Structured care for men who want to get tested for prostate cancer

FINDINGS FROM CAPIO S:T GÖRAN PROSTATE CANCER CENTER

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Conflicts of interest
Henrik Grönberg holds patents related to the Stockholm3 blood sample and may receive compensation in connection with the use of the Stockholm3 test. The other authors have no conflicts of interest.

In Sweden, 10,474 men were diagnosed with prostate cancer in 2016. About 5% of men in Sweden can be expected to die of prostate cancer as cause of death. [1]

It has now been several years since Professor Jonas Hugosson and his colleagues in Gothenburg were able to demonstrate that early diagnosis of prostate cancer in the form of screening with the prostate-specific antigen (PSA) blood sample reduces the risk of dying of prostate cancer and suffering from advanced metastatic disease [2]. This is entirely in line with the findings of the major European screening study ERSPC [3] but not with the american PLCO study that was negative [4]. The Swedish National Board of Health and Welfare, which recently made a comparison of all scientific literature, comes to the conclusion that population-based screening with PSA reduces mortality in prostate cancer.

Stockholm3 can improve diagnostic precision

Prostate cancer diagnosis has developed rapidly, and several diagnostic tools have been suggested to increase the precision of finding prostate cancer requiring treatment.

One example is the blood-based Stockholm3 test that uses a combination of clinical information, protein levels and genetic information to identify significant prostate cancer. Another example is targeted prostate biopsies with magnetic resonance imaging (MRI) that can identify the location of a possibly significant cancer. Both the Stockholm3 test and MRI followed by targeted prostate biopsies have proved to show very promising results [5,6]. A recently published study with 532 Swedish and Norwegian men using both Stockholm3 and MRI shows that a combination of both further increases the precision. The Stockholm3 test accounted for about 2/3 and MRI for about 1/3 of the improvement [7].

This means that fewer men need to undergo medical examinations (prostate biopsies or MRI) and also entails a reduction in overdiagnoses in which men with a harmless tumor receive a cancer diagnosis. In order to reduce the prostate cancer mortality, it is also important that the sensitivity of finding men with significant cancer with new diagnostics is at least as good as with today's diagnostics. Another important aspect is that new diagnostics should be introduced within the framework of today's financial resources, and that critical resources such as human resources, technical equipment and other infrastructure are not exceeded.

Here we describe our initial experience of using structured nurse-led diagnosis and the Stockholm3 test in combination with MRI followed by targeted biopsies for prostate cancer diagnosis.

