 100</td>
<td>73 250 100</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>32 935 734</td>
<td>54 673 318</td>
<td>76 410 903</td>
<td>98 148 487</td>
</tr>
<tr>
<td>Prevalence</td>
<td>0</td>
<td>21 737 584</td>
<td>43 475 169</td>
<td>65 212 753</td>
</tr>
<tr>
<td>Incidence</td>
<td>32 935 734</td>
<td>32 935 734</td>
<td>32 935 734</td>
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</tr>
</tbody>
</table>

**Per patient (mean):**

<table>
<thead>
<tr>
<th>Year 1</th>
<th>Year 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>135 980</td>
<td>143 428</td>
</tr>
</tbody>
</table>

Figure 13: Cost associated with RA tomorrow with the ISAC technique for diagnosis.

Conclusion

The total cost saving for the implementation of ISAC with the estimation for 3600 patients (year 4) is 154 611 602 SEK or approx. 154 million SEK.

Thus, ISAC provides savings of 42 845 SEK or 23% for each patient.

**Year 1:** The average saving between the cases is 34 614 SEK per patient.
Year 4: The average saving between the cases is 42,845 SEK per patient.

The differences in cost saving between year 1 and 4 are due to the remission which constitute treatment saving and less days of sick leave. This also shows that that biggest savings is seen in long term.

6.2 SWOT-analysis
The SWOT analysis is made with the perspective of TFS IDD and the new product ISAC.

Product Strengths

- The new product ISAC will help physicians make more specific diagnosis of RA. ISAC will make the diagnosis easier and reduce the time for the result to be analysed.
- ISAC is based on a technique for identifying auto-antibodies. The guidelines from ACR and Socialstyrelsen recommend physicians to take tests like ISAC into account when diagnosing a patient.
- TFS IDD has a 40% market share in Germany on CCP2 tests and has the knowledge of diagnostic tools.
- ISAC can diagnose 18% more patients than the CCP2 test.
- The product is developed in cooperation with KI and Prof Klareskog in Rheumatology. This creates an opportunity for pre-marketing to early adopters
- Long term cost savings are possible for both hospitals and the healthcare system, which will impact the use of medications, reduce hospital admissions and delay disability pensions.

Weaknesses

- ISAC is more expensive than other CCP2 tests on the market today. This will require marketing efforts to provide proof of principle and results to convince the physician and healthcare providers to invest in ISAC testing programs
- 67% of all patients have the ACPA disease and can be diagnosed with this method earlier today. It is not yet proven if it is possible to diagnose the remaining 33% of the patients. The disease of these patients is not fully investigated to make any conclusions about the up come and development.

Opportunities

- Increasing number of patients can be diagnosed at an early stage of the disease and according to the new research early diagnosis is crucial for successful longterm therapeutic results and added quality of life for the patient.
- Future developments and research can provide ISAC with a tool for make a suggestion of what medication will be in most effect in the patient depending on witch sub type of RA the patient suffer from.
Threats

- Competition developing similar ELISA tests
- Development of new biotechnological assays based on unknown technologies
- Political contradictions towards the increased costs in connection to the diagnosis.
- Price erosion and cheaper method
- New criteria and political intervention for diagnosis from Socialstyrelsen and the government healthcare politicians.
7 Discussion

The aim of this report is to provide TFS IDD insights of the market for a new products implementation. In the above a platform has been presented regarding the patient prevalence and incidence and associated cost for diagnosis and treatment. The above discussion has proved that there are longterm benefits for the affected patient, for the healthcare provider (hospital) and the healthcare system in general. The estimates have clearly shown that there is a market potential for ISAC that can create a healthy revenues and profitability for TFS IDD. However, this requires a market access strategy that will be discussed in the following section of the report.

Socialstyrelsen writes in their guidelines that a patient with an undifferentiated arthritis is supposed to be tested for RA with a CCP technique. Within this context the guidelines suggest that if a patient have stiffness or pain in joints a test should be done. This makes the market for the TFS IDD product ISAC larger than present and also makes the market introduction easier as the guideline demands a test for ACPA antibodies in arthritis patients.

