What is important for a clinician doing translational research?

Julia S. Johansen
Departments of Oncology and Medicine
Herlev Hospital, University of Copenhagen
Denmark
Danish Cancer Biobank

- First visit
  - Blood samples
  - Tissue samples

- Clinical databases and other sources for clinical informations
- National registries

- Biopsy/Surgery
- During treatment with chemotherapy and biologics

Max 14 days

Requisition
Why suddenly a focus on biomarkers?
Expences to cancer therapy is rapidly increasing

### De dyreste kræftlægemidler

11 af de 30 mest omkostningstunge lægemidler i dansk sygehusbehandling er kræftmidler

<table>
<thead>
<tr>
<th>Placering på top 30-listen</th>
<th>Lægemiddel</th>
<th>Kræfttype</th>
<th>Omsætning i mio. kr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Herceptin</td>
<td>Brystkræft/kræft i mavesækken</td>
<td>202</td>
</tr>
<tr>
<td>6</td>
<td>Mabthera</td>
<td>Lymfeknudekræft/leukæmi</td>
<td>154</td>
</tr>
<tr>
<td>8</td>
<td>Avastin</td>
<td>Tyk- og endetarms-/bryst-/lungekræft</td>
<td>119</td>
</tr>
<tr>
<td>13</td>
<td>Glivec</td>
<td>Leukæmi</td>
<td>82</td>
</tr>
<tr>
<td>14</td>
<td>Femar</td>
<td>Brystkræft</td>
<td>81</td>
</tr>
<tr>
<td>19</td>
<td>Erbitux</td>
<td>Tyk- og endetarmskræft</td>
<td>54</td>
</tr>
<tr>
<td>20</td>
<td>Neulasta</td>
<td>Leukæmi</td>
<td>53</td>
</tr>
<tr>
<td>22</td>
<td>Zoladex</td>
<td>Prostata-/brystkræft</td>
<td>47</td>
</tr>
<tr>
<td>24</td>
<td>Alimta</td>
<td>Lungekræft</td>
<td>46</td>
</tr>
<tr>
<td>26</td>
<td>Velcade</td>
<td>Knoglemarvskræft</td>
<td>44</td>
</tr>
<tr>
<td>29</td>
<td>Tarceva</td>
<td>Lunge-/bugspytkirtelkræft</td>
<td>39</td>
</tr>
</tbody>
</table>

**Samlet:** 921

Kilde: Amgros, omsætningstal april 2010 til marts 2011
Obs: Det samlede forbrug af medicin på sygehusene var i samme periode 5,6 mia. kr.
STOR DEL AF MEDICINUDGIFTER GÅR TIL MONOKLONALE ANTI-STOFFER

Udgifter til sygehusmedicin indkøbt via Amgros (priser efter rabat).

Udgifterne til monoklonale antistoffer var fra april 2011 til marts 2012 1,7 mia. kr. og udgjorde 30 pct. af medicinudgifterne.

Kilde: Amgros 2011 · Grafik: MAK

Ingeniøren 29. april 2012
BIOLOGISK MEDICIN HITTER
Biologiske lægemidler baseret på monoklonale antistoffer indtager i alt syv pladser på sygehusmedicinens top-10 i Danmark.

Humira (leddegigt)
Remicade (leddegigt)
Enbrel
Herceptin (brystkræft)
Lucentis (synsvækkelse)
Mabthera (lymfeknudekræft)
Avonex
Avastin (kræft)
Privigen
Tysabri (multipel sclerose)

Ingeniøren 29. april 2012
Atkinson 2001:
A Biomarker (Biological marker) is in general defined as ”a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention”.

The definition does not include specific technologies except that the biomarker should be possible to measure objectively.

A good biomarker should ultimatively provide to a clinical decision that is followed by a more positive clinical endpoint for the patient, like reduction of time to disease progression, a better life quality, a reduction in health expenses.

PubMed February 2013: "Biomarkers” = 600.241 articles  
"Cancer Biomarkers” = 15.364 articles
The field of biomarker discovery is just in the beginning

Useful cancer biomarkers should:
- reach abnormal levels (either increased or decreased compared with controls) in conjunction with disease development
- fluctuate in relation to disease severity
- normalize following successful treatment
- identify patients who will respond to different treatments

In patients with cancer a few biomarkers are now used to select patients for treatment with “biologics” e.g.:
HER2 3+: Trastuzumab for treatment of breast cancer
KRAS wildtype: Cetuximab for treatment of colorectal cancer
BRAF mutations: Vemurafenib for treatment of melanoma
Prognostic biomarkers can forecast disease recurrence, progression, or death independent of treatment.

