Een behandeling op maat voor iedere patient: wat betekent dat in de praktijk?

Emile Voest
Need for personalised cancer treatment

Scenario: patient with metastasized colorectal cancer
Doctor suggests treatment with systemic treatment

Will I suffer from side-effects?
Will this drug work for me?
Are there alternatives?
Need for personalised cancer treatment

- Only subset of patients respond to approved treatments such as chemotherapy and targeted treatments
- Limited but rapidly increasing set of genetic markers but no biomarkers for classical chemotherapy

<table>
<thead>
<tr>
<th>Treatment regimen</th>
<th>Response rate (%)</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPOX-B&lt;sup&gt;1&lt;/sup&gt;</td>
<td>53</td>
<td>Genotoxic + anti-VEGF</td>
</tr>
<tr>
<td>Irinotecan&lt;sup&gt;2&lt;/sup&gt;</td>
<td>13</td>
<td>Genotoxic</td>
</tr>
<tr>
<td>Cetuximab (unselected for KRAS status)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>8</td>
<td>Anti-EGFR</td>
</tr>
<tr>
<td>Cetuximab (KRASwt)&lt;sup&gt;4&lt;/sup&gt;</td>
<td>20</td>
<td>Anti-EGFR</td>
</tr>
</tbody>
</table>

1) Schmiegel et al. *Ann Oncol* 2013;24:1580  
3) Jonker et al. *NEJM* 2007;357:20  
Cancer cells: THESE CELLS ARE INCREDIBLY COMPLEX!

Courtesy L. Wessels
The genome, our DNA

organism  cell  chromosome  DNA

Changes in our DNA (mutaties) can cause diseases such as cancer: Normal DNA means no cancer!!

~3 billion letters: G, A, T, C

Courtesy of E. Cuppen
DNA sequencing technology is rapidly advancing.
Personalized Cancer Treatment: The dilemma

Every patient is unique

Groups quickly become small, especially in combination with available treatments: large experimental cohorts required!
Impact of targeted therapy on survival

- Trastuzumab
- Vemurafenib
- Erlotinib
- Crizotinib
- Nivolumab

**Progression free survival**

- Soloman 2014 NEJM – First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer
- Robert 2015 NEJM – Nivolumab in Previously Untreated Melanoma without BRAF Mutation

**Overall survival**

- Zhou 2011 Lancet Oncol – Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study
Better use of existing medication
Better use of existing medication?

**Her2 overexpression** occurs in many other tumor types:
- Gastric cancer: 10-30%
- Esophageal cancer: 0-83%
- Ovarian cancer: 20-30%
- Endometrial cancer: 21-47%
- Lung cancer: 20%

Etc.

**Her2 based treatment in gastric cancer** has also resulted in **improved survival**
Similar mutations can be found across tumor types

Table 1 BRAF mutations in human cancer

<table>
<thead>
<tr>
<th>Nucleotide</th>
<th>(1) Mel. STC</th>
<th>(2) Mel.</th>
<th>(3) Colo. ca.</th>
<th>(4) Ovarian*</th>
<th>(5) Sarcoma</th>
<th>(6) Other†</th>
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<td>4</td>
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No. samples screened: 15, 9, 33, 35, 182, 104, 923

Per cent: 80%, 67%, 12%, 14%, 0.5%, 0%

Response rate BRAF V600E mutant tumor to vemurafenib:

- 80% in melanoma
- Only 5% in colorectal cancer

Davies 2002 Nature
Kopetz 2010 JCO
Prahallad 2012 Nature
Every patient has multiple tumors: Highly branched evolution in ovarian cancer

Primary tumor

Metastases omentum

Control (blood)

Metastases ovary

TP53 I102N
SBK2
THBS3
MSH3

TP53 P278L
TAF1
DNAH11
PIK3R5
...

Metastases
Reconstructing tumor history

Mate-pair data
1,420 somatic breakpoints

Common in all

Common in 1.1, 1.2, 1.4 & 1.5

Common in 1.1 & 1.2

Common in 1.4 & 1.5

Common in 1.7, 1.8, 1.9 & 1.10

1.1 1.2 1.4 1.5 1.7 1.8 1.9 1.10
Intrapatient variability: mixed responses to treatment and the value of paired biopsies

<table>
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<tr>
<th>Date sample collection</th>
<th>Treatment phase</th>
<th>Biopsy / Surgery</th>
<th>Material</th>
<th>Response to treatment</th>
<th>Specimen</th>
<th>Tumor %</th>
<th>Conc ng/µl</th>
<th>Volume</th>
<th>DNA yield (ng)</th>
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</tbody>
</table>
Bringing data together!