In Germany, with ten times more inhabitants than in Sweden, approximately 420 000 CCP tests provided by TFS IDD are made every year. Making an estimation with the same proportions in Sweden gives approximately 100 000 tests in Sweden annually. Thus, TFS IDD has the possibility to change the diagnostic toolbox of the physician with a new and more specific method. This should make it possible to sell more tests than estimated in this report.

There are 81 million inhabitants in Germany and 9 millions in Sweden. 420 000 EliA tests in Germany annually which is 40 % of all tests done with CCP technology in Germany. The total number of tests are 1 050 000. The percentages of the Germans tested are 1,15%. I assume the same relation in Sweden witch makes a number of approximately 103 500 tests in Sweden annually.108

Research from KI and TFS IDD has shown that ISAC today is “as good as” the current CCP test. ISAC have also the ability to identify 18% more patients than CCP2 test and have the ability to sub-differentiate the patients. As described in chapter 4.6, this differentiation can in the future become the key of finding an individual treatment for all kind of RA patients.

In this study the focus is on a small target group with women between 35-65 years of age and the ones with the genetically ACPA(+) disease. This leaves a large group of patients that is not accounted for. 67% of all RA patients that have the ACPA disease and can be diagnosed with ISAC but yet it is not secured how the remaining patients without ACPA molecules are diagnosed. The molecular cause of the disease for these patients is unknown and thus cannot yet be diagnosed.

108 Meister, S. E-mail conversation, (2012)
Earlier in the report three questions was presented as to be essential for the sales process and acceptance by the early adaptors. Here are the answers to these questions based on a perspective of a successful launch and market success.

*Does the product work? How does it differ from other similar products? Specificity and Sensitivity?*

As seen in the latest research report, the product can find 18% more patients than the methods used today and have the ability to sub-differentiate. More research is needed to secure if ISAC can be used on the 33% of patients where there still exist an uncertainty regarding the diagnosis. A new, innovative method shall have the focus on saving money for the healthcare provider and this requires that ISAC can be used by clinics without sending serum to a laboratory. The difference in specificity and sensitivity between the methods is important to know before a start of implementation.

*Will the product change the behaviour in our clinics? What impacts will there be in our daily work?*

The ISAC method will make tests easier to do as less serum is needed and the time to get test result will be reduced. The result is time- and cost savings for the healthcare provider. The serum is the same as for the existing methods, which makes no big difference between ISAC and the CCP2/CCP3 platform taking the test. If the test can be used without laboratory a nurse or physician at the clinic can make the test, which shorter the time for test result and lower the time for administration. The patient might just need one visit for diagnosis, which also creates cost savings.

*How is the patients effected? Will there be a difference for the patients?*

The difference for the patient will be earlier diagnosis. The “not knowing” period will be shorter and the time for adaption is increasing. This will result in patients staying healthy longer and being able to work longer.

**The cost and cost savings**

The results from the cost estimations show that ISAC will be a cost saver product. The saving for an average patient (year 4, 3600 patients) is approx. 45 000 SEK annually. This will generate total savings of more than 154 million SEK annually during the 4th year after introduction of ISAC.

The prevalence of RA in Sweden is approximately 0,77% in 2008 according to Neovius.\(^{109}\) This makes a total number of patients in Sweden today of 60 025 (7 795 572 >16 years inhabitants). Assume implementation of ISAC today and let us look at the numbers in a long term. The saving for 60 000 patients is 2,5 billion SEK and a lot of QALY gained for the patients with the earlier diagnosis.

---

The important attributes for the implementation will be the features of the product, how ISAC can make the diagnosis and treatment easier for physicians and nurses at clinics.

The timeline for the patient (Figure 1) show a schematic picture of what the joint research community believes is possible with earlier diagnosis and the possibility to turn the disease to remission. Remission is not the same as saying that the patient will be fully recovered but that that the patient for a longer time can live without suffering from major joint destructions and can continue working. This is an important knowledge and an incentive for investment. The importance will be to see the winnings in soft values, QALY and happiness.

7.1 Market access strategy
To be efficacious in the launching of ISAC the key for success is to start the market introduction with the early adaptors. TFS IDD should use its knowledge to develop the product so that it integrates with the infrastructure and routines of the RA specialist clinics. What features will make the product worth using for them. Is there something that can be “sold” together with ISAC that makes the diagnosis even easier? Packaging solutions?

