NCMM

Centre for Molecular Medicine Norway

Nordic EMBL partnership for Molecular Medicine

From disease mechanisms to clinical practice

”

Hvis det ikke var for stor variabilitet mellom pasientene, ville medisin vært en eksakt vitenskap og ikke en kunst.

Sir William Osler
Johns Hopkins School of Medicine
Baltimore 1892

Human genome – what does our genes do?

Nature, 437: 1241-42, 2005 – reproduced with permission

GENOMICS

Understanding human diversity

David B. Goldstein and Gianpiero L. Cavalleri

Variation : 1 per mille or 6-10 millions small differences that together constitute our **individual genetic "make-up"**

”The normal is the rarest thing in the world”
- Vi er alle unike

- *~10 millioner SNPer skiller 2 individer fra hverandre*
- *30 – 80 SNPer er tilstrekkelig til å identifisere et individ*
- *SNPer arves i blokker som kalles haplotyper*

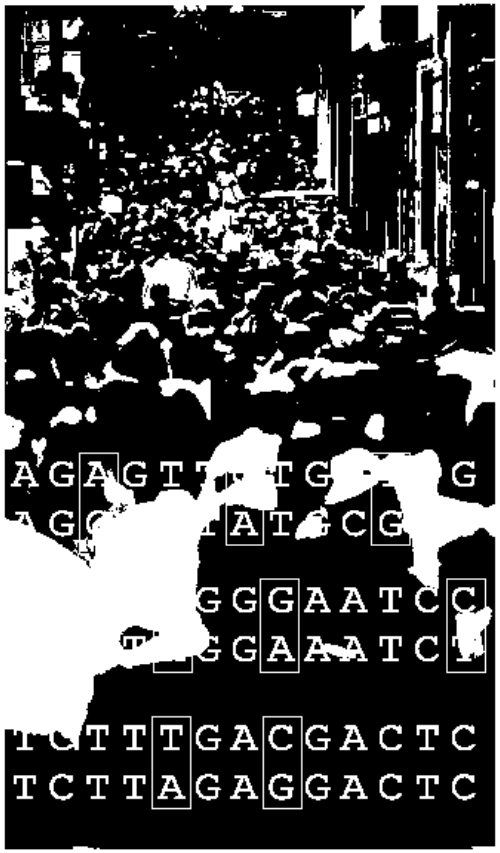
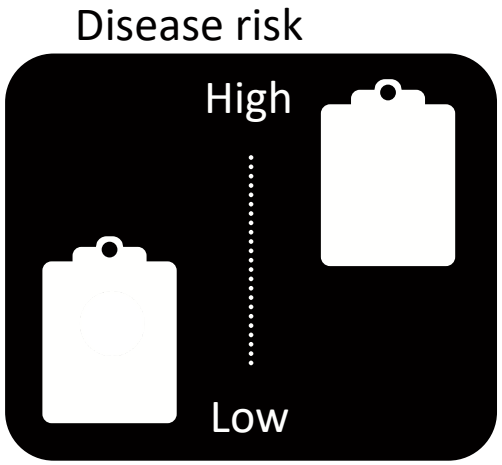
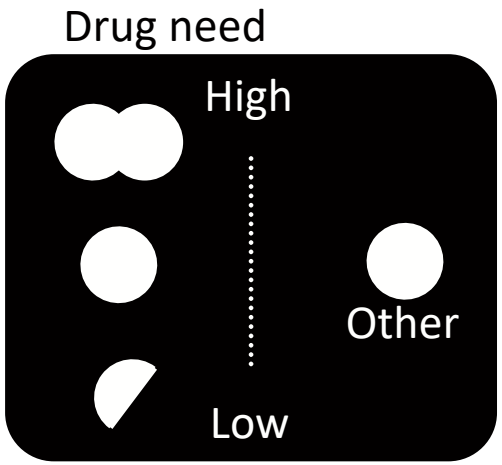


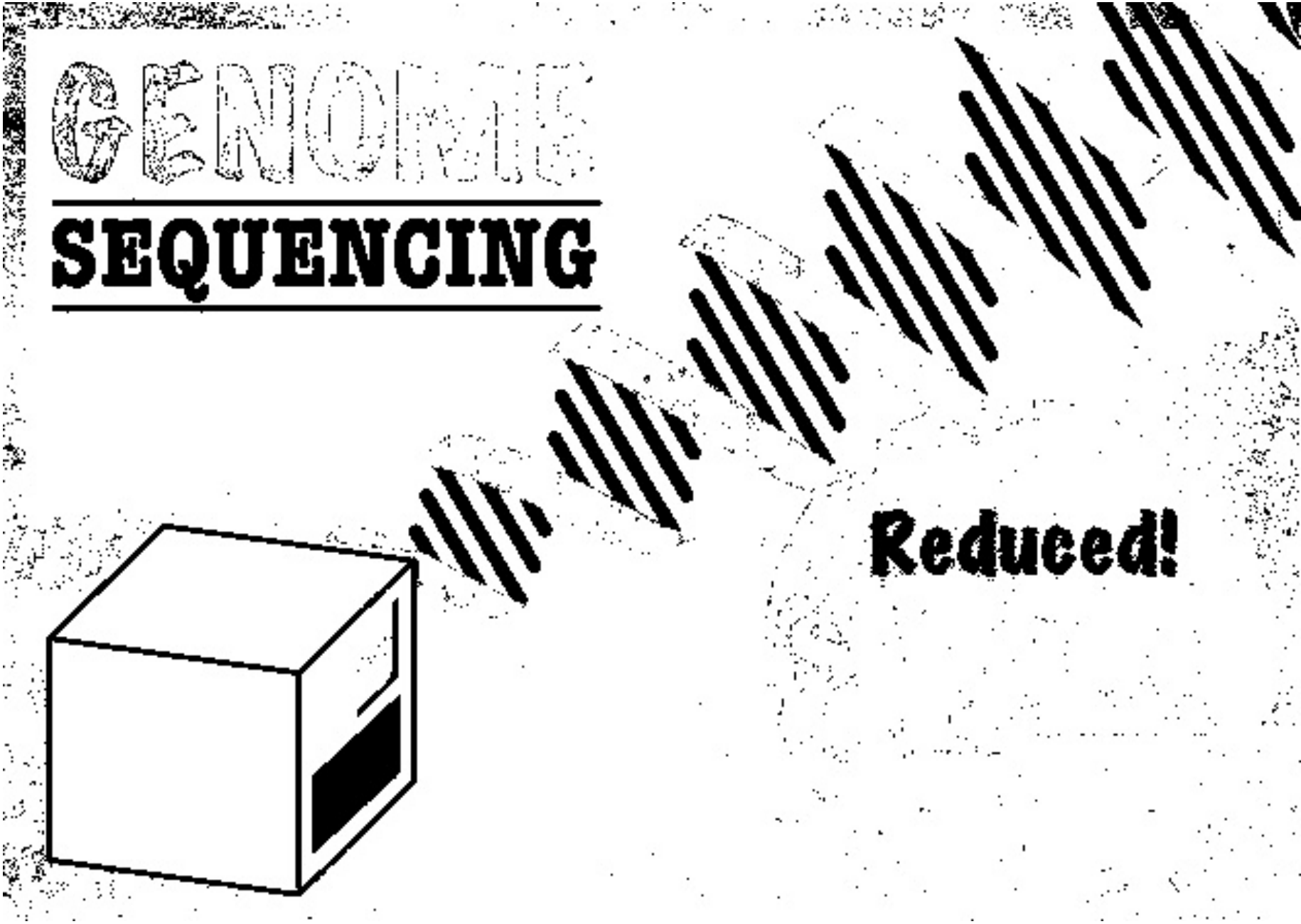
Figure 1 The most common sources of variation between humans are single nucleotide polymorphisms (SNPs) — single base differences between genome sequences. Fragments of two sequences, with eight SNPs, are shown.

Variability; SNPs





SCIENCE SHAPED



Source: Hayden, E.C., Nature , 507 (294-295), 2014

Evidence-based vs tailored medicine

Access to Precision Medicine

N-of-One works with you and your medical team to create a diagnostic and treatment strategy tailored to YOUR specific tumor type and molecular profile

Learn More

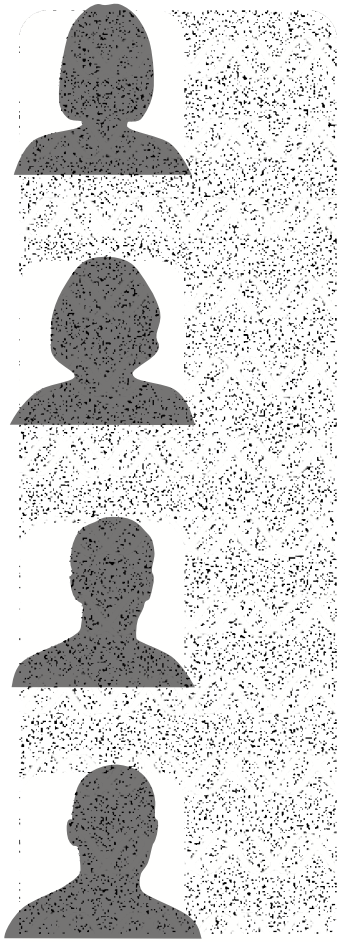
N-of-1 Trials: A New Future?

Eric B. Larson, MD, MPH

Group Health Research Institute, Seattle, WA, USA.