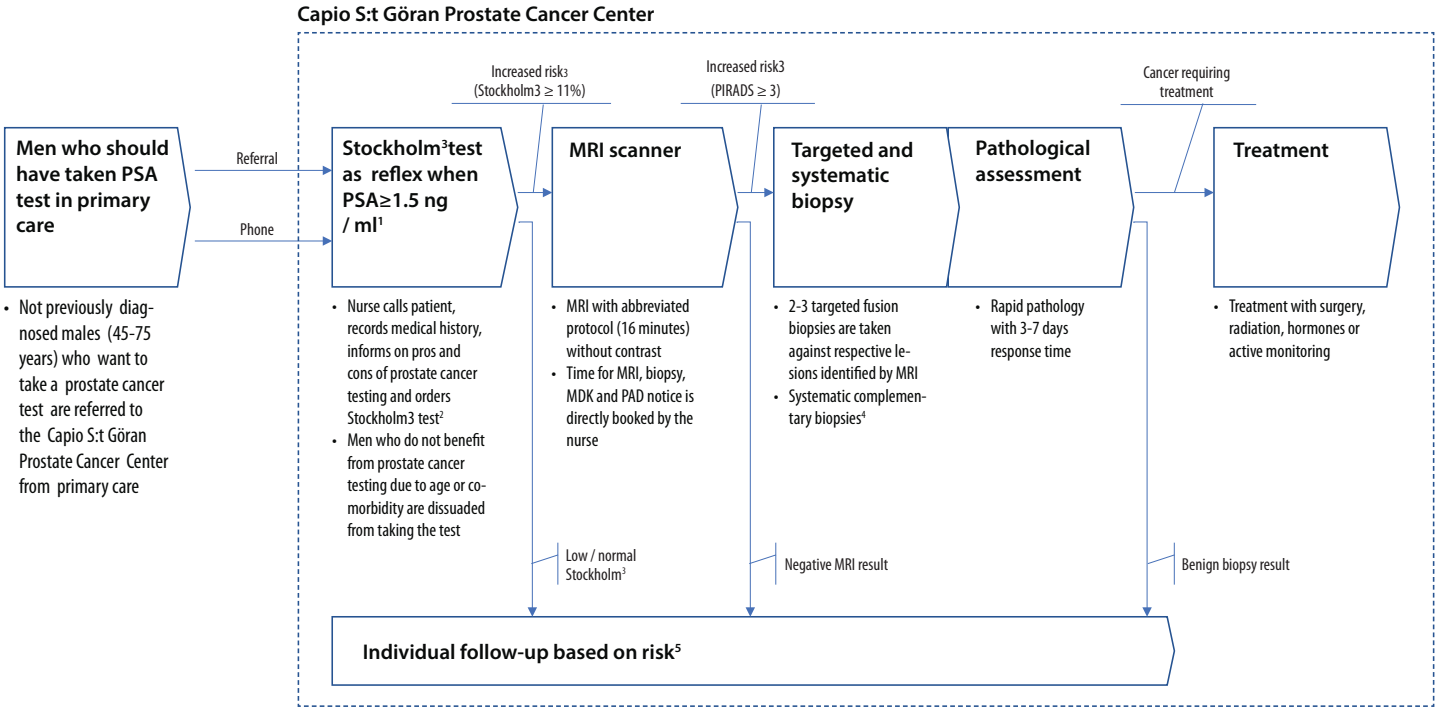
The Capio S:t Göran Model for Prostate Cancer Diagnosis

The Capio S:t Göran hospital is located in central Stockholm and is mandated by the Stockholm County Council to handle approximately 25% of prostate cancer care in Stockholm, which is equivalent to approximately 500 new prostate cancer cases per year. In 2017, Capio S:t Göran Prostate Cancer Center was established with the aim to provide cost-effective prostate cancer diagnostics using new diagnostic methods and efficient and structured processes. Clinical research to improve prostate cancer diagnosis is an integral part of the work at the Prostate Cancer Center.

Based on published results from the Stockholm3 test and MRI followed by targeted prostate biopsies [6.7], we have chosen to establish a diagnostic chain structured as follows (see Figure 1: Standardized care process Capio S:t Göran Prostate Cancer Center):

1. Men of relevant age (45-75 years) who have not previously been diagnosed with prostate cancer and who request prostate cancer testing either contact the Prostate Cancer Center or are referred from general practitioners.
2. A nurse contacts the man by phone and asks questions for risk stratification and to identify men who do not benefit from a prostate cancer diagnosis. Men who do not benefit from testing because of, for example, high age or comorbidity, are discouraged from testing. We have chosen not to offer prostate cancer testing to men over 80 years to reduce the known problem of over-testing among elderly men [8]. On this occasion, the man is also informed of the pros and cons of prostate cancer testing according to the Swedish National Board of Health and

