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 congential 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 sybtypes 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

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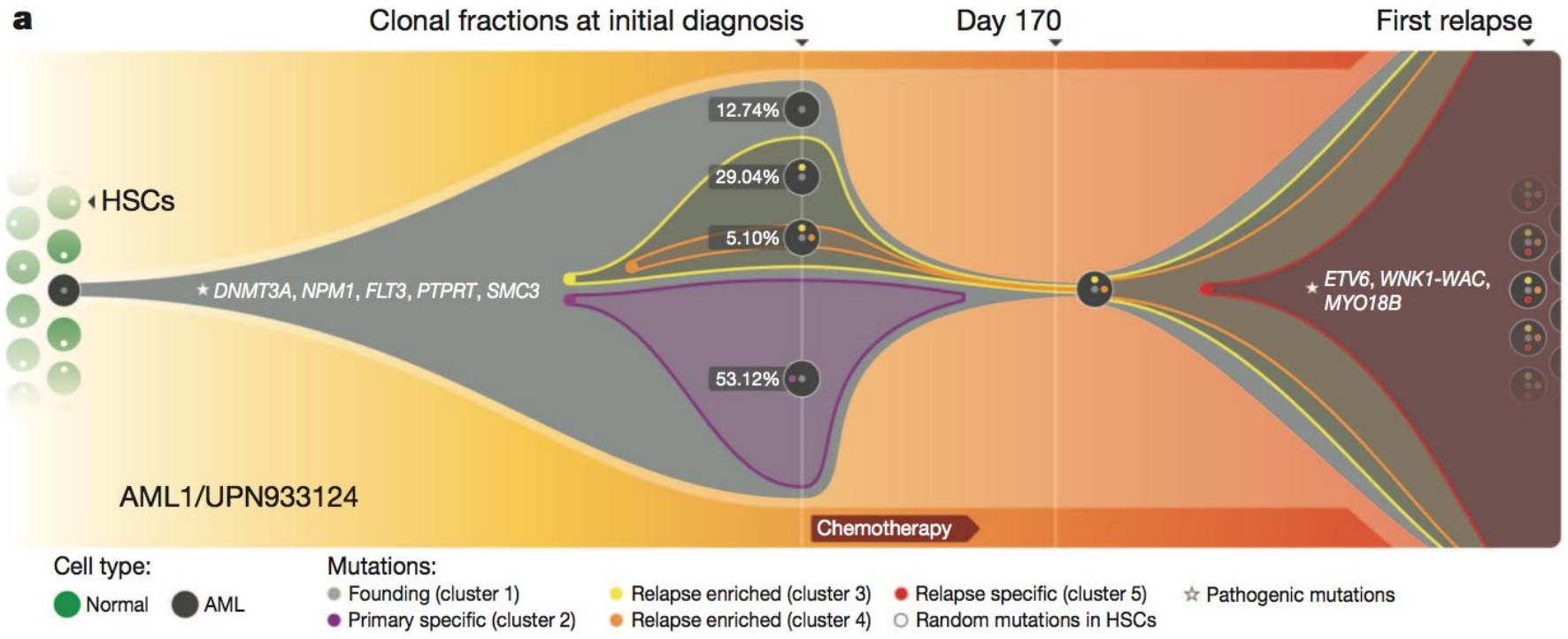
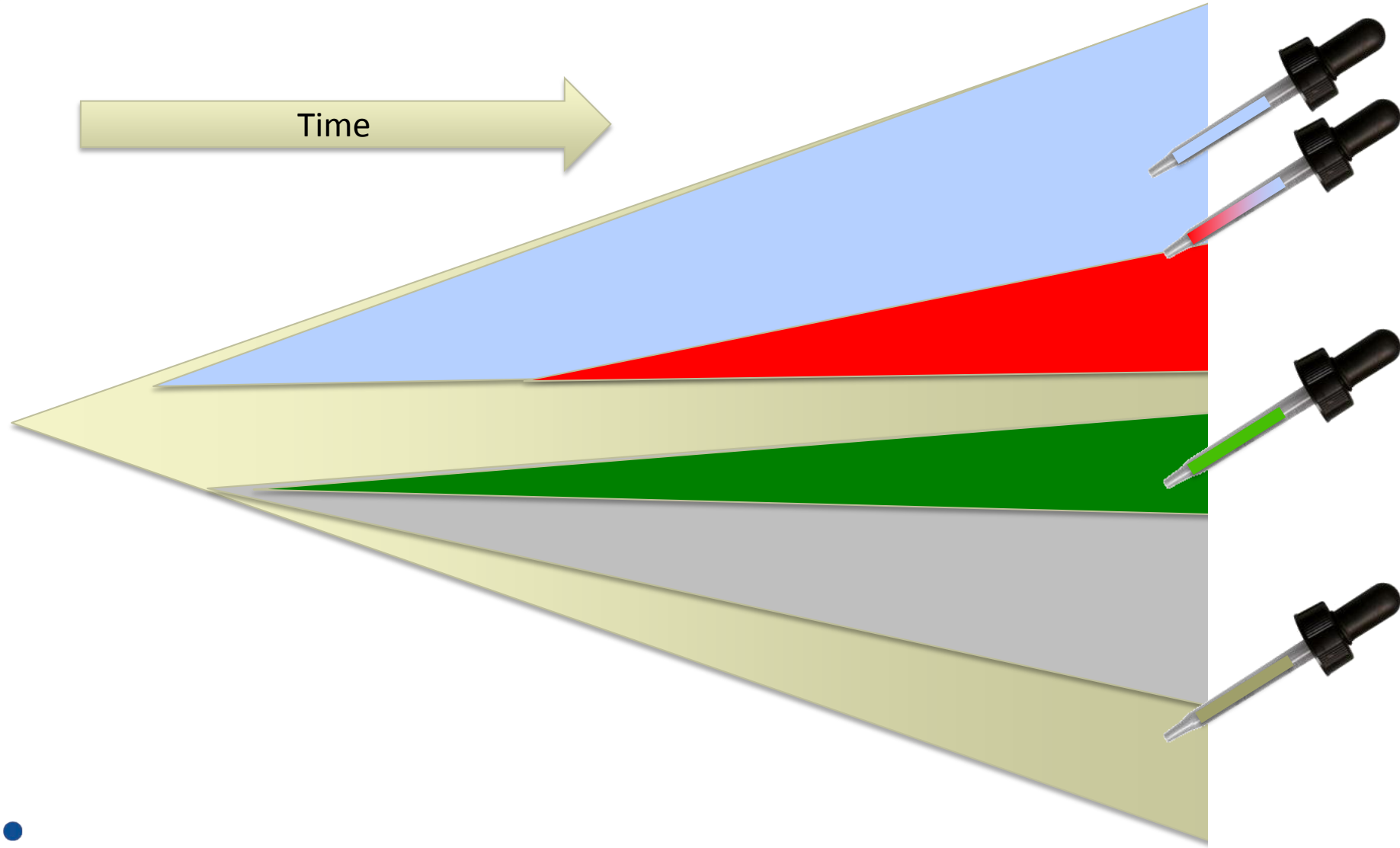