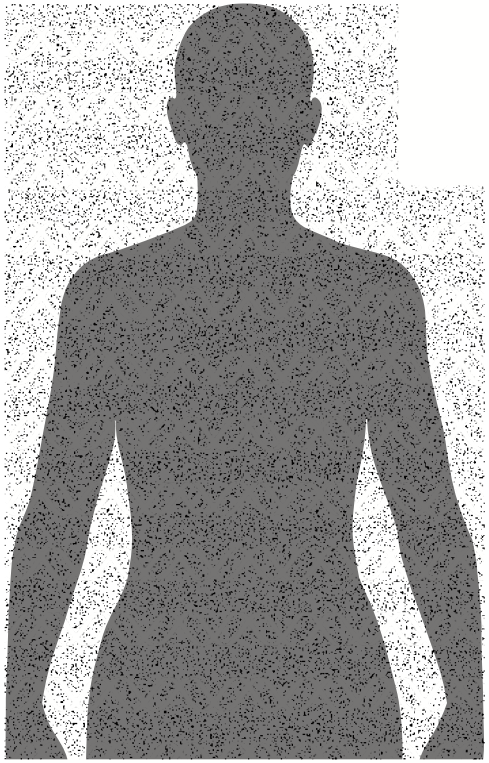
Personalized medicine: a competitor of evidence-based medicine?

10.2217/PME.11.93 © 2012 Future Medicine Ltd *Personalized Medicine* (2012) **9**(2), 211–221 ISSN 1741-0541 **211**



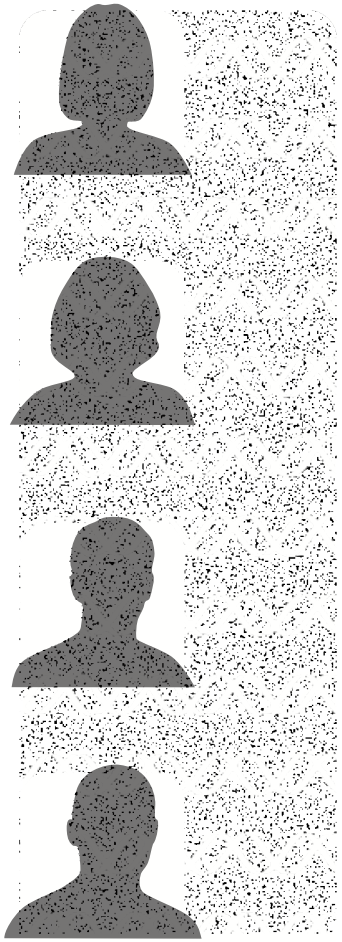
Utfordring med individualisert medisin

- Hver pasient sin sykdom
- En sykdom i hver pasient
- Alle observations er n=1
- Utfordrer sykdomsklassifikasjon og diagnosesystemer



Framtid i molekylærmedisin

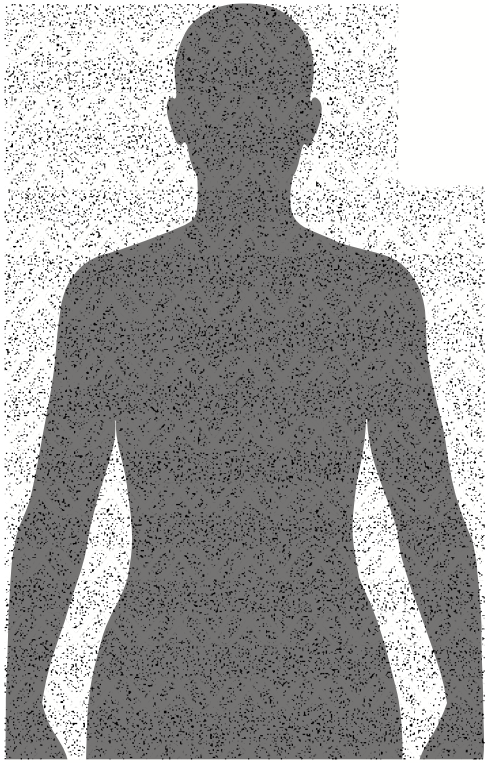
- Kjenne alle sykdomsgener
- Kunne diagnostisere feil i alle disse (dog uten at det nødvendigvis finnes behandling)
- Ha mulighet til å iverksette forebyggende tiltak
- Koble spesifikk diagnostikk med målstyrt og individuell behandling
- DETTE HAR ALLEREDE STARTET I KREFTBEHANDLING



Dyrt og eksklusivt?

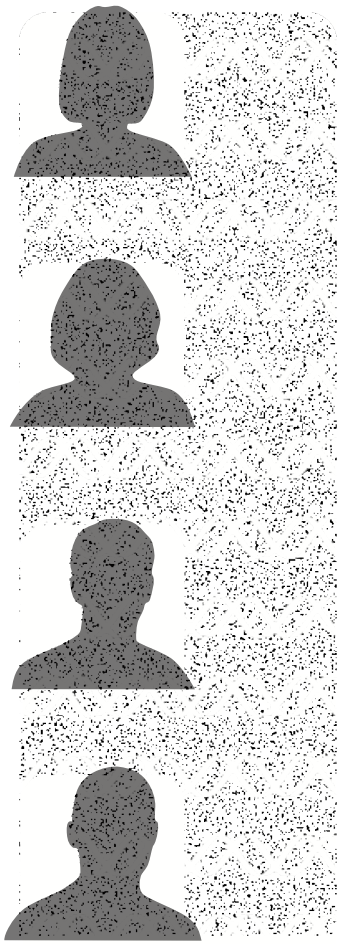
- Internasjonal utvikling
- Forventning
- Kan bli dyrt, eksklusivt og bare tilgjengelig i rike land
- Gradvis og asynkront
- Betalingsvilje og prioriteringsspørsmål
- Presendens

..Eller investering i fremtidig pasient-nytte og bedre helseøkonomi?



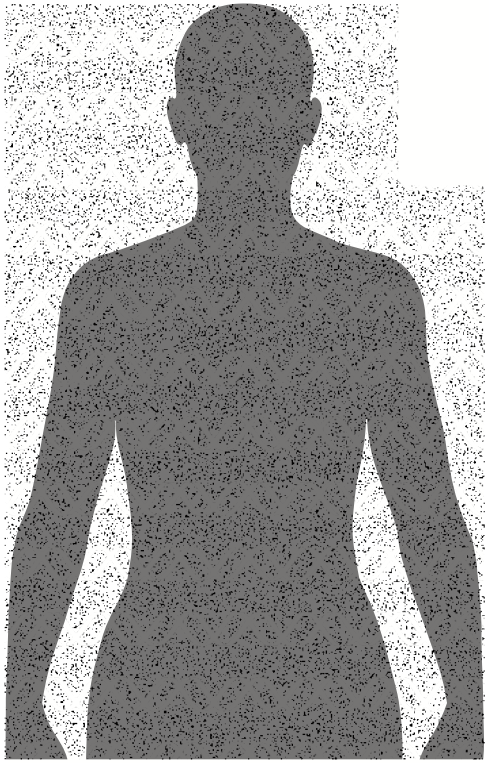
- Behandling rettet mot årsak i hver enkelt pasient
- God behandlingseffekt hos de man behandler og dermed god effekt av ”investeringen”
- Ikke behandle pasienter som man vet ikke vil ha effekt -unngår bivirkninger, falske håp og sparer kostnader
- Kostnadseffektive intervensjoner i livsstil i riskogrupper
- Forskning og utvikling som foregår i dag kan gi fremtidig pasient-nytte og mulig helseøkonomisk gevinst

Investeringer i skreddersydd medisin?



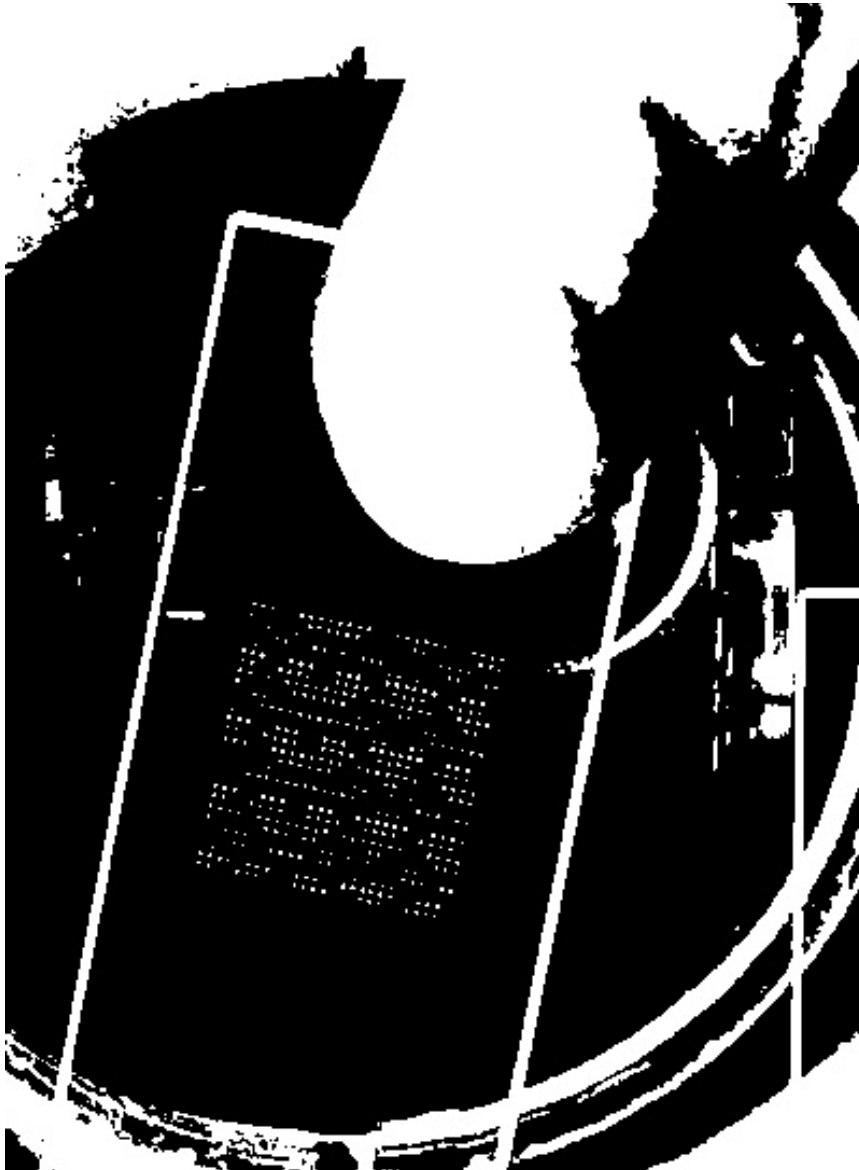
- Internasjonal utvikling – ønske om nasjonale tilbud
- Krever infrastruktur og ekspertise
- Kunnskap om særskilte genetiske risikofaktorer for norsk befolkning
- Prising viktig faktor –Pris per pasient opp når mengden pasienter går ned pga stratifisering, men god effekt på de som behandles. Samtidig ikke ta ut hele innsparingen i økt pris, dvs balanse.
- ”Utgifter” til medisinisk forskning innen dette fagområdet kan sees som investeringskostnader i et helseøkonomisk perspektiv