Figure 1: Standardized care process Capio S:t Göran Prostate Cancer Center



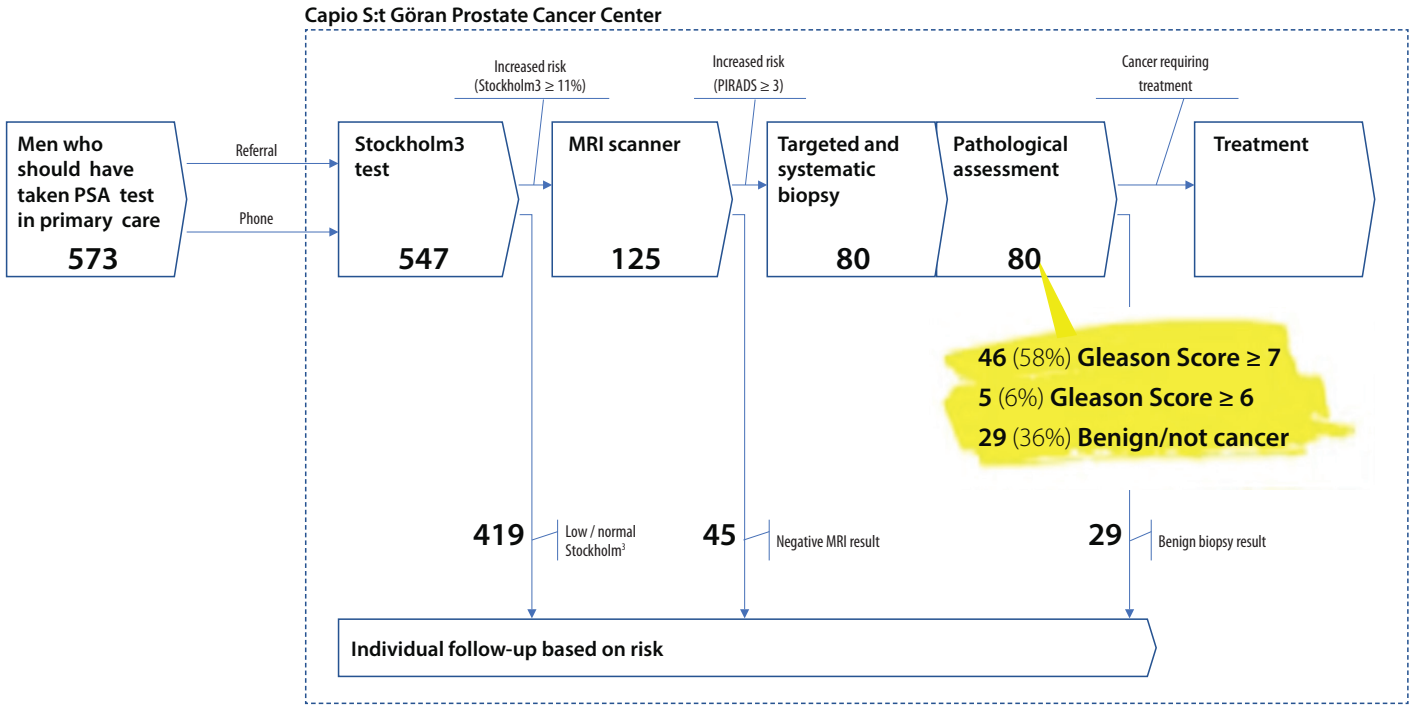
1) The Stockholm3 test is a reflex test. In practical terms, that means that a PSA test is performed first. If the PSA level is higher than or equal to 1.5 ng / ml, the Stockholm3 test is automatically performed without the patient having to provide additional blood samples. Reflex texting saves money within healthcare by analyzing only if necessary (in this case, if PSA is higher than 1.5 ng / ml). At the same time, reflex testing facilitates the procedure for the patient, who only needs to provide one blood sample. 2) In addition to the oral information, the corresponding information, including the Swedish National Board of Health and Welfare's information sheet about the pros and cons of PSA sampling, is sent to the patient's home address. 3) Increased risk means increased risk for treatment-requiring prostate cancer defined as Gleason Score ≥ 7. 4) Systemic biopsies have been taken in all patients with PI-RADS score ≥ 3. To reduce overdiagnosis, now only systematic biopsies are taken on men with PI-RADS score 4-5. 5) Men with Stockholm3 Risk Score <5% (low risk) are followed up after 6 years. Men with Stockholm3 Risk Score 6-10% (normal risk) are followed up after 2 years. Men with Stockholm3 Risk Score ≥ 11% and PI-RADS score 1-2 are followed up after 2 years. Men with Stockholm3 Risk Score ≥ 11%, PI-RADS score ≥ 3 and negative biopsy are followed up after 2 years.

Welfare's guidelines. In addition to the oral information, the corresponding information, including the Swedish National Board of Health and Welfare's information informational sheet about the pros and cons of PSA sampling, is sent to the patient's home address.