Predictive biomarkers can identify groups of patients who are likely to have increased sensitivity or resistance to a given therapy.

Some biomarkers can be both prognostic and predictive.

Some biomarkers can be used:
- to diagnose patients
- for monitoring patients
- as surrogate endpoints
Why do we not have more useful biomarkers for selection of patients with cancer who will benefit from treatment with the different biologics?

- It is difficult to identify new biomarkers without large biobanks and corresponding clinical databases
- It is expensive to establish biobanks
How can we identify the patients who will benefit from the treatment?

Personalized medicine - The Goal

Metastatic cancer

- Good Signature
  - Estrogen receptor status
  - HER2 expression
  - KRAS mutation
  - Standard Therapy

- Poor Signature
  - Profil A
  - Profil B
  - Profil C
  - Targeted Individualized Combinational Therapy

Biomarkers
Biological therapy of patients with colorectal cancer
2 different pathways

Angiogenesis (VEGF)

Bevacizumab, Aflibercept, Regorafenib

Epidermal Growth Factor Receptor (EGFR)

Cetuximab, Panitumumab
Better survival of patients with metastatic colorectal cancer

- No treatment 1957-1980s
- Monochemotherapy 5-FU/LV 1990s
- FOLFOX, FOLFIRI 2000s
- Combination of chemotherapy + MAbs 2004
- BIOMARKERS 2008: combination of chemotherapy + MAbs

Mean survival time from diagnosis (months)
Clinical problem:

- How can we identify the right biological therapy for a patient with colorectal cancer and potential resectable liver metastases?

- If the "wrong" treatment is given – then the liver metastases will progress during 3 months of treatment with non-effective therapy.
Patients with colorectal cancer and liver metastases are very different

**Group I**

The liver metastases can be operated without any pretreatment

10-20%

**Group II**

Maybe the liver metastases can be operated after treatment with biologics

15-30%

**Group III**

Not possible to operate the liver metastases

50%

What treatment?
Case I:
44 year old man with colorectal cancer and liver metastases

5/2006 Diagnose

1. Chemo + antibody

2. Chemo + antibody

Liver metastases are resectable
The patient is operated
Patient is alive 01/2013
Case II:
44 year old man with colorectal cancer and liver metastases

Diagnose

1. Chemo + biological treatment with no effect

MDT: Liver metastases are not resectable
Patients with colorectal cancer and liver metastases have a better survival if the metastases are resected.
KRAS wild type is the only biomarker used in patients with metastatic colorectal cancer to select treatment with cetuximab or panitumumab.

### Table 2 | Randomized studies of EGFR mAb therapies in metastatic CRC

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>KRAS wild type*</th>
<th>KRAS mutant*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n (%)</td>
<td>RR (%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Monotherapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amado et al. (2008)²⁹</td>
<td>Panitumab vs BSC</td>
<td>427</td>
<td>243 (57)</td>
<td>0 vs 17</td>
</tr>
<tr>
<td>Karapetis et al. (2008)⁰</td>
<td>Cetuximab vs BSC</td>
<td>394</td>
<td>130 (58)</td>
<td>0 vs 13</td>
</tr>
<tr>
<td><strong>Combination therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van Cutsem et al. (2009)²²</td>
<td>Cetuximab + FOLFIRI vs FOLFIRI</td>
<td>540</td>
<td>348 (64)</td>
<td>43 vs 59</td>
</tr>
<tr>
<td>Bokemeyer et al. (2009)²¹</td>
<td>Cetuximab + FOLFOX vs FOLFOX</td>
<td>233</td>
<td>134 (58)</td>
<td>37 vs 60</td>
</tr>
<tr>
<td>Siena et al. (2010)²⁴</td>
<td>Panitumumab + FOLFOX vs FOLFOX</td>
<td>1,096</td>
<td>656 (60)</td>
<td>48 vs 55</td>
</tr>
<tr>
<td>Peeters et al. (2010)²⁵</td>
<td>Panitumumab + FOLFIRI vs FOLFIRI</td>
<td>1,083</td>
<td>597 (55)</td>
<td>10 vs 35</td>
</tr>
</tbody>
</table>