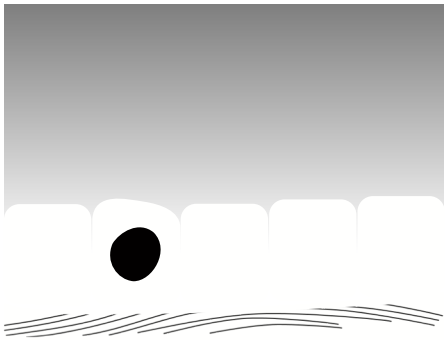
Hva kan gjøres nå?



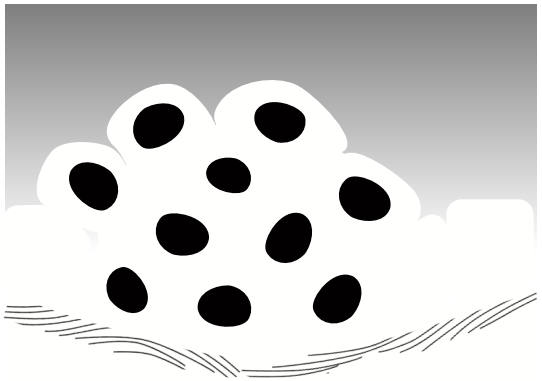
- Industrien:
  - ”One-drug-fits-all” forlates
  - Companion diagnostics
  - Stratifisering
- Offentlig sektor:
  - Standarder for individbasert behandling
  - Bekreftende undersøkelser og helseøkonomi
  - Biobankmaterialer og helsedata - rask validering av nye tester
  - Kvalifiserte avgjørelser med bakgrunn i klinisk effekt, pasientnytte og god samfunns- og helseøkonomi

