Background and current diagnostics for prostate cancer

The STHLM3 Study and how the STHLM3 Test can replace PSA

STHLM3 MR/Fusion study
Prostate cancer is the most common cancer in Norway

4,836 cancers
988 deaths
39,355 prevalence
3,256
636
41,224

Source: Norwegian Kreftregisteret
Do I have prostate cancer/how large is my risk of getting prostate cancer?
Current diagnostics of prostate cancer is suboptimal

- Blood test: PSA
- Biopsy: 12 cores biopsies
- Pathology: Gleason Scoring
- Treatment: Surgery or Radiation, Active Surveillance, Chemotherapy
Current diagnostics of prostate cancer is suboptimal

- **Low specificity**: 2 out of 3 positive tests are incorrect
- **Low sensitivity**: 30-50% of all aggressive cancers are missed
Current diagnostics of prostate cancer is suboptimal

- Misses aggressive cancers: 10-30% is missed
- Identifies many indolent cancers: 1 out of 2 cancers are Gleason Score 6
- High risk for infection: 1 out of 50 biopsies lead to serious infections
Current diagnostics of prostate cancer is suboptimal

- **Operator dependence**: Large variance between pathologist
- **Non-optimal use of information**: Genomic information is not used
- **Scare resource**: Lack of uro-pathologist leads to waiting times
We need

Better test than PSA
Better biopsy procedures
Better prognostics than Gleason
Structure the testing

To get

Improved sensitivity
Improved specificity
Less harm
Good health economy
Prostate cancer diagnostics could be significantly improved

Blood test
- PSA
  - STHLM3 Test

Biopsy
- 12 cores biopsies
  - MRI guided biopsies

Pathology
- Gleason Scoring
  - Genomic profiling of the tumor

Treatment
- Surgery or Radiation
- Active Surveillance
- Chemotherapy

+ Improved sensitivity and specificity
+ Less harm
+ Same/lower costs
The STHLM3 Study
Data from The Stockholm PSA Registry shows a de-facto, unstructured, screening with PSA in Stockholm

**Stockholm PSA- and Biopsiregister**

Data from 420,000 men

All testing in Stockholm since 2003

Complete records
- All PSA-test
- All biopsy/pathology results
- Detailed information on all cancers

130,000 PSA tests and 5,000 biopsies taken yearly

65% of all men aged 50-69 has taken at least one PSA-test in the last 5 years

2,000 prostate cancers/year
Today’s unstructured screening with PSA yields both low specificity and sensitivity

Low specificity

- **38%** of men with PSA < 1 takes a new test in 2.5 years
- **60%** of all biopsies are negative
- **50%** of all cancers diagnosed are Gleason 6

Low sensitivity

- **30-50%** of all aggressive cancers are not diagnosed
The un-structured testing in Stockholm shows a significant underdiagnostics

<table>
<thead>
<tr>
<th>Exemple 1</th>
<th>Exemple 2</th>
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<tbody>
<tr>
<td>Proportion of men that have done biopsy within 2 years after a PSA-test with above guidelines value</td>
<td>Out of men diagnosed with advanced prostate cancer (T3/4,N1,M1, PSA&gt;20), 17 % have taken a PSA-test with above guideline values 6 months or earlier without any actions taken</td>
</tr>
<tr>
<td><strong>PSA-value</strong></td>
<td><strong>Age group</strong></td>
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<tr>
<td>3 - 4</td>
<td>45%</td>
</tr>
<tr>
<td>4 - 10</td>
<td>65%</td>
</tr>
<tr>
<td>&gt; 10</td>
<td>70%</td>
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</table>

Many cases don’t follow guidelines

Opportunity of early diagnostics is often missed

Source: Manuscript in preparation
Prostate cancer diagnostics is complex and hard

Case 1
62 year old healthy man with no symptoms. First PSA 14, a second PSA 10.2 after 1 month, palpable normal prostate.

Case 2
58 year old healthy man with no symptoms. He had had three PSA between 4.0-4.5 during the last year.