3. The man receives a referral for a blood sampling with the Stockholm3 test. Stockholm3 is a reflex test performed if the PSA level is higher than 1.5 ng / ml that results in a risk score for a significant prostate cancer (where significant prostate cancer is defined as Gleason Score ≥ 7 cancer). In practical terms, that means that a PSA test is performed first. If the PSA level is higher than 1.5 ng / ml, the Stockholm3 test is automatically performed without the patient having to provide additional blood samples. Reflex texting saves money within healthcare by analyzing only if necessary (in this case, if PSA is higher than 1.5 ng / ml). At the same time, reflex testing facilitates the procedure for the patient, who only needs to provide one blood sample.
4. Men with a Stockholm3 Risk Score ≥ 11% are considered to be at increased risk for significant prostate cancer. (11% corresponds to the risk of a significant prostate cancer at PSA = 3 ng / ml.) These men undergo a 16-minute MRI without contrast containing T2-weighted, T1-weighted and functional diffusion-weighted images (DWI). In the MRI review, the findings are classified according to PI-RADS v2 [9]. In cases of suspected changes (lesions with PI-RADS score ≥ 3), tissue sampling is offered with a combination of systematic and targeted biopsies. In the startup, we have chosen to perform both systematic and targeted biopsies on all men with suspected changes. We have changed this in spring 2018, and men with a PI-RADS score 3 now only undergo targeted biopsies. This is done to reduce the risk of overdiagnosis of low risk cancer. For men with a PI-RADS score 4-5 there is a need for staging the entire prostate prior to surgery. Therefore, both targeted and systematic biopsies are performed on these men. Men with low or normal risk in the Stockholm3 test or a negative MRI (PI-RADS score 1-2) are recommended to take a new blood sample test in 6 and 2 years respectively.

In the Capio S:t Göran Model, we have chosen to work with dedicated nurses who operate a standardized care process. The nurse independently organizes sampling and provides information on the Stockholm3 test. The nurse organizes the MRI and booking of follow-up diagnostics for men with increased risk of prostate cancer according to the Stockholm3 test, and reports whether the result of the MRI scan is normal (PI-RADS score 1-2). This means that the patient meets his urologist for the first time in the event of biopsy. If the result of the prostate biopsy is benign, the responsible urologist calls

Figure 2: Early medical results (results for the period 20171015-20180515)



the patient directly, but if signs of cancer show or in case of special circumstances, a visit with the urologist is arranged. This approach has increased the number of patients who get to meet their urologist and is generally perceived as positive, also by those men with low risk in the Stockholm3 test, who have negative MRI results or receive prostate biopsy results that are benign.

At the Prostate Cancer Center, we have worked hard to shorten lead times. The focus has been on reducing time from increased risk until a clear diagnosis can be made. The abbreviated MRI protocol enables more MRI scans per unit of time (3 patients / hour), which increases the accessibility to this critical resource. Together with Unilabs, we have also developed a process for biopsy evaluation with PAD responses within 3-7 days, enabling a therapy discussion at a multidisciplinary conference within 1 week of the biopsy event.

Early medical results

During the period from October 15th, 2017 to May 15th, 2018, we have systematically offered the Capio S:t Göran Model to all men who come for early prostate cancer diagnosis at some 10 primary care units in Stockholm. Below we report our experiences from that period (see Figure 2: Early medical results).

Figure 3: Cost of 100 planned biopsies depending on diagnostic strategy. What happens if systematic biopsies are replaced by alternative strategies?