Skreddersydd medisin og individ-tilpasset kreftbehandling

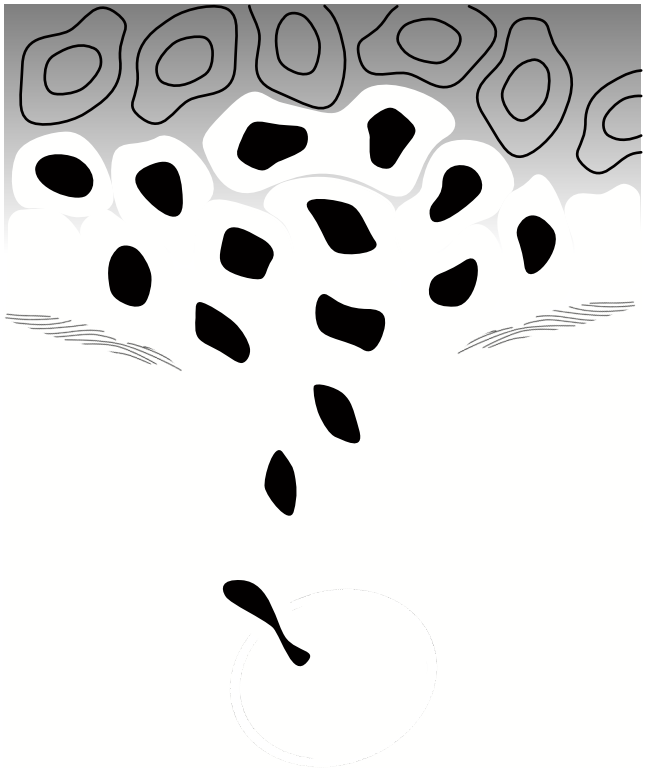




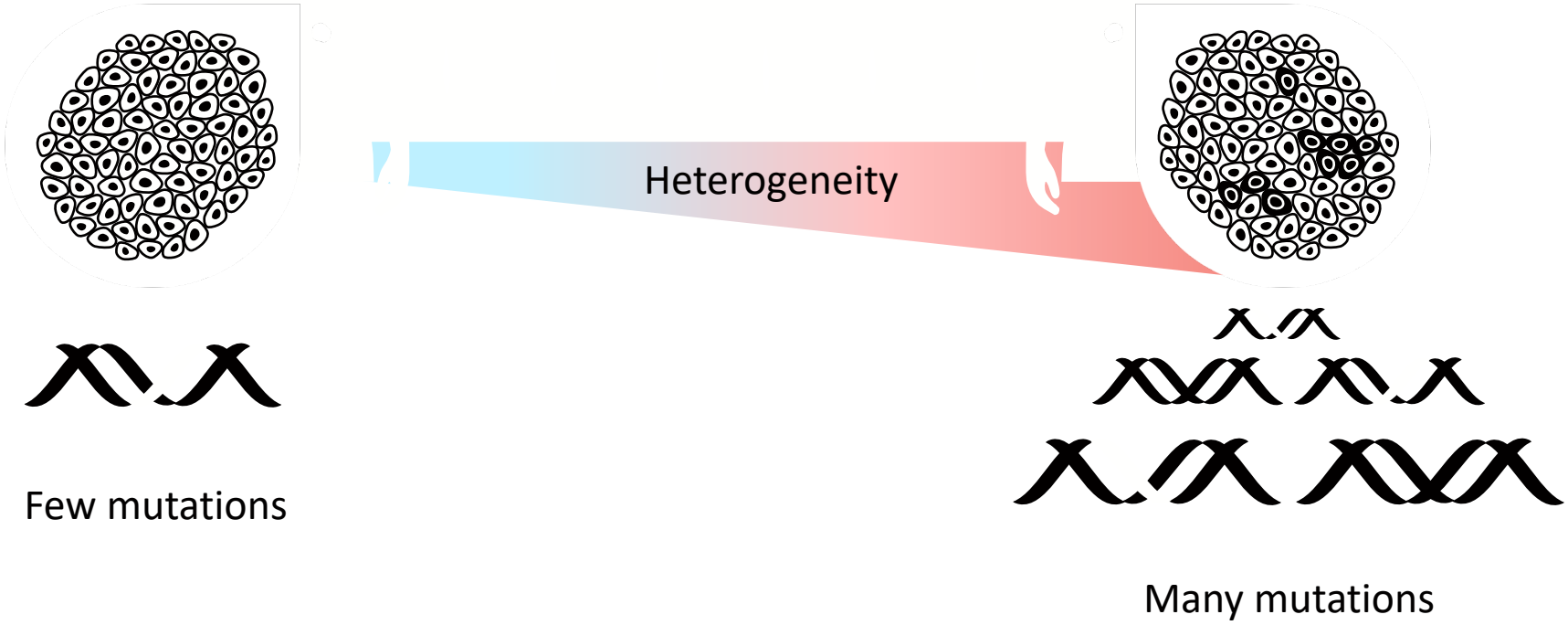
Mutation

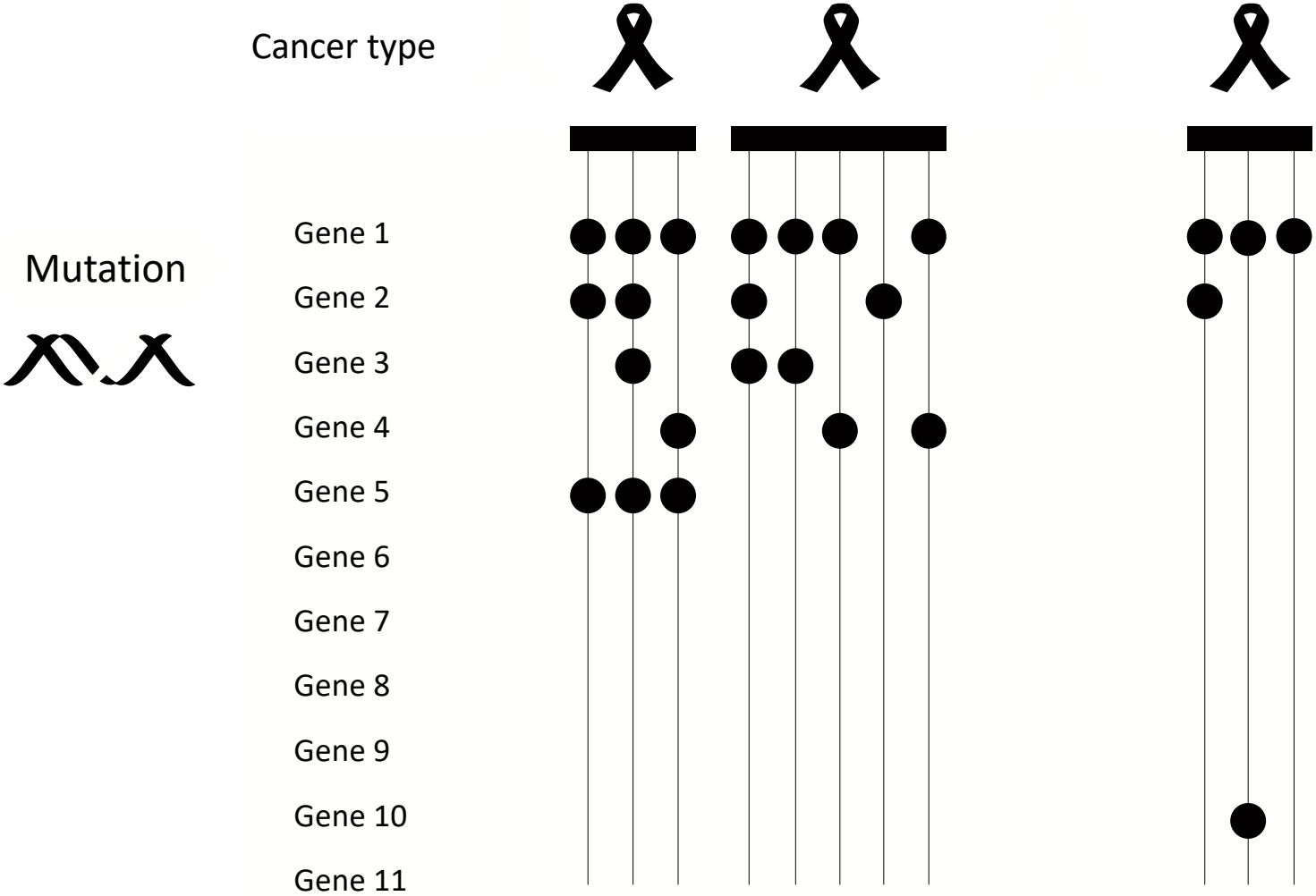


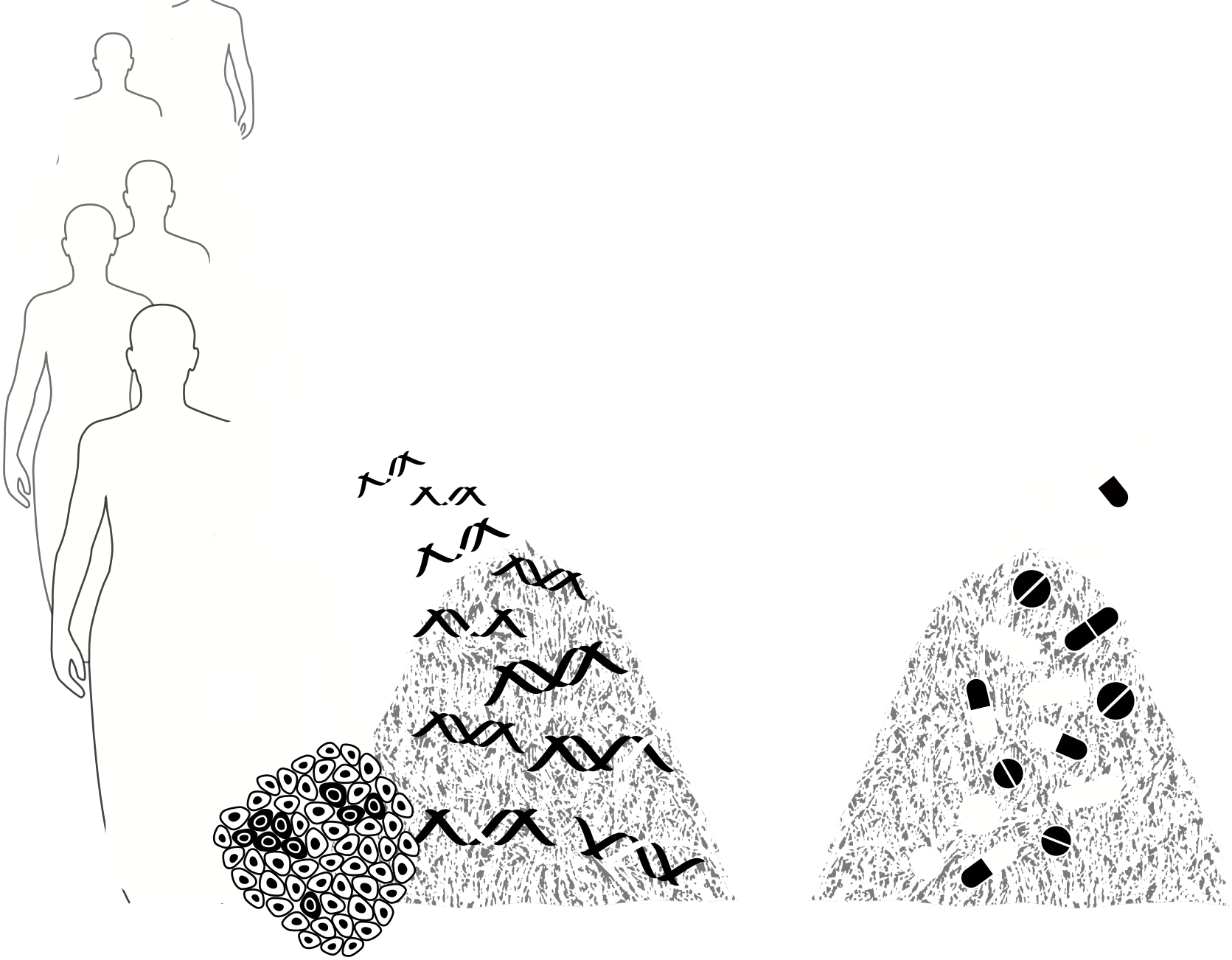
Uncontrolled cell growth



Breach of boundaries


Heterogeneity
Few mutations
Many mutations


Cancer type
Mutation
Gene 1
Gene 2
Gene 3
Gene 4
Gene 5
Gene 6
Gene 7
Gene 8
Gene 9
Gene 10
Gene 11