The TFS IDD should also use early adaptors for spreading the word to other colleagues at clinics and conferences. The best implementation and the most successful the product will be if it matures with the market. The early adaptors can also be a part of the market testing, the penultimate step in the product development process that have been discussed in chapter 4.2.1. The first customers should be the RA specialists at the largest university hospitals in Sweden. The implementation can bee seen as a pyramid, where a successful strategy starts from the top, to a small specific target group. Then larger and larger target group will be reached until it the market is covered.

The strategy is to implement the product as a tool for clinics and the physician or specialist. The positive change in working conditions will be for the physicians and the wins of the product will first be seen here. The laboratories will not gain the same benefit and will not be affected as much by the new technique.

After a successful implementation in Sweden it is time to launch ISAC internationally and look at other potential markets. The situation with health care systems, public sector and insurance companies are different in all countries and it is therefore important to get to know the market before an implementation. Several countries, such as the other Scandinavian countries and several countries in Europe have a similar healthcare system as Sweden and should be prioritized.

Market access requires extensive collaboration between industry, academia and the healthcare system in cooperation with the patient community to get successful. New pharmaceutical products need support from government organizations, in this case Socialstyrelsen who makes the diagnosis guidelines and academia, researchers and specialist on RA. Cooperation with academia and TFS IDD already exists and
transpiration exists between the actors. This cooperation will support the implementation and increase the credibility of the method.

The RA guidelines form Socialstyrelsen from 2010 will most likely remain the same for many years to come. This guideline will not change over night and TFS IDD can be sure that the development effort and investment in ISAC will not be wasted in short term. The guidelines are not affected by any other external factors or companies. The only uncertainty that can be for seen with the guidelines is how well the healthcare system and physicians adhere to them.

7.2 The advantages and disadvantages of the method

The estimates are based on the two methods; cost of illness and cost of minimization. The estimates are not mathematical advanced but rather straight forward. In the first question presented above the calculations is seen from the state perspective of the even though it is suggested that the physicians is the primary target group for initial marketing and sales. The Swedish state/healthcare system will make the largest cost savings but also have the ability to fund the development of this kind of technology. The physicians are the first target group but the state and the various healthcare institutions will be the important actors later on.

Which costs are chosen is discussed earlier, the direct and indirect costs. When a real cost of minimization is produced I suggest that the intangible are included to make the results more secure.

The selected time perspective is 4 years where ISAC is implemented the first year. It is assumed that all patients are diagnosed with CCP2 method or ISAC and that all of them are correctly diagnosed. That is why I am making the estimations with the incidence number of patients and not the number of patients that every year is investigated for possible RA. The 4-years period is chosen due to the political mandate period and that budgets often are made for that time period. This makes it easy to see the impact.

The perspective of the calculations is done from both a retrospective and a prospective view using the two different methods. This makes a comparison possible between costs for the different diagnostic methods. When conducting a cost of minimization analysis it is important that the two alternative methods are equivalent. In this case this has been secured.

A complete sensitivity analysis has not been done. The costs are evaluated and discussed below in the next section.

7.3 Reliability of results

The calculations in this work are based on research results and numbers shown in different articles about RA. The data used in the calculations are given in the articles and are probably based on assumptions and thus there is a margin of error in the simulations.
The articles have been carefully selected and sources checked as far as possible. The different research studies are from different years during the last decade. Save for economic changes and budgets, the estimates are as accurate as is possible and the latest available data and statistics have been used.

Even though care has been taken to secure the accuracy of the data and the results, some inconsistencies may exist. The data used is based on the entire population, including both men and women from the age of 16. Thus the percentage of women suffering from RA is approximately 70% of the total number of patients. An assumption that relations are not dependent of the gender or age of the patient related to the RA diagnosis is made. The relation between the two calculations “today” and “tomorrow” are the same and if data for the specific target group the proportions will be the same.

A possibility exists to increase the accuracy of the health economic data from the STURE register, which has not been accessible for the work.