Cost assumptions [SEK]	
Stockholm3	2 300 [3]
MRI	4 000 [5]
Biopsy + PAD	12 000 [5]
Treatment	100 000 [5]

Cost of 100 planned biopsies[1] [MSEK]

Diagnostic strategy	Diagnostic	Treatment	Total
1. Systematic biopsies[4]	1,2	4,9	6,1
2. MRI followed by targeted and systematic biopsies[6]	1,4	5,5	6,9
3. Stockolm3 + MRI followed by targeted and systematic biopsies[8]	1,3	4,4	5,7

1 Cost estimates are based on the patient's completion of the current diagnostics (typically based on elevated PSA), and that he his scheduled for systematic biopsies. The data for each strategy is based on a recently published study of 533 Swedish and Norwegian men who performed both the Stockholm3 test and MRI [7]. All data were standardized according to 100 planned cases. 2 Price list Karolinska University laboratory (https://www.karolinska.se/KUL/Alla-anvisningar/Anvisning/10245) 4 This strategy corresponds to the current clinical practice, that is, continued examination with systematic biopsies. Total Cost = Cost Diagnostics + Cost Treatment = 100 x [cost Biopsy + PAD] + number of cancers x [cost Treatment] = 100 x 12 000 + 49 x 100 000. Number of cancers based on [7] 5 Estimation of price level in Stockholm 6 This strategy means that all men first undergo an MRI scan. Men with PIRADS ≥ 3 undergo targeted and systematic biopsies. Men with PIRADS <3 do not undergo biopsy. Total Cost = Cost Diagnostics + Cost Treatment = 100 x [cost MRI] + number of biopsies x [cost biopsy + PAD] + number of cancers x [Cost Treatment]. 100 x 4 000 + 87 x 12 000 + 56 x 100 000. Number of biopsies and number of cancers based on [7] 7 The cost of treatment includes the options of surgery, radiation or active monitoring. 8 This strategy means that all men first have the Stockholm3 test performed. Men with Stockholm3 Risk Score ≥ 11% undergo an MRI scan. Men with PIRADS ≥ 3 undergo targeted and systematic biopsies. Men with PIRADS <3 do not undergo biopsy. Total Cost = Cost Diagnostics + Cost Treatment = 100 x [cost Stockholm3] + number of MRIs x [cost MRI] + number of biopsies x [cost biopsy + PAD] + number of cancers x [Cost Treatment]. Number of MRIs, number of biopsies and number of cancers based on [7]

547 men underwent prostate cancer testing after contacting their primary care unit or contacting us directly by telephone. The average age of these men was 63 years, the youngest being 33 and the oldest 84 years old. 71% of the men were between 50-70 years old. The median time from the referral or the reference to the telephone call by the nurse was less than 1 day. 128 (23%) of men had a Stockholm3 test indicating increased prostate cancer risk (Stockholm3 Risk Score ≥ 11%). By comparison, 34% of men who provided blood samples and were between 50-70 years had a PSA level over the national limit for biopsy (PSA ≥ 3 ng / ml).

All 128 men with a Stockholm3 Risk Score ≥ 11% were recommended MRI examination. The willingness to comply and undergo a MRI scan was 98%, which meant that 125 men had an MRI scan performed. The distribution of findings of the MRI examination is shown in Figure 2. 45 (38%) men undergoing MRI had no pathological findings in the examination and therefore did not undergo prostate biopsy.

80 (62%) of men who underwent MRI were recommended prostate biopsy due to the MRI findings. The biopsy results are shown in Figure 2. In 46/80 (58%) of men who had a biopsy performed, significant Gleason Score ≥ 7 cancers was identified, but only 5/80 (6%) showed low grade cancer (Gleason Score 6). This means that just over 8% of the 547 tested men had a significant cancer that required treatment. By comparison, approximately 3% of prostate cancer was found in the first screening round in the well-established Gothenburg Study [2].

Process optimization to reduce lead times

Thanks to standardized and nurse-led processes, abbreviated MRI protocols and rapid pathology, we have been able to reduce the time from well-grounded suspicion of prostate cancer to initiated treatment from approximately 200 days in 2015 to 60 days (mean value), which is within the target level of Swedish standardized prostate cancer care. With the help of further process optimization, we expect to further reduce lead times.