HELSE SØR-ØST

KREFTFORENINGEN

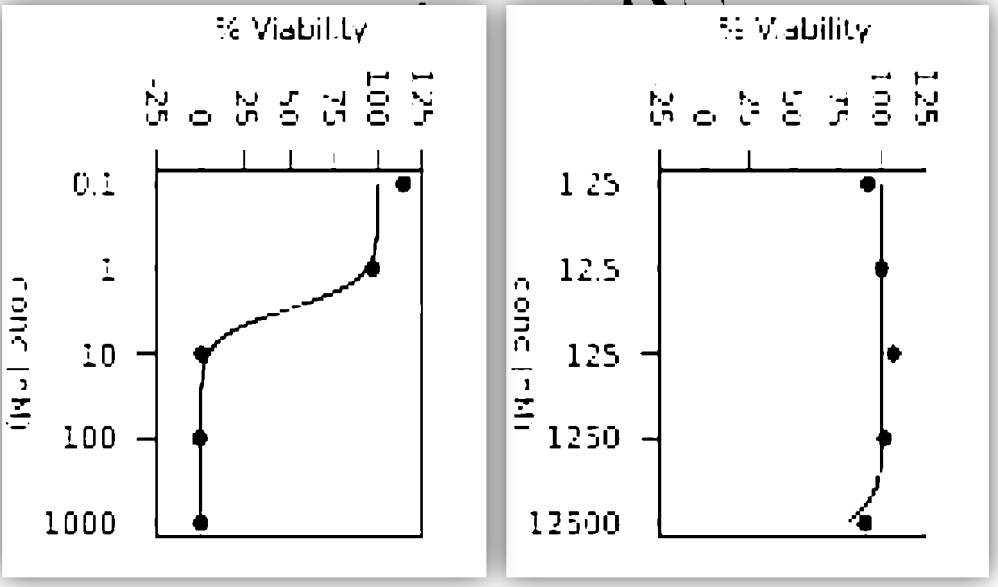
Oslo University Hospital

The Research Council of Norway

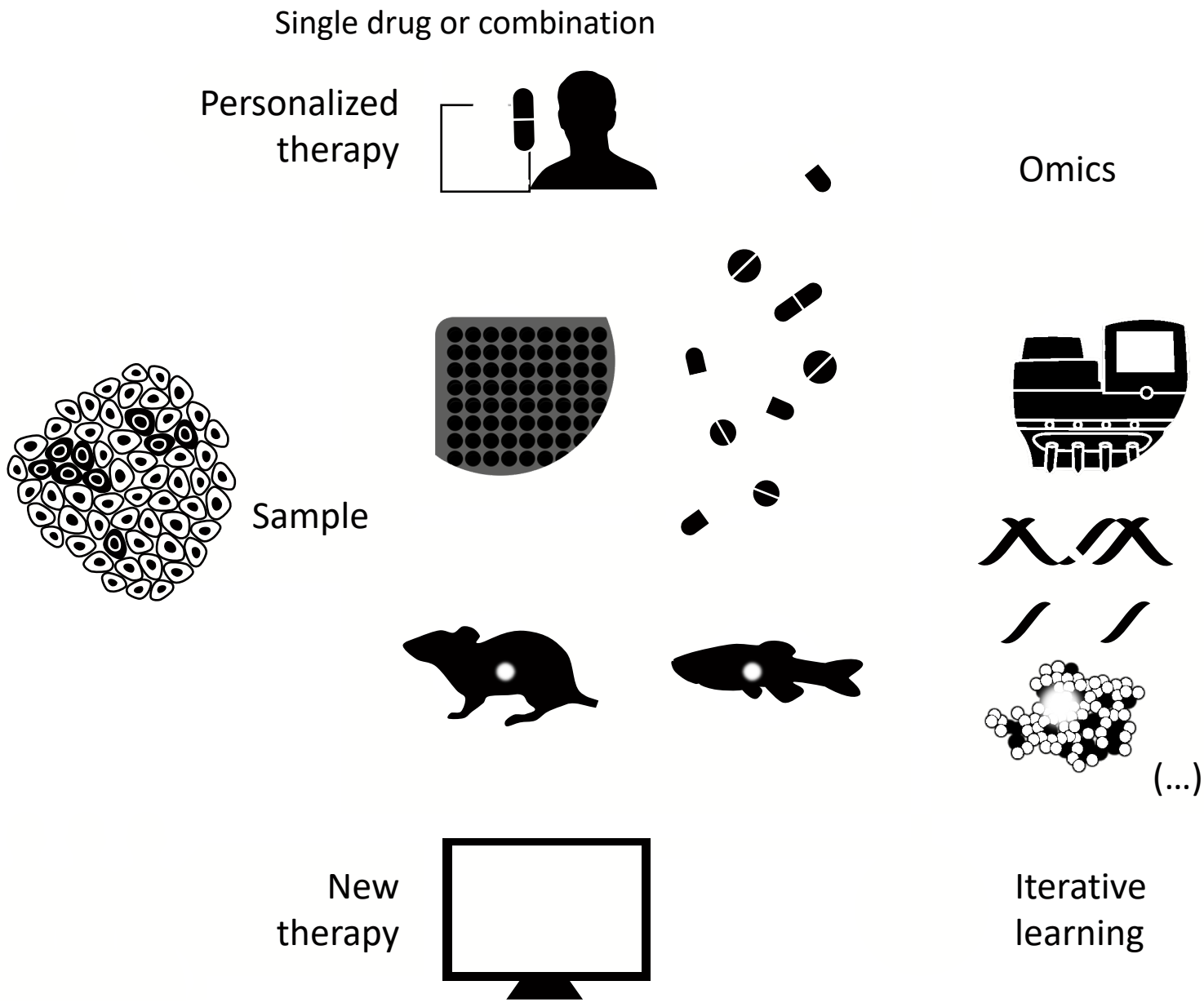
Hematology pipeline project: Taskén / Munthe / Tjønnfjord & Schjesvold / Frigessi groups / NOR-OPENSCREEN

NOMM

Oslo University Hospital

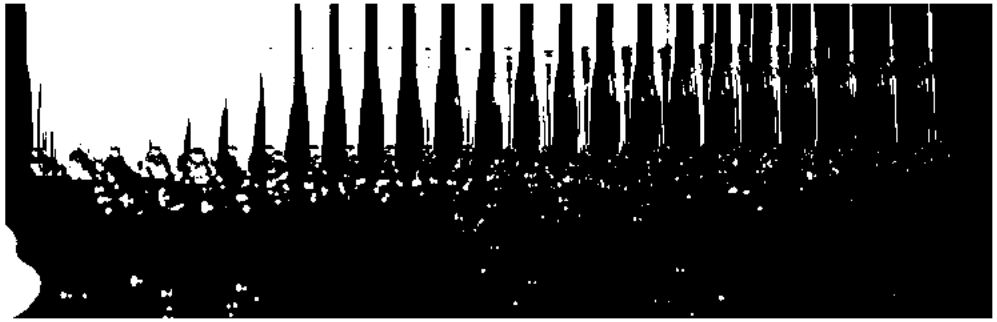

% Viability
125
100
75
50
25
0
-25
12.5
1.25
12500
1250
125
12.5
1.25
[Na+] (mM)

% Viability
125
100
75
50
25
0
-25
1000
100
10
1
0.1
[Na+] (mM)


Single drug or combination
Personalized therapy
Omics
Sample
(...)
New therapy
Iterative learning