*For all results presented in the table, results from the control arms are shown first before the experimental arm. KRAS mutational analysis extended into 1,063 patients; KRAS wild type (n=666); PFS 8.4 months (C) versus 9.9 (Ab) months (HR 0.696; P=0.0012); OS 20.0 months (C) versus 23.5 months (Ab) (HR: 0.796; P=0.0093).²⁸ Abbreviations: BSC, best supportive care; m, months; NA, not applicable; RR, response rate; OS, overall survival; PFS, progression-free survival; w, weeks.
POTENTIAL RELATIONSHIP BETWEEN KRAS STATUS AND RESPONSE TO EGFR MONOCLONAL ANTIBODIES, ALONE OR IN COMBINATION WITH IRINOTECAN, IN CHEMOREFRUCTORY PATIENTS

- Nonresponder KRAS mutant 40%
- Nonresponder KRAS wildtype 60%
  - Nonresponder BraF mutation 10%
  - Loss of PTEN or PI3K mutation 10%
  - Reason unknown % unknown
  - Responds to standard dose 22%
  - Responds to increased dose 5%
- KRAS wildtype
- KRAS mutant

Modified after Wong R. J Clin Oncol 2008
Expences to cetuximab decreased by 25% in one Department of Oncology (Herlev Hospital) after testing for KRAS mutation in patients with metastatic colorectal cancer.
Cost-effectiveness analysis of screening for KRAS and BRAF mutations in metastatic colorectal cancer.
Ajah S. Behl et al.

Abstract
BACKGROUND:
In 2009, the American Society of Clinical Oncology recommended that patients with metastatic colorectal cancer (mCRC) who are candidates for anti-epidermal growth factor receptor (EGFR) therapy have their tumors tested for KRAS mutations because tumors with such mutations do not respond to anti-EGFR therapy. Limiting anti-EGFR therapy to those without KRAS mutations will reserve treatment for those likely to benefit while avoiding unnecessary costs and harm to those who would not. Similarly, tumors with BRAF genetic mutations may not respond to anti-EGFR therapy, though this is less clear. Economic analyses of mutation testing have not fully explored the roles of alternative therapies and resection of metastases.

METHODS:
This paper is based on a decision analytic framework that forms the basis of a cost-effectiveness analysis of screening for KRAS and BRAF mutations in mCRC in the context of treatment with cetuximab. A cohort of 50 000 patients with mCRC is simulated 10 000 times, with attributes randomly assigned on the basis of distributions from randomized controlled trials.

RESULTS:
Screening for both KRAS and BRAF mutations compared with the base strategy (of no anti-EGFR therapy) increases expected overall survival by 0.034 years at a cost of $22 033, yielding an incremental cost-effectiveness ratio of approximately $650 000 per additional year of life. Compared with anti-EGFR therapy without screening, adding KRAS testing saves approximately $7500 per patient; adding BRAF testing saves another $1023, with little reduction in expected survival.

CONCLUSIONS:
Screening for KRAS and BRAF mutation improves the cost-effectiveness of anti-EGFR therapy, but the incremental cost effectiveness ratio remains above the generally accepted threshold for acceptable cost effectiveness ratio of $100 000/quality adjusted life year.
Sources of blood-based biomarkers to be used in the routine clinical evaluation

Hanash SM et al. Emerging molecular biomarkers—blood-based strategies to detect and monitor cancer
Nat Rev Clin Oncol 2011:220
A proposed flowchart of the contributions of molecular tests, particularly blood-based tests, to a continuum of applications from risk assessment to molecular diagnosis, targeted therapy and disease monitoring.

