A knowledge based system for the prediction of metastatic disease in patients with malignant melanoma
• Skin cancer
  – Malignant melanoma

• Prediction model

• Next steps
Skin cancer in general

• Basal cell carcinoma (metastasis rare)

• Spindle cell carcinoma (metastasis rare)

• Malignant melanoma - responsible for death about 90% of skin cancer (fast metastasis)

Metastasis is defined as a spreading of tumour cells in distant regions of the body with an additional growth of a further tumour.
Malignant melanoma

Incidence in Europe

- 1996-1998:
  - Female: 7.4
  - Male: 6.9
- 1998-2000:
  - Female: 12.1
  - Male: 11.9
- 2009:
  - Female: 18.7
  - Male: 16.8
Malignant melanoma

Diagnosis

• ABCDE-rule (80% diag. sensitivity)
• Dermoscopy (90% diag. sensitivity)

Follow-up examinations detecting metastasis

• Chest X-ray
•Computed tomography (CT)
• Magnetic resonance tomography (MRT)
• Positron emission tomography (PET)
• Serum parameters – “Tumour markers”
Malignant melanoma

Possible benefits
- Increasing the wellbeing of the patients
- Reduction of stress caused by additional examinations
Prediction model

- Prediction of metastatic events in patients with melanoma

Knowledge base with combined results (programmed in Arden-Syntax):

1. Interpretation of tumour markers
2. Pre-test probability for metastasis
3. Interpretation of the current probability of metastasis
Interpretation of tumour markers

Tumour markers are circulating macro molecules which will be obtained from blood or other body fluids.

Our Hypothesis
The presence of metastatic disease correlates with the concentration of tumour markers.
Melanoma tumour markers
S100β, MIA, LDH (493 records)

<table>
<thead>
<tr>
<th>Marker</th>
<th>Median (min-max)</th>
<th>IQR</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Sensitivity / Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100β</td>
<td>0.06 (0.002-7.81)</td>
<td>0.05</td>
<td>0.06</td>
<td>0.94</td>
<td>61.43% / 58.40%</td>
</tr>
<tr>
<td>MIA</td>
<td>7.175 (0.003-1023)</td>
<td>4.475</td>
<td>0.86</td>
<td>0.95</td>
<td>63.86% / 66.09%</td>
</tr>
<tr>
<td>LDH</td>
<td>175 (90-2842)</td>
<td>54</td>
<td>0.92</td>
<td>0.97</td>
<td>69.05% / 67.23%</td>
</tr>
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</table>

3D visualization of tumour markers (S100β, MIA, LDH)

Blue = no metastasis
Red = metastasis
Methods

(1) Multivariate statistical methods
   • Logistic regression

(2) Machine Learning
   • Artificial neural network (scaled conjugate gradient optimization with 20 hidden neurons)
## Interpretation of tumour markers

### Results - Logistic regression

<table>
<thead>
<tr>
<th></th>
<th>Data set pos/neg</th>
<th>AUC</th>
<th>95% Asymptotic CI</th>
<th>max. sensitivity / specificity</th>
<th>Asymptotic sign.</th>
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<tr>
<td>S100β</td>
<td>469 / 70 / 399</td>
<td>0.676</td>
<td>0.601 – 0.750</td>
<td>61.40% / 58.40%</td>
<td>&lt;0.0001</td>
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<tr>
<td>MIA</td>
<td>489 / 83 / 406</td>
<td>0.720</td>
<td>0.651 – 0.790</td>
<td>63.90% / 66.01%</td>
<td>&lt;0.0001</td>
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<tr>
<td>LDH</td>
<td>280 / 42 / 238</td>
<td>0.724</td>
<td>0.630 – 0.818</td>
<td>69.00% / 71.00%</td>
<td>&lt;0.0001</td>
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# Interpretation of tumour markers

## Results - Artificial neural network

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</tr>
</thead>
<tbody>
<tr>
<td>S100β/MIA/LDH incl. MV</td>
<td>85 / 408</td>
<td>0.739</td>
<td>0.673 – 0.805</td>
<td>67.10% / 69.12%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>S100β/MIA/LDH</td>
<td>37 / 233</td>
<td>0.734</td>
<td>0.631 – 0.837</td>
<td>73.00% / 68.67%</td>
<td>&lt;0.0001</td>
</tr>
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Pre-test probability

The estimation of pre-test probability is of utmost importance for accurate clinical reasoning.¹

Already Thomas Bayes engaged oneself with the pre-test probability of events.²

¹http://www.merck.com/mmpe/sec22/ch328/ch328e.html
²http://en.wikipedia.org/wiki/Thomas_Bayes
Pre-test probability

Calculation of the probability for metastasis and tumour stage classification (TNM-classification):

- **Tumour** (Tumour thickness, Ulceration, Mitosis)
- **Nodes** (Number of the nodes)
- **Metastasis** (Localization of the metastasis)
Current probability of survival

Original hazard model

\[ h(x) = \lambda e^{\beta x} \]
\[ h'(x) = \lambda \beta e^{\beta x} \]

Enhanced hazard model

\[ h(x) = \lambda e^{\beta x} + \gamma e^{\delta x} \]
\[ h'(x) = \lambda \beta e^{\beta x} + \gamma \delta e^{\delta x} \]

![Graph showing survival probability over time for different stages](image-url)
Next steps

• Implementation in AKIM

• Prospective studies

• Evaluating the performance of the system
Summary

• Combination of tumour markers improves accuracy of information

• Computer assisted computation of the pre-test probability

• Optimal function fitting of the survival curve