www.openscreen.no

Home News Services About Contact

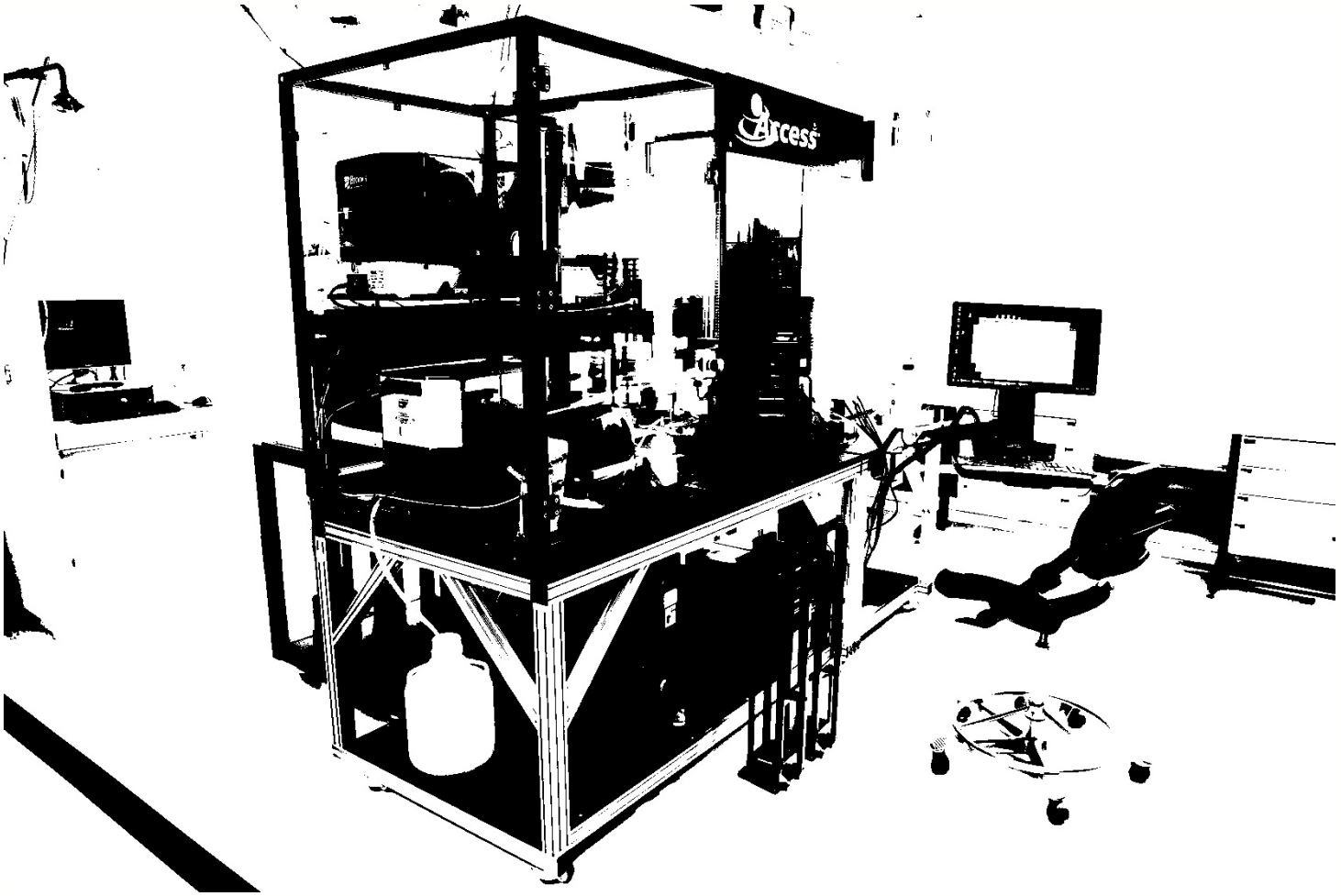


Latest news

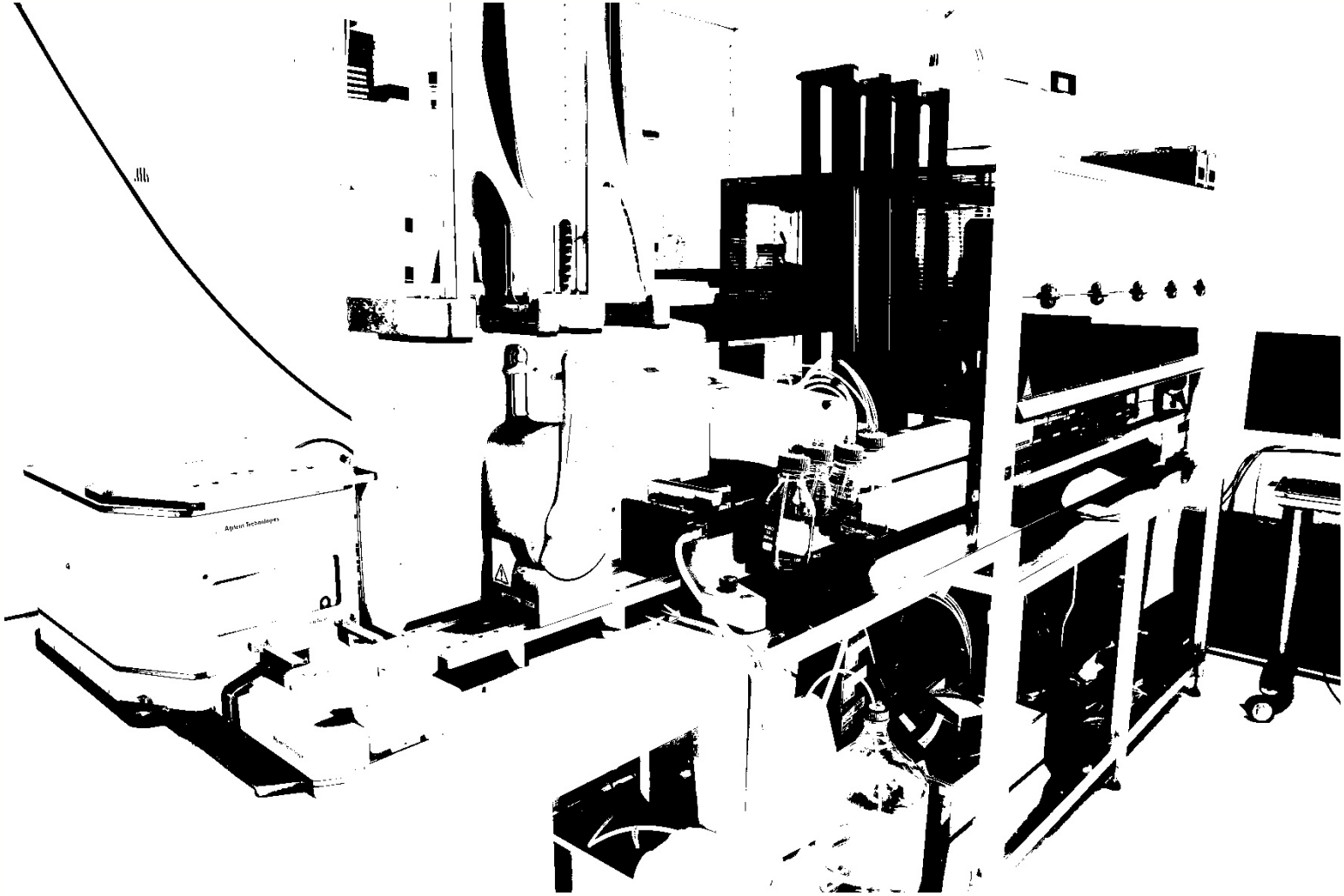
Welcome to NOR-OPENSCREEN

Publications

Automated workstation_1



Automated workstation_2



Method – drug sensitivity screens

384 assay- and compound plates → Compound administration → Adding assay reagents or cells to compunds → Incubation → Detection readout → Data output → Data analysis

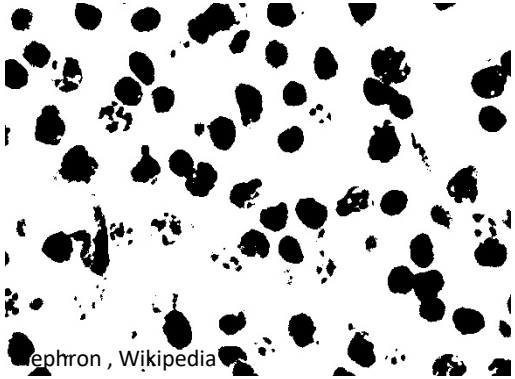
Sigma LOPAC1280	1 280	Library of pharmacologically active compounds.
Prestwick	1 280	Collection of FDA approved drugs
SelleckChem	384	Cambridge Cancer Compound Library, Collection of cancer-targeted compounds
SelleckChem*	193	Known kinase inhibitors
Biomol*	80	Known kinase inhibitors
Biomol*	80	Bioactives
Enzo	477	Target and Pathway Libraries
Tocris Biosciences	1 120	Tocris Tocriscreen Mini, selection of biologically active compounds
SelleckChem	1 650	Bioactive Compound Library
PPI library	~1200	Protein protein disruptors
ChemBioNet	~17000	Diversity collection
Enamine	~28500	Diversity collection
Chembridge	~18000	Diversity collection

Anne Jorunn Stokka

Pipeline for individually tailoring new treatments for relapsed, intractable chronic lymphocytic leukemia and multiple myeloma

We will develop a fast approach to assist clinical decisions in individualized cancer therapy

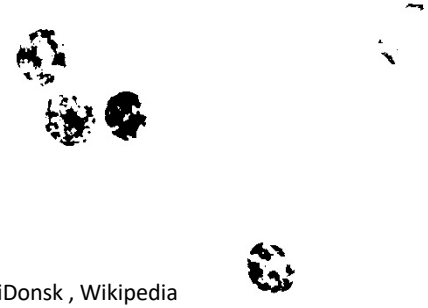
Multiple Myeloma (MM)



ephron , Wikipedia

- Plasma cell neoplasm
- Accounts for 10% of all haematologic malignancies
- Median age at diagnosis: 66 years
- Improved 5 year survival, but still incurable

Chronic lymphocytic leukemia (CLL)



VashiDonsk , Wikipedia

- B cell cancer
- Most common leukemia in the Western world
  - accounts for ~40% of all adult leukemias
- Median age at diagnosis: 72 years
- A slowly progressive disease

A. CLL treatment at present

	<70 years and fit no p53-dysfunction	<70 years and fit p53-dysfunction	>70 years and fit no 53-dysfunction	>70 years, unfit or comorbidity no 53-dysfunction	>70 years p53-dysfunction
	Chemo-immuno-therapy FCR	Chemoimmuno-therapy HDMP + alemtuzumab Allogeneic stem cell tx.	Chemo-immuno-therapy BR	Chemoimmuno-therapy CR	?? **Signal pathway inhibitors (+ mAb)**
<2 years	Signal pathway inhibitors + mAb (?) Allogeneic stem cell tx.	Signal pathway inhibitors + mAb (?) Allogeneic stem cell tx.	Signal pathway inhibitors (+ mAb)	Signal pathway inhibitors (+ mAb)	?? **Signal pathway inhibitors (+ mAb)**
>2 years	Retreatment	?? Signal pathway inhibitors (+ mAb)	Retreatment	Retreatment	?? **Signal pathway inhibitors (+ mAb)**
	??	??	??	??	??

B. Multiple myeloma treatment at present

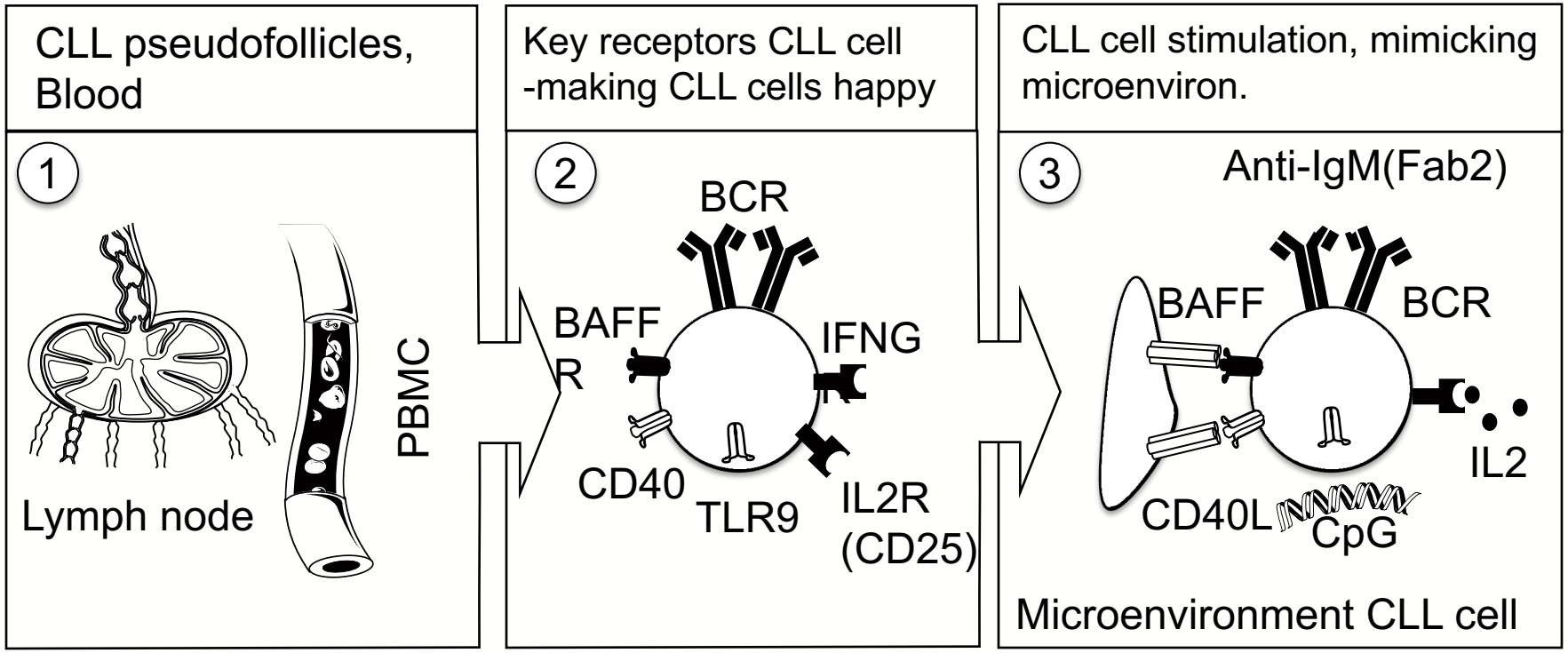
	<65 years of age	>65 years of age
	Induction with Cy/Vel/Dex. HMAS consolidation	MPT
Retreatment <1 year	Thal/Dex, Len/Dex	Thal/Dex, Len/Dex
Retreatment >1 year	Reinduction HMAS consolidation	Retreatment
	??	??