General population screening for cancer risk
Family history and/or genetics
+ other clinical risk factors + blood-based biomarker profile

Individuals found to be at high risk
Blood-based screening for early detection

Positive blood-based screen
Imaging modality + diagnostic biomarkers

Definitive molecular diagnosis
Tissue biopsy with molecular profiling

Assessment of response to personalized therapy
Molecular tests to determine effectiveness of targeted therapeutics

Patient follow up
Blood-based tests to monitor for disease regression, progression or recurrence
Future biomarkers to predict treatment failure

- Genetic changes (e.g. KRAS mutation)
- MicroRNA expression profiles
- Protein changes (e.g. HER2 protein expression)
- Development of auto-antibodies against the treatment
- ?
2013 Biomarker research is difficult and expensive
Can we copy Danish Cancer Biobank?
Leddegigt
Biological treatment for patients with rheumatoid arthritis

Den "molekylær targeterede æra"

1999
Remicade 13.08.1999

2000
Anakinra 2001
Enbrel 03.02.2000

2003
Humira 08.09.2003

2006
Orenzcia 05.06.2006
Rituximab 2004

2009
Simponi 01.10.2009
Cimzia 01.10.2009
RoActemra 16.01.2009

...æra af molekylær targeteret terapi

RA
SA
### Den dyreste sygehusmedicin

<table>
<thead>
<tr>
<th>Navn</th>
<th>Behandlings-område</th>
<th>2010 i mio. kr.</th>
<th>Vækst indeks på et år</th>
<th>Biologisk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humira</td>
<td>Gigtbeh.</td>
<td>369</td>
<td>116</td>
<td>Ja</td>
</tr>
<tr>
<td>Remicade</td>
<td>Gigtbeh.</td>
<td>272</td>
<td>110</td>
<td>Ja</td>
</tr>
<tr>
<td>Enbrel</td>
<td>Gigtbeh.</td>
<td>224</td>
<td>106</td>
<td>Ja</td>
</tr>
<tr>
<td>Herceptin</td>
<td>Brystkræft</td>
<td>193</td>
<td>105</td>
<td>Ja</td>
</tr>
<tr>
<td>Lucentis</td>
<td>Øjenmiddel</td>
<td>194</td>
<td>134</td>
<td>Ja</td>
</tr>
<tr>
<td>Mabthera</td>
<td>Lymfeknudekræft + svær leddegigt</td>
<td>155</td>
<td>109</td>
<td>Ja</td>
</tr>
<tr>
<td>Avonex</td>
<td>Sklerose-beh.</td>
<td>132</td>
<td>103</td>
<td>Ja</td>
</tr>
<tr>
<td>Avastin</td>
<td>Mave-/tarmkræft, lungekræft + andet</td>
<td>119</td>
<td>110</td>
<td>Ja</td>
</tr>
</tbody>
</table>

Kilde: Amgros

Cost in 2010 to biological treatment of patients with rheumatoid arthritis in Denmark was: 1.020.000.000 kr.
Cohort: RA bio,
UDKAST 07. Mar 2012 12:52

966 patienter
DANBIO – Årsrapporten 2011

Cohort: RA biol, Drug series: All bio drugs,
UDKAST 07. Mar 2012 12:52

- Etanercept
- Adalimumab
- Rituximab
- Tocilizumab
- Infliximab
- Golimumab
- Abatacept
- Certolizumab
• 30% of the patients with rheumatoid arthritis will not have any effect of the first type of biological therapy

• If a Danish RheumaBiobank was established we could identify new biomarkers for treatment response
Reasons for treatment failure

• Genetic changes
• MicroRNA expression profiles
• Protein changes
• Development of auto-antibodies against the drug
• 🤔🤔
First observations that the material of inheritance was abnormal in cancer cells and consequent proposal that cancers are clones arising due to somatic changes

Description of the double helical structure of DNA

First recurrent chromosomal rearrangement in cancer

First somatic driver mutation and first cancer gene identified

Second-generation sequencing technologies

First sequence of all exons in a cancer

First complete cancer genome sequence

400 known cancer genes

Thousands of complete cancer genome sequences

Cancer genome sequences as a routine diagnostic?
Future control of patients

History

Clinical characteristics

PT/CT, MRI, CT, UL

Genes, RNA, microRNA, proteins, metabolites and next generation sequencing

Patient
Conclusions

- There is a huge need for new and better biomarkers
- Very few cancer biomarkers can today predict treatment response
- Biomarkers will be combined
- Next generation sequencing will be of great benefit but is also a challenge
Patients are different and have different clinical responses and side-effects to the treatment - New biomarkers can hopefully identity patients who will respond to the therapy
The doctor wants:

Treatments with a benefit for the patient and no severe side effects

The patient wants:

The right treatment from the beginning
The Danish Cancer Biobank will be a GREAT resource for discovery of new clinical useful biomarkers for evaluation of treatment response to biologics.

Discovery of new biomarkers is difficult but needed.