Challenges for the application of genome sequence in cancer research and medicine

Norwegian Cancer Genomics Consortium

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All patients are different ...

- Normal genetic variation *and congenital mutations* will affect
  - cancer risk and disease properties
  - Immune response
  - Interactions between cancer cells and surrounding tissue
  - Pharmacokinetics and therapy response
  - Side effects

- Genome sequencing reveals huge "private" genetic variation
  - We do not know yet how to interpret this
All cancers are different

• Every type has different subtypes originating from cell types with different properties
• Within each subtype there are different mutation spectra and thus different mechanisms that “drive” the cancer
• Also within each tumour there are subpopulations of cells with different mutations and properties
Clonal evolution of cancer mutations

Clonal evolution of a tumour
Resistant sub-population of a tumour
Mosaic amplification of target genes

(B) Intermingled subpopulations with mutually exclusive EGFR (red) or MET (green) amplification.

Snuderl et al. Cancer Cell 2011
New targeted therapies

- Require deeper biological understanding
  - Sensitive tumours may be treated
  - Resistant tumours may be given other options
- Costly treatment may be prioritized better
- Some patients with other tumour types may be eligible for already approved treatments
Genome-wide detection of tumour mutations

- Need normal control from each patient (blood)
- Both are sequenced, differences in tumour sample are mutations
  - Are mutations common across samples?
  - Is the mutated gene active?
  - Is it noise, a driver or an Achilles heel?
  - What fraction of the tumour is mutated?
Personalized medicine – the hype …

N-of-One—On the Leading Edge of a Revolution in Cancer Care

Patients want the best possible medical care, especially when they are fighting cancer. But there are obstacles:

- Cancer treatment is one of the fastest moving fields in medicine. The explosion of research is overwhelming, and it is challenging to keep current.
- Doctors don’t always agree on the best way to treat particular cancers.
- Medical information travels slowly. It can take a year or more for breakthroughs to become standard practice.
- Cancer treatments are extremely expensive and often have serious side effects, particularly when they target all dividing cells including healthy ones.
- For rare and advanced cancers, the best options are often found in clinical trials, but finding the right trial to enter can be difficult.
NCGC Phase 1

- Full exome, i.e. “all genes” (≈2% of genome)
- Approx 1000 sample pairs

- Cancer types:
  - Breast
  - Lymphoma
  - Leukemia
  - Colon
  - Malignant melanoma
  - Sarcoma
  - Multiple myeloma
  - Prostate
Norwegian Cancer Genomics I
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NCGC data logistics

- Clinical data
- Sequence
- Bioinformatics
- Myeloma
- Lymphoma
- Leukemia
- Colon
- Melanoma
- Myeloma
- Prostate
- Breast
- Sarcoma

Filtering, somatic mutations only

Secure storage and transfer

Selected mutations

Cancer registry

Clinical data

Accumulated national data

OUS/UiO

UiB

NTNU

[UiT]
Secure and Non-secure Data

Sensitive data
- Personal genomes
- High data security

Somatic mutation data
- Low data security

Sequencing
- Mutation detection

Hospital Secure
- Closed Network

Downstream functional analysis and therapeutic interpretation

Collaboration with
- Center for Cancer Biomedicine
- HSØ Genomics facility
- HSØ Bioinformatics Core Facility
- University of Oslo IT (USIT)
NCGC Objectives

- Establish a national network for the implementation of (genome-based) personalization of cancer medicine
- Provide and disseminate deep sequencing methodology for detection of cancer mutations
- Perform research to determine the usefulness of mutation screens to guide cancer treatment
NCGC Objectives

• Establish, provide and disseminate bioinformatic methods and tools to interpret the clinical impact of tumour mutations

• Establish a national tumour mutation database together with the Cancer Registry

• Initiate a dialogue with the health service on how cancer treatment should be personalized

• Investigate health economic scenarios for the introduction of these treatment strategies

• Lay a foundation for equal access to these kind of diagnostics across all regions.
... the Norwegian approach is wise to take account of other equally vital considerations such as having nationally agreed protocols and systems to handle and process new testing and data, as well as efforts to underpin health professional and public education, and provide health economic impact data. ...
Ethical questions?

• In a research setting – looking only at somatic mutations

  ✓ Genomic privacy – data protection
  ✓ Right of access to personal research data?
  ✓ Should the treating clinician be informed about possibly actionable mutations?
    • How certain do the data need to be?
Ethical questions?

• In a research setting – looking at the germ line
  ✓ Genomic privacy – data protection
  ✓ Right of access to personal research data?
  ✓ How to handle possible high-risk variants or mutations (inherited or *de novo*)
  ✓ Reuse of data in other contexts
    • We have to be faithful to the consents
Ethical questions?

- In a clinical setting
  - Results need to be validated by clinically approved lab
  - Treating new patient groups with therapies approved for other cancers
    - Side effects probably the same, but do they work?
    - Personalization leads to break-down of the randomized trial concept
**Introduction**

We were today (29/3-2012) informed that our project will be funded by a substantial grant from the Norwegian Research Council, under the Program for publicly initiated clinical cancer studies!

After the presentation at Cancer Crosslinks in January, our national strategy for genomics-based cancer medicine gets international attention:

The July 2012 special issue on cancer technologies gives special attention to our project (see int'l coverage).