Cy: cyclophosphamide, Vel: Velcade; Dex: Dexamethasone
MPT: Melphalan, prednisone, thalidomide
Thal: Thalidomide; Dex: Dexamethasone; Len: Lenalidomide

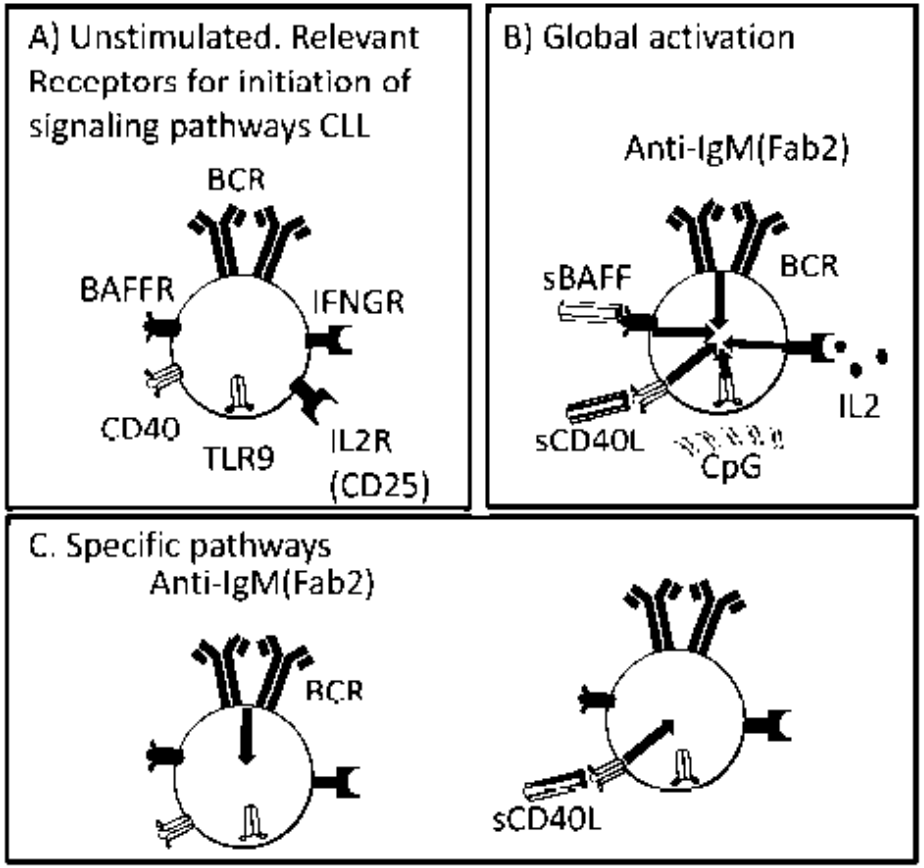
Chemoimmuno-therapy. FCR = fludarabin + cyclophosphamide, BR = bendamustine + rituximab, CR = chlorambucil + rituximab
Signal pathway inhibitors = ibrutinib (Bruton's kinase inhibitor), idelalisib (PI3K inhibitor), fostamatinib (SYK inhibitor)
mAbs = anti-CD20 antibodies rituximab, ofatumumab, obinutuzumab and anti-CD52 antibody alemtuzumab

Figure 3. Treatment options for MM and CLL at present

WP1. Bioassays and Drug Discovery. CLL



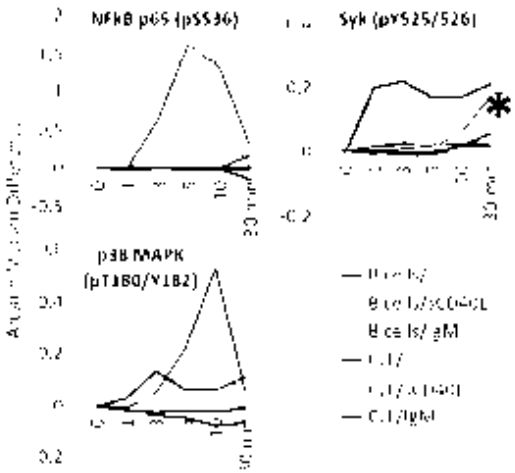
Ludvig A. Munthe

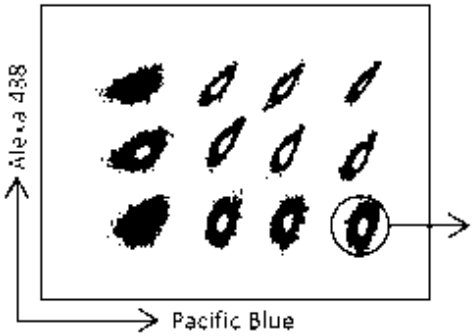


1 Purify and stimulate cells

2 Fix, barcode and stain with Abs

3 Analyze by FACS



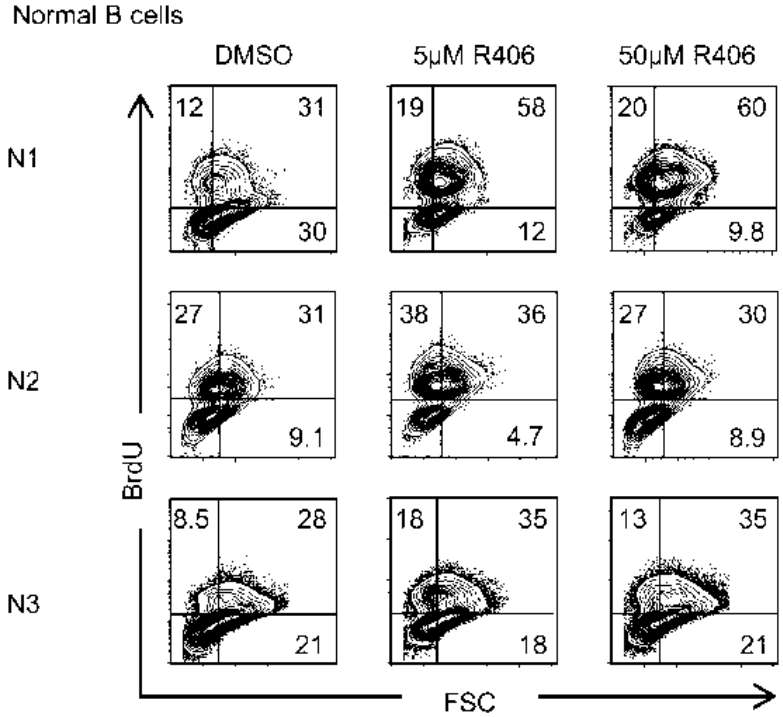


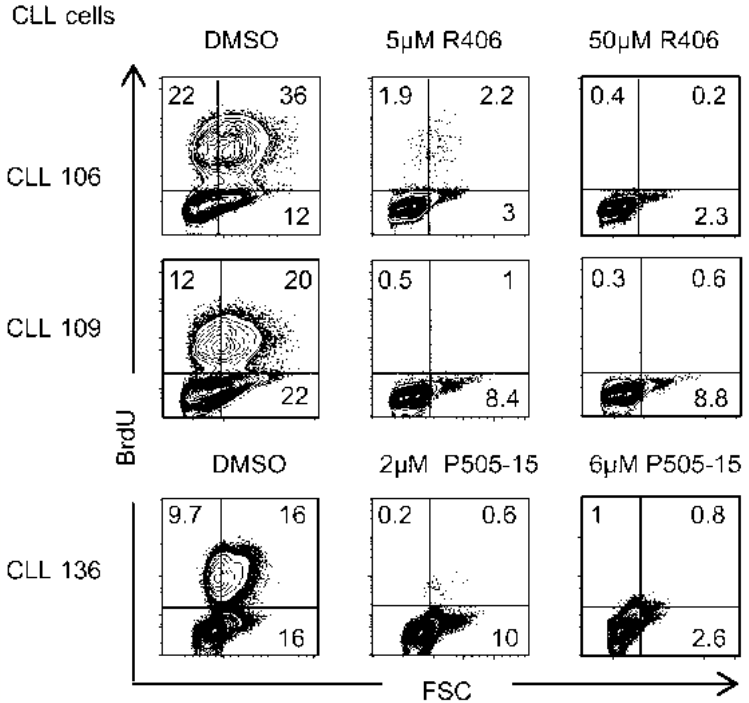
5 Analysis

4 Extract numerical data

Sigrid Skånland / Anna Ribes / Johannes Landskron / Ludvig A. Munthe

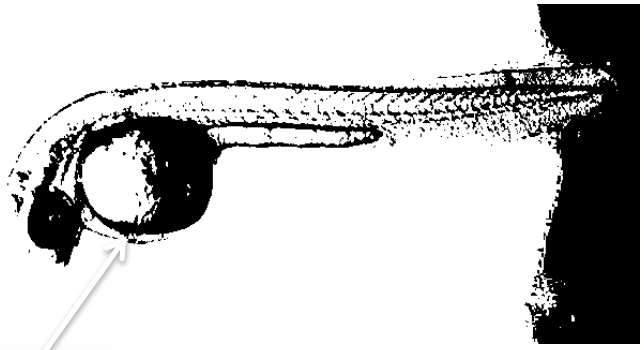
SYK Inhibitors Reduce CLL Proliferation





Parente-Ribes, Skånland, Bürgler *et al*, 2016, Haematologica

Zebrafish xenotransplantation as *in vivo* screening platform for hematopoietic malignancies

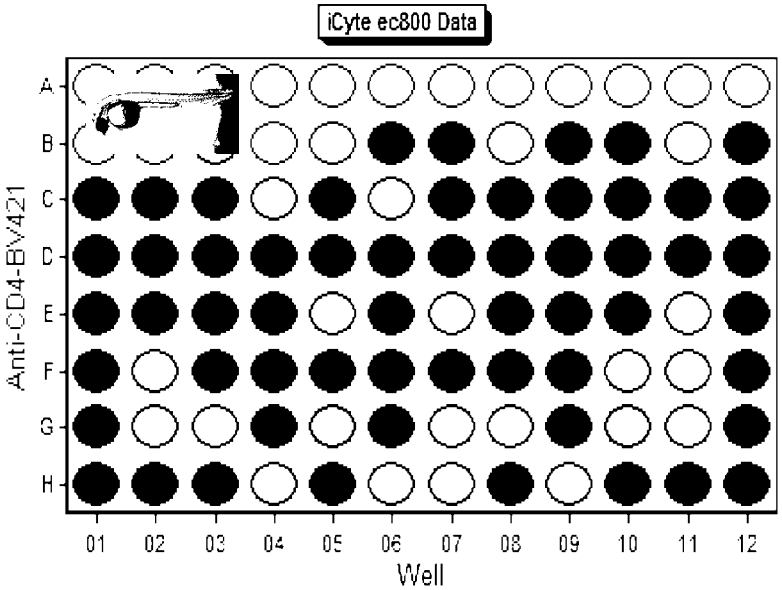


Rag2-/- zebrafish
(48h post fertilization)