DATABASE:
SYSTEMATIC DATA INTEGRATION AND MINING

Patient data
Treatment and response
Pathology and lab
Genomic data

eZIS/EPD
eCRF
LMS pathology
Research DB

Public data

Patient rapport
Biomarker discovery

Patient
Medical Specialist
Pharma

Future patient

Society
Insurance companies

Stakeholders
Voor gepersonaliseerde zorg bij kanker

We weten tegenwoordig ongelooflijk veel meer over hoe kanker werkt, maar helaas heeft dat nog niet geleid tot grote veranderingen in de manier waarop we kanker kunnen behandelen. Dit komt in grote mate doordat we nog steeds een behandeling kiezen die voor de meeste mensen met dezelfde vorm van kanker werkt en niet is afgestemd op de individuele patiënt. Het Center for Personalized Cancer Treatment (CPCT) probeert hier verandering in te brengen door het genetische materiaal, het DNA, op een dusdanige manier te analyseren aan het begin van het behandeltraject zodat in de toekomst voor elke patiënt een behandeling op maat kan worden aangeboden.
• CPCT Aim:
  • participation of NKI and all 8 UMCs
  • Followed by all 28 large teaching hospitals
National scaling: Hartwig Medical Foundation

Centralized Facility in a Not-for-Profit Foundation setup
- Made possible through philanthropy (2 to 3 years)
- Whole genome sequencing using **Illumina Xten** setup for > 7000 patients
- Integrate clinical and genetic data
- Provide input for individual patient reporting
- Provide access to cohort information for research to benefit future patient care

Location: Matrix VI, Amsterdam Science Park
Operational: Summer 2015
Return of genetic results in oncology:
Patient oriented flow chart on tiered consent

Components of DNA guided decision making

- Ethics
- Biobanking
- Education
- Big data/ict

- Genome data analysis and interpretation
- Large scale genome sequencing
- Data sharing (national/international)
- Standardisation and integration of clinical data
- Returning genetic data to patients and physicians
A new dimension in personalized medicine: Tumour organoids

- Human colorectal cancer organoids
- Living tumors of individual patients

Sato et al. Gastroenterology 2011
Genetic similarity organoid and biopsy

Biopsy procedure

- Biopsy specimen
- DNA isolation
- DNA sequencing AB SOLiD 2000 gene set
- Compare tumor biopsy and tumor organoid

Organoid culture

- Compare tumor biopsy and tumor organoid

Biopsy and Organoid overlap:

- **Biopsy**
  - 114 genes
  - 0 overlap
  - 13 common genes

- **Organoid**
  - 120 genes
  - 9 overlap
  - 0 common genes

- **Biopsy**
  - 124 genes
  - 0 overlap
  - 7 common genes

- **Organoid**
  - 126 genes
  - 0 overlap
  - 15 common genes

- **Biopsy**
  - 132 genes
  - 0 overlap
  - 9 common genes

- **Organoid**
  - 0 overlap
  - 0 common genes
First patient included in TUMOROID trial

Untreated control  5 µM 5-FU

D14

TUM-1

![Graph showing relative viability vs. [5-FU] (µM)]
Additionally, significant savings potential for payors from personalized medicine in preventing adverse events

<table>
<thead>
<tr>
<th>Value drivers for payors</th>
<th>Drug</th>
<th>AEs avoided per year (K)</th>
<th>Estimated cost per AE ($K)</th>
<th>Estimated savings through genotyping ($M)</th>
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</thead>
<tbody>
<tr>
<td>Reduce non-responder drug spend</td>
<td>Drug A</td>
<td>~150</td>
<td>12</td>
<td>~1.800</td>
</tr>
<tr>
<td>Reduction of Adverse events</td>
<td>Drug B</td>
<td>~20</td>
<td>25</td>
<td>~500</td>
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<tr>
<td>Utilization of generics</td>
<td>Drug C</td>
<td>~15</td>
<td>5</td>
<td>~75</td>
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<tr>
<td>Patients back to work quickly</td>
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<td></td>
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</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Total potential savings of over 2 bln per year in the US just for these three drugs

SOURCE: Provider patient population pilot in US
Conclusions

• We are making progress!!!!

• Many new drugs have reached the market

• Finding the right patient for the right drug is the challenge!

• Imaging, DNA, CTC, organoids will provide better insight in who and how to treat