Health-economic calculation

It is of utmost importance that new tools in healthcare are introduced in a manner that is reasonable in terms of health-economics. We have done a health-economic evaluation of the direct healthcare costs for diagnostics and treatment respectively. We have evaluated three different strategies based on assumptions that apply in Stockholm. (see Figure 3: Cost of 100 planned biopsies depending on diagnostic strategy):

- Strategy 1 means continuing as before, i. e., testing with PSA and implementing systemic biopsies if the PSA level is elevated (PSA ≥ 3 ng / ml)
- Strategy 2 means that men with elevated PSA levels perform MRI. Men with positive MRI results (PI-RADS score ≥ 3) then undergo targeted and systematic biopsies
- Strategy 3 means that a Stockholm3 test is performed initially. Only those men who have an increased Stockholm3 test result (Stockholm3 Risk Score ≥ 11%) then have an MRI performed, followed by targeted and systematic biopsies if the MRI result is positive.

The health-economic analysis indicates that the cost is lowest when combining Stockholm3 with MRI followed by targeted and systematic biopsies (Strategy 3). The reason why costs are lowest in this strategy is that both unnecessary MRIs and unnecessary biopsies are avoided, and because of lower costs with fewer men in active monitoring compared to other methods.

The need for improved prostate cancer diagnostics tools

There is a broad consensus that early diagnosis of prostate cancer reduces mortality in prostate cancer, but that it is also associated with widespread diagnosis of benign tumors (overdiagnosis) and complications caused by examination and treatment (infections, treatment-induced incontinence and impotence). It is therefore of utmost importance that new prostate cancer diagnosis is designed to perform with higher precision than previously possible. This has also been noted by the Swedish National Board of Health and Welfare, which discouraged screening based on existing knowledge in 2014, when only the PSA test was available.

The performance of the Capio S:t Göran model in the light of alternative strategies

Our model enables an improved prostate cancer diagnosis, where over 50% of the men who have undergone a biopsy have a significant prostate cancer (increased specificity), while the number of men with small cancers not requiring treatment decreases (reduced overdiagnosis). This is to be compared with population-based figures from other Stockholm areas indicating that only about 20-25% of men who undergo biopsy in today's care have significant prostate cancer [10]. With 8% of men tested on Capio S:t Göran having significant cancer, these figures are also higher than figures from other parts of Stockholm [10] and previous screening studies [2]. Together with other research [4,6] it indicates that our diagnostics also have a high sensitivity.

The Capio S:t Göran Model that we have adopted at the Prostate Cancer Center is one of several possible strategies for improving prostate cancer diagnosis. Other examples include using PSA and MRI without the addition of other blood tests as in the ongoing Göteborg2 study and the vision for prostate cancer centers presented in Läkartidningen [11,12]. Another example is the model proposed in Region Skåne in southern Sweden where the Stockholm3 test is intended for the use as reflex for men with PSA levels between 3-10 and normal palpation findings. Additional options include using only PSA followed by traditional (systematic) biopsies or using combinations of MRI and / or alternative blood samples such as 4K Score or Prostate Health Index.

Within this plethora of possible strategies lie several challenges. First, the scientific support for the individual strategy needs to be carefully evaluated, which often requires resources and special skills. Furthermore, each individual strategy is characterized by special requirements in terms of resources, such as access to MRI equipment and time slots, radiological skills, pathologists, urologists, nurses, and so on. Finally, health-economic considerations need to be made to enable effective resource utilization in the healthcare sector.

Changed resource needs

The use of MRI in prostate cancer diagnosis will increase the need for MRI examinations, but also for radiologists with special knowledge in MRI prostate examinations. At the same time, reduction of the number of biopsies and the number of low-grade cancers will in turn reduce the need for resources in pathology and also in urology. It is also expected that this will eventually be further adjusted with the introduction of artificial intelligence in radiological and pathological imaging methods.

What the follow-up for a man with increased prostate cancer risk according to the Stockholm3 test but with negative MRI scan results (PI-RADS score 1-2) will look like exactly is still unclear, but can eventually be evaluated in this structured approach. In summary, the new diagnostics bring about changing resource needs that need to be followed up continuously.

Capio S:t Göran's Model and systematic screening - opportunities and obstacles

During the spring of 2018, the Swedish National Board of Health and Welfare presented a new screening recommendation and found in its preliminary decision that health care should not recommend screening for prostate cancer. Both the decision and the scientific basis for the supplementary test of the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) have been debated extensively in national media [13], and the process has sparked several regional initiatives aiming for the introduction of a more structured prostate cancer diagnosis.

The experiences made at the Capio S:t Göran Prostate Cancer Center are evident: A structured care for men who want to get tested for prostate cancer, within which the blood based Stockholm3 test is combined with MRI and followed by targeted biopsies, is (i) feasible and (ii) associated with high sensitivity to finding significant prostate cancer. At the same time, the proportion of detected low-grade tumors, as well as the number of men who need to undergo examination, decreases sharply compared to traditional examinations procedures. This can be done in a health-economically advantageous manner, with short lead times and with a reduced need for medical appointments at the urological center. The feedback from patients has been spontaneously good, and the comments we received relate to good accessibility, clear recommendations and short lead times.

Credentials

1. Socialstyrelsen. www.socialstyrelsen.se
2. Hugosson J, Carlsson S, Aus G, et al. Mortality results from the Göteborg randomized population-based prostate-cancer screening trial. Lancet Oncol. 2010 Aug;11(8):725-32. doi: 10.1016/S1470-2045(10)70146-7.
3. Schröder FH, Hugosson J, Roobol MJ, et al. Screening and prostate cancer mortality: results of the European Randomised Study of Screening for Prostate Cancer (ERSPC) at 13 years of follow-up. Lancet. 2014 Dec 6;384(9959):2027-35. doi: 10.1016/S0140-6736(14)60525-0.
4. Wilt TJ, Brawer MK, Jones KM, et al; Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med. 2012 Jul 19;367(3):203-13. doi: 10.1056/NEJMoa1113162.
5. Kasivisvanathan V, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. New England J Medicine 2018 2018 Fb
6. Grönberg H, Adolfsson J, Aly M, et al. Prostate cancer screening in men aged 50-69 years (STHLM3): a prospective population-based diagnostic study. Lancet Oncol. 2015 Dec 16;16(1667-76):2027-35. doi: 10.1016/S1470-2045(15)00361-7
7. Grönberg H, Eklund M, Picker W, et al, Prostate cancer diagnostics using a combination of the Stockholm3 blood-test and multiparametric magnetic resonance imaging; Eur Urol. June 2018. https://doi.org/10.1016/j.eururo.2018.06.022
8. Nordström T, Aly M, Clements MS, et al. Prostate-specific antigen (PSA) testing is prevalent and increasing in Stockholm County, Sweden, Despite no recommendations for PSA screening: results from a population-based study, 2003-2011. Eur Urol. 2013 Mar;63(3):419-25. doi: 10.1016/j.eururo.2012.10.001.
9. https://www.acr.org/-/media/ACR/Files/RADS/Pi-RADS/PI-RADS-V2.pdf Purysko A, et al. PI-RADS Version 2: A Pictorial Update. RadioGraphics 2016. Doi: 10.1148/rg.2016150234
10. Aly M, Clements M, Weibull C, et al. Poor Follow-up After Elevated Prostate-specific Antigen Tests: A Population-based Cohort Study. Eur Urol. Focus 2018. doi: 10.1016/j.euf.2018.02.001
11. Grenabo Bergdahl A, Wilderäng U, Aus G, et al. Role of Magnetic Resonance Imaging in Prostate Cancer Screening: A Pilot Study Within the Göteborg Randomised Screening Trial. Eur Urol. 2016 Oct;70(4):566-573. doi: 10.1016/j.eururo.2015.12.006
12. Bratt O, Ahlgren G, Börjedahl AC, et al. The Prostate Cancer Center - the hub of future prostate cancer care. Läkartidningen 2017;114:D77U
13. There are several examples, see for example DN: https://www.dn.se/nyheter/amina-manzoor-starka-kanslor-andrar-inte-kunskapslaget/ eller Dagens Medicin https://www.dagensmedicin.se/artiklar/2018/05/23/socialstyrelsen-det-svaraste-beslutet-vi-tagit/ eller Svenska Dagbladet https://www.svd.se/sbu-har-tappat-bort-det-vetenskapliga