CM-DiI, GFP or dsRed
labeled cells

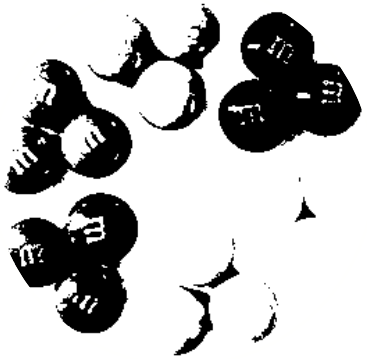
Patient blood or BM sample

Leukemic cell lines (Jurkat, etc)

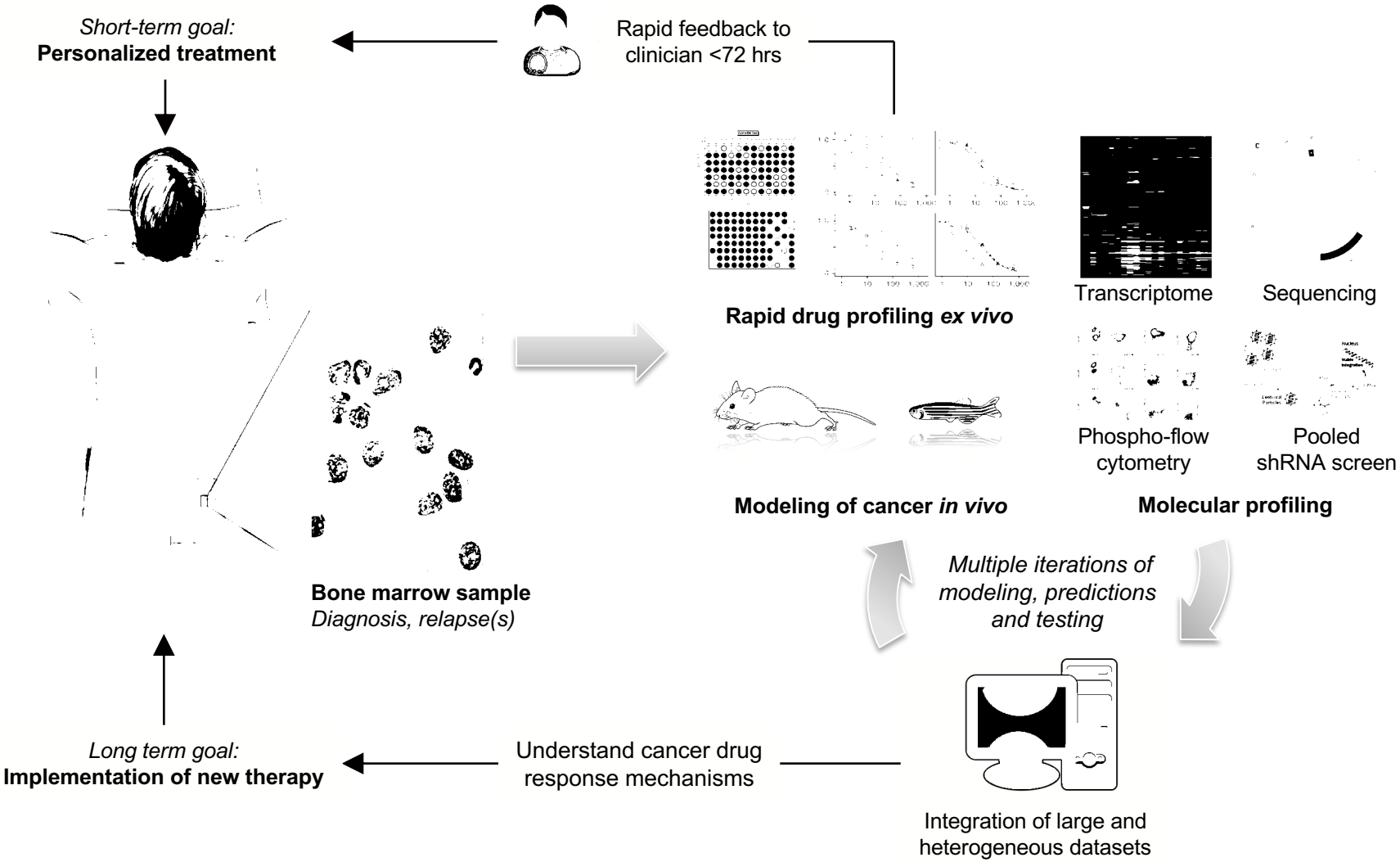


in vivo chemical screen

« *Integrate heterogeneous data from pFLOW analyses and drug sensitivity screens in order to predict patient responses*



Improving cancer treatment through personalized medicine and iterative learning



Protokoll – indiv
behandling

A PHASE 1 MULTICENTRE OPEN-LABEL S
CANCER CELL SCREENING IN PERSONALI
MALIGNANCIES

Forespørsel om de

Ny behan

TITTEL: En fase I mutlisenter, åpen, studie
behandling av B-celle kreft

[A phase 1 multicentre open-label study of
malignancies]

Medikamenter i bruk ved KLL

Alkylerende midler:
Cyklofosfamid, klorambucil er prototypene
Bendamustin er mye brukt nå
Ifosfamid, trofosfamid, melfalan, busulfan, treosulfan kan være aktuelle

Antracykliner:
Doksorubicin er prototyopen
Epirubicin, idarubicin, daunorubicin og mitoksantron kan være aktuelle

Folsyreantagonister:
Metotreksat

Purinanaloger:
Merkaptopurin, fludarabin, cladribin, pentostatin

Vinkalkaloider:
Vinkristin, vinblastin

Kortikosteroider:
Prednison, metylprednisolon

Immunmodulerende medikamenter:
Lenalinomid

Signalveishemmere:
Brutonkinase hemmer; ibrutinib
PI3K-hemmer; idelalisib
SYK-hemmere; fostamatinib, P505-15, entospletinib
Protein-kinase hemmer; flavopiridol
BCL-2 hemmere; oblimersen, obaloclax, ABT-263

Monoklonale antistoffer:
Anti-CD20 antistoffer; rituximab, ofatumumab obinotuzumab
Anti-CD52 antistoffer; alemtuzumab
Anti-CD23 antistoffer; lumiliximab
Anti-CD38 antistoffer; daratumumab
Anti-CD40 antistoffer; lucatumumab

Pipeline for treatments i

Heterogeneous da pathways and test sensitivity screenir support clinical de

BLODKREFT FORENINGEN
Torggata 16
0181 Oslo
post@blodkreftforeningen.no
Telefon 97 62 75 11
www.blodkreftforeningen.no

Professor Kjetil Taskén
Centre for Molecular Medicine Norway

Oslo, 10th of October 2016

RE: User-participation in project on development of individualised therapies for hematological cancer

This letter to confirm that Blodkreftforeningen (The Blood Cancer Society in Norway) is informed about the project application from Professors Kjetil Taskén, Jorrit Enserink and Arnoldo Frigessi and colleagues entitled "*Pipeline for individually tailoring new treatments in hematological cancers*" to the Norwegian Research Council.

We have reviewed the project synopsis and understand that this proposal will gather several ongoing research projects that directly screen patient samples for drug sensitivity and will aim to provide tools to predict and find optimal combinations of drugs for each patient to assist clinicians in individualizing therapies for patients that have exploited other treatment opportunities.

We are enthusiastic about these plans as we foresee potential future patient benefit for Norwegian patients. We have been asked to participate in user activities relating to the project (steering committee and user discussion panels). We will be happy to participate and help setting up such activities as the project develops.

Best regards
Blodkreftforeningen

Eddy Grønset
Head of secretary

Cancer Drug Sensitivity Screening - Utfordringer

- Liste med legemidler som kan virke, evt kombinasjoner som kan gi synergi
- Støtte kliniske beslutninger om individualiserte behandlingsvalg
- Lister med legemidler som kan være fra 20 til 400 legemidler i bruk eller i utvikling
- “Off-label” bruk, ukjente interaksjoner
- Randomiserte studier vil teste algoritmen for utvalg av legemidler, ikke de enkelte legemidler
- Internasjonale konsortier for å aggregere data om hvert enkelt legemiddel? – “Basket design?

SKREDDERSYDD MEDISIN vil føre til en redefinisjon av begrepet *”evidens-basert medisin”* siden det ikke bare vil være mulig å bestemme *om* en behandling har effekt men også *hvem* som har nytte av behandlingen.

Kjetil Taskén group

NCMM, UiO/OUH

The Research Council of Norway

HELSE SØR-ØST

EMBL

Oslo University Hospital

SEVENTH FRAMEWORK PROGRAMME

norden

NordForsk

NORWEGIAN CANCER SOCIETY

K.G. Jebsen Inflammation Research Centre

KG JEBSEN CENTER for Cancer Immunotherapy

novo nordisk fonden

Prosjekt-team

NCMM, UiO/OUS

Kjetil Taskén

Andrea Cremaschi

Johanne Uthus Hermansen

Deepak Balaji Thimiri Govinda Raj

Sigrid Skånland

Andre partnere:

Bjørn Tore Gjertsen

Jorrit