Ding, et al. & John F. DiPersio NATURE, VOL 481 p506, 2012

Clonal evolution of a tumour



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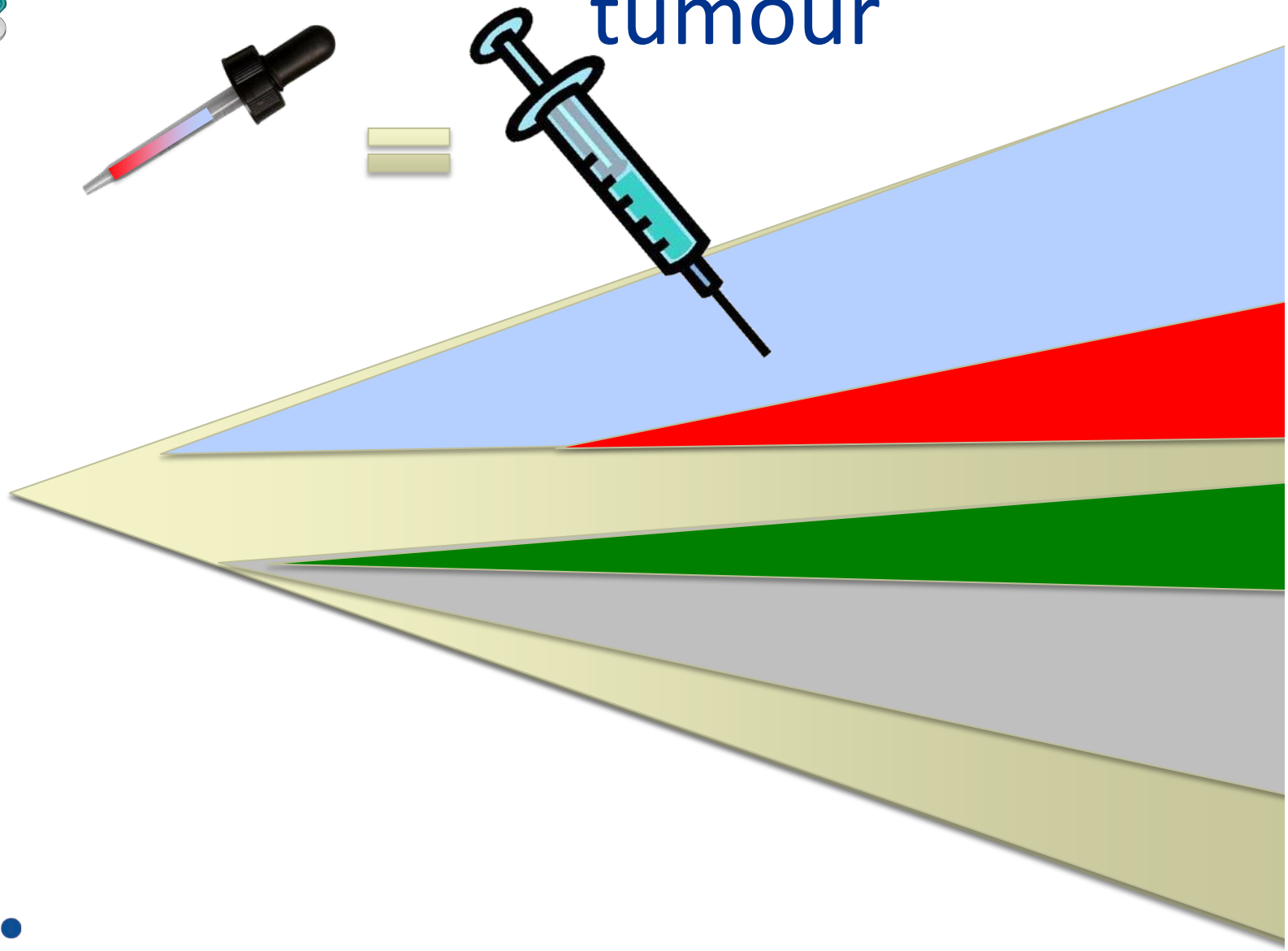
Resistant sub-population of a tumour



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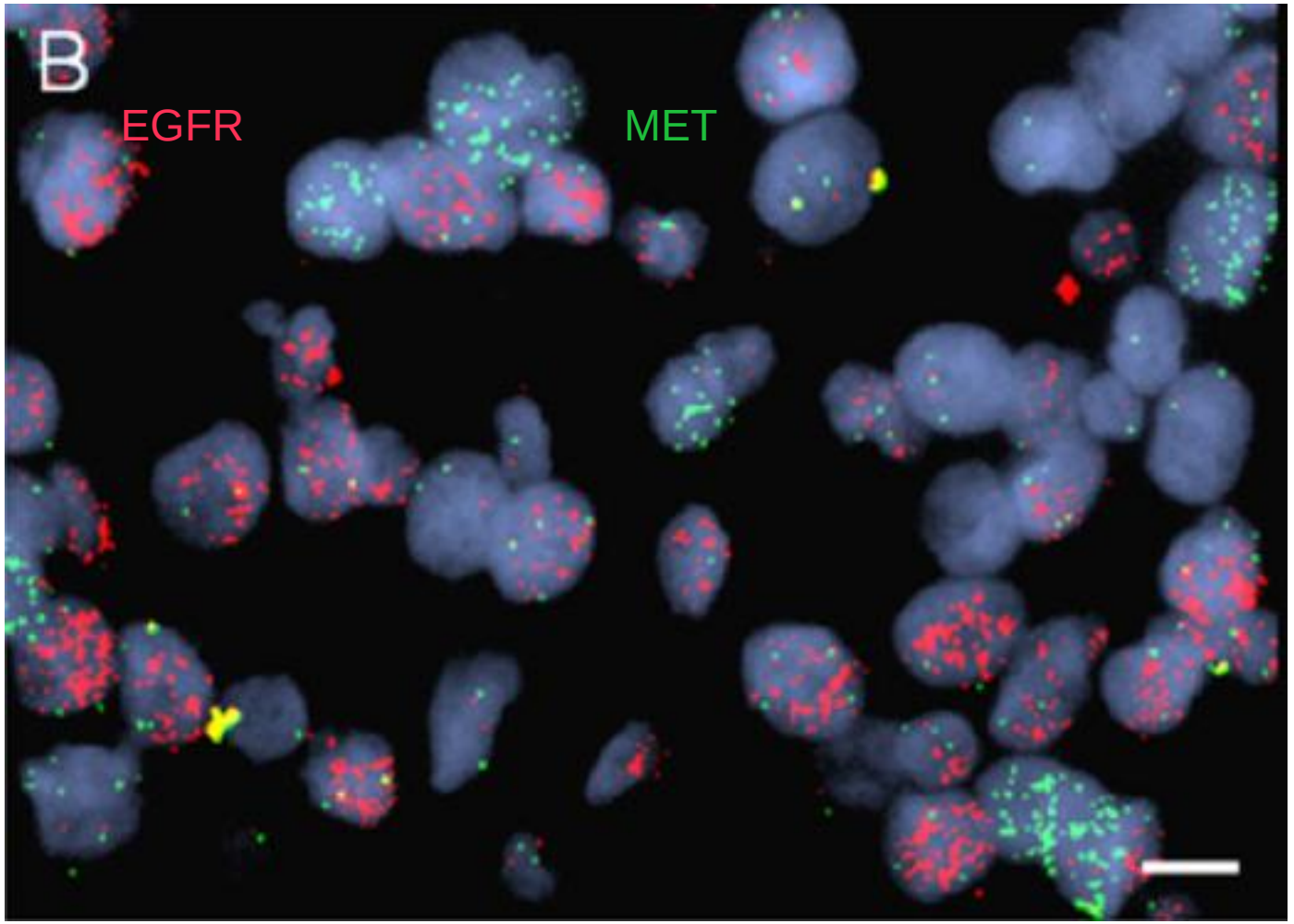
Mosaic amplification of target genes



(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 treaments

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 …

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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.

Watch Jennifer Carter featured on:

Is MY cancer different?™

providing an Expert Insight on the

EVOLUTION OF CANCER TREATMENT

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

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CANCER Registry of Norway

Oslo University Hospital

Haukeland University Hospital

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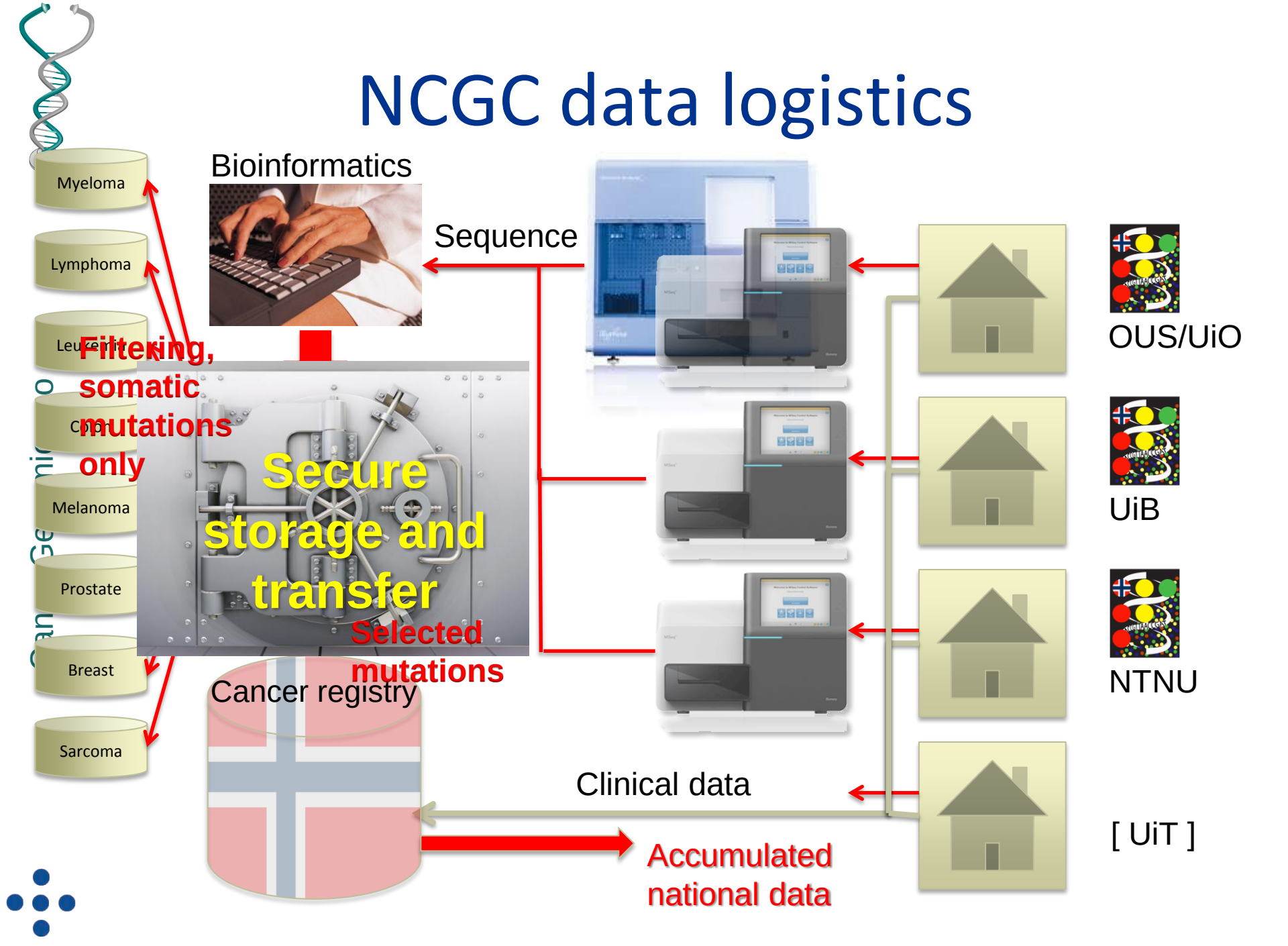
NCGC data logistics



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

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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.

Norwegian Cancer Genomics Consortium

A national health service collaboration to establish and evaluate genome-based diagnostics for cancer therapy decisions

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Holistic approach to clinical cancer genomics in Norway

7 February 2012 | By

Sources: Nature, Ge

Norway has taken
towards creating a
genomic diagnostics

The first clinical
next-generation seque
technologies have been widely

… 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

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  - Kick-off at the OCC Cancer Crosslinks Meeting in January
  - Project presentation at Cancer Crosslinks Jan 2012
  - Presentation at the Dagens Medisin Arena
- Related projects
- Relevant meetings

Introduction

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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:

nature biotechnology

The July 2012 special issue on cancer technologies giives special attention to our project (see intl coverage)

nature International weekly journal of science

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