### 7.4 Future studies

“The main advantage of ACPA lies in their proven ability to predict the development of RA and their potential use as a criterion for RA even at baseline”

It is proven that ISAC can sub-differentiate the ACPA-patients. This result will be essential for the success of the product. The differences between the CCP2 tests and ISAC are limited. To incentivize the physician to switch from CCP2 to ISAC it is important to use sales arguments such as sub-differentiation as it creates added-value for the patient. If the product is able to predict the aggressiveness and development of the disease and provide guidance for the therapy and medical treatment scheme it will be a best seller.

For the future it is recommended that TFS IDD make a more specific health economic study and market strategy. This report does not include in-depth customers interviews or a competitive market analysis. In chapter 4.6.1 there was a discussion about sensitivity and specificity of ISAC.

When the research around ISAC is completed TFS IDD need to conduct a comparison between the sensitivity and specificity in ACR guidelines with CCP2 and ACR guidelines with ISAC. Key issues are: What is the rate between the number of false positive and false negative and the number of patients correctly diagnosed?

The outcome will be important for the market acceptance and a fast rollout of the product.

---

8 Conclusion

"Despite earlier and more aggressive use of a growing number of antirheumatic therapeutic options, the rapid and often irreversible work loss around diagnosis remains as does a large unmet need for patients with established RA... The unmet need is already present at the time of diagnosis... This indicates also that effective treatment has potential to prevent major economic losses for society." 111

There is a need for patients to be diagnosed earlier and use available methods for preventive medication. This can be done using ISAC and still save costs for the state creating an incentive for the physicians and society to make the investment.

New diagnostic methods are compared with existing ones. Around existing methods, the hospitals, laboratories and physicians have built an extensive knowledgebase and infrastructure. A new technology has to compete with this infrastructure and replace existing products. The healthcare system requires substantial incentives in order to do this transaction. A new test has to be as simple as possible to use and ISAC needs to be quick test that can be used by smaller, non-specialist clinics to gain wide acceptance and to reach a larger market. Profits will be enormous if all patients seeking medical advice for any type of stiffness in joints. The ISAC must be able to provide a “yes or no” answer without the need of a dedicated laboratory response and specialist involvement.

As seen above there are a lot of costs associated with RA for both the patient and the society and it has been shown that substantial savings are possible, up to 23% for each patient compared to present methods. In addition, there is a great value for each additional year of working life for the patient, this value is extremely difficult to predict.

ISAC has the ability to provide QALY for patients suffering from RA via earlier diagnosis. TFS IDD is not fully done with the development of the product and more research is needed to provide proof that real profits are available for the society and healthcare system. With the guidelines from Socialstyrelsen and the backup from excellent research at KI the platform exists and in combination with the reliability of the product it is possible to establish a new worldwide diagnostic tool.

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Fjärde upplagan


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**Oral information**

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## 10 List of abbreviation

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACPA</td>
<td>Anti-Citrullinated Peptide Antibodies</td>
</tr>
<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>Anti-Cyclic Citrullinated Peptide</td>
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<tr>
<td>COI</td>
<td>Cost of Illness Analysis</td>
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<tr>
<td>DMARD</td>
<td>Disease Modifying Anti-Rheumatic Drugs</td>
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<tr>
<td>ELISA</td>
<td>Enzyme-Linked Immunosorbent Assay</td>
</tr>
<tr>
<td>ISAC</td>
<td>Immunocap ISAC</td>
</tr>
<tr>
<td>LIF</td>
<td>“De Forskande Läkemedelsföretagen”</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality-Adjusted Life Years</td>
</tr>
<tr>
<td>RA</td>
<td>Rheumatoid Arthritis</td>
</tr>
<tr>
<td>RF</td>
<td>Rheumatoid Factor</td>
</tr>
<tr>
<td>ROI</td>
<td>Return of investment</td>
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<tr>
<td>TLV</td>
<td>Tandvårds och Läkemedelsförmånsverket</td>
</tr>
<tr>
<td>TNF-Blockade</td>
<td>Tumor Necrosis Factor-Blockade</td>
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<tr>
<td>TSF IDD</td>
<td>Thermo Fisher Scientific ImmunoDiagnostic Division</td>
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