Recommendation from 50 Nordic Prostate Cancer Specialists

<table>
<thead>
<tr>
<th>New PSA</th>
<th>Biopsy</th>
<th>MRI</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>49%</td>
<td>33%</td>
<td>18%</td>
<td>30%</td>
</tr>
<tr>
<td>22%</td>
<td>54%</td>
<td>24%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Source: Meeting November 2014 with 50 Nordic prostate cancer specialists
Cooperation between Karolinska Institutet and Stockholm County Council provides excellent value to both parties

- 2.2 million inhabitants
- EUR 5 billion annual health budget

- Improved health economics
- Solution to unstructured screening issue

- Access to 250,000 men
- Access to testing and downstream healthcare
STHLM3 is collaboration between Stockholm County Council and Karolinska Institutet to develop a better prostate cancer test

<table>
<thead>
<tr>
<th>Objective</th>
<th>Conditions</th>
<th>Method</th>
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<tr>
<td>• Develop a new prostate cancer test that can replace PSA</td>
<td>• Identify at least as many aggressive cancers as PSA&lt;br&gt;• Significantly reduce number of biopsies&lt;br&gt;• Demonstrate good health economy</td>
<td>• Combine many existing markers</td>
</tr>
</tbody>
</table>
STHLM3 combines biomarkers and clinical data into the STHLM3 Test to predict aggressive prostate cancer.

\[
\text{STHLM3 Test} = f
\]

- Protein markers
- 232 Genetic markers
- Clinical data

**Risk factors**
- Age
- Family history
- Previous biopsy

**Prostate Exam**
- Prostate volume*
- DRE*

**Markers**
- Total PSA
- Free PSA
- Intact PSA
- hK2
- MSMB
- MIC-1

* Only measured on biopsied men
We have followed a structured process to identify the best markers for the STHLM3 Test

Step 1
Literature Search
- Literature screening of 1,000+ potential plasma and genetic markers

Step 2
STHLM2 Cohort
- [26,000 men]
- 150+ plasma markers evaluated

Step 3
STHLM3 Training
- [11,130 men]
- STHLM3 Test calibrated
- Collection on PSA 1-3 data
- Test of logistics

Step 4
STHLM3 Validation
- [47,688 men]
- Prospective evaluation of STHLM3 Test
STHLM3 has – in cooperation with LifeTechnologies and Thermo Fisher Scientific – developed two chips enabling high-throughput testing.

- Customized biomarker chip
- Customized SNP chip

Karolinska University Hospital is setting up the method for clinical use.
We have built a high-throughput infrastructure with a capacity to handle 500+ participants/day

- 75+ local labs covering the whole Stockholm area sampling using normal clinical protocol
- 20 urologists using the same standardized 10-12 core needle protocol
- 300-500 samples/day
- Daily transports to lab
- Centralized, highly automated analysis of Best Possible panel
- 20-25 biopsies/day
- Automated answer letter within 1 week
- Single pathologist grading all biopsies
All participants receive an individual answer with recommendation on follow-up care

STHLM3 Design

PSA<1

Low risk of prostate cancer
Testing is recommended in 6-10 years

PSA≥1

STHLM3 Test

Men in Stockholm aged 50-69

PSA<1

Normal risk of prostate cancer
Testing is recommended in 2-4 years

PSA≥3 and/or S3T ≥ τ

Increased risk of prostate cancer
Biopsy is recommended

PSA<1

1≤PSA<3
and S3T< τ

PSA≥3 and/or S3T ≥ τ
145,905 men in Stockholm invited

58,818 men recruited

6,777 biopsies conducted

79,969 core biopsies evaluated
We have conducted two analyses

1. Screening by invitation
   What happens if we conduct a population based screening by invitation with the STHLM3 Test with the same sensitivity as PSA≥3 to find aggressive prostate cancer?

2. Current clinical practice
   What happens if we exchange today’s diagnostics with the STHLM3 Test with the same sensitivity to find aggressive prostate cancer as today’s clinical practice?

1. Final data
   In press Lancet Oncology, Nov 10th

2. Preliminary data
   Manuscript in preparation
The result shows that STHLM3 can replace PSA as a first screening for prostate cancer

Key results STHLM3

Less biopsies
More aggressive cancers found
Less non-aggressive cancers found
Positive health economy

1.000+ Swedish men can avoid cancer diagnosis yearly!

Healthcare saves money due to less unnecessary biopsies and less treatment of non-aggressive cancers

We have asked the Swedish Institute for Health Economy (IHE) to evaluate the health economy of STHLM3

An health economy analysis has been conducted by the Swedish Institute for Health Economy (IHE)

The Swedish National Board of Health and Welfare (Socialstyrelsen) has used IHE for evaluation of health economy regarding breast- and colorectal cancer

IHE has applied a similar health economy model for evaluation of prostate cancer

The costs in the model are based on actual costs in Stockholm with conservative assumptions

The STHLM3 Test:
- Saves money
- Gains improved quality of life
Going forward, IHE has evaluated four alternatives

1. **Do nothing – continue with current unstructured PSA-screening**
   - Expensive and inefficient
   - Unnecessary biopsies and treatment

2. **Replace current practice with STHLM3 Test and detect equal number of Gleason Score 7+ as today**
   - Saves money
   - Reduces number of biopsies and GS6
   - Reduces unnecessary treatments

3. **Replace current practice with STHLM3 Test and complete equal number of biopsies as today**
   - Reduces mortality
   - Saves money
   - Reduces GS6, increases GS≥7
   - Reduces unnecessary treatments

4. **Implement structured by-invitation screening with STHLM3 Model**
   - Reduces mortality
   - Saves money
   - Increases number of biopsies and treatments

"This is not ethical"
The STHLM3 Test will have a simple answer to aid the general practitioner and urologist

All STHLM3 variables are concluded in one single answer

Result from the STHLM3 Test

Result
- Increased value

Recommendation
- Increased risk for prostate cancer, referral to urologist is recommended

Example of results and recommendation

Normal value
- Low risk of prostate cancer, new test is recommended in 4-6 yrs

Increased value
- Normal risk of prostate cancer, new test is recommended in 2 yrs

Increased risk for prostate cancer, referral to urologist is recommended

STHLM3 Test = \[ f \]
- Protein markers
- 232 Genetic markers
- Clinical data
The STHLM3 Test can replace PSA

Advantages for the patient
+ **Increased possibility** of early detection of prostate cancer
+ **Reduced risk of infection**: Reduced risk to conduct biopsy (and unnecessary treatments)
+ **Increased quality of life**: Many patients will not need to be tested in many years

Advantages for healthcare
+ **Reduced costs** due to less unnecessary biopsies and pathology, and reduced treatments
+ **Reduced resource need** within urology, pathology and oncology
+ **More equal care** due to simpler answer and recommendations to aid the physician

Advantages for the physician
+ **Simpler and safer decision** regarding next step
STHLM3 MRI/Fusion Study
## STHLM3 MRI/Fusion Study

<table>
<thead>
<tr>
<th>Question</th>
<th>Can MRI guided biopsies replace 12-core standard biopsies</th>
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<tbody>
<tr>
<td>Primary outcome</td>
<td>Number of aggressive prostate cancer in biopsy</td>
</tr>
<tr>
<td>Secondary outcome</td>
<td>Health economy</td>
</tr>
<tr>
<td>N</td>
<td>8,000 tested with STHLM3, 1,000 biopsied</td>
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<tr>
<td>Timing</td>
<td>2016</td>
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STHLM3 MRI/Fusion design

Men aged 50-69 living in Stockholm

Screening with STHLM3 Test (n=8,000)

1,000 men with ≥10% risk of Gleason Score ≥7 in biopsy

Positive MRI

12 core systematic biopsy

Fusion guided targeted biopsies

Negative MRI

12 core systematic biopsy
In summary...
An improved prostate cancer diagnostic chain is already partly ready for implementation

**STHLM3 Test**
- In clinic 2016

**STHLM3 MRI/Fusion Study**
- Results expected late 2016

**STHLM Biopsy Study**
- Results expected 2016/17

- **STHLM3 Test**
- **MRI with guided biopsies**
- **Genomic profiling of the tumor**

- **Men at low/normal risk**
- **No cancer in biopsy**

- **Individualized follow-up**
- **Individualized treatments**
# Acknowledgements

<table>
<thead>
<tr>
<th>STHLM3 Core</th>
<th>Martin Eklund</th>
<th>Jan Adolfsson</th>
<th>Mark Clememets</th>
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## Funding

![Funding Image]
STHLM 3

Improved Prostate Cancer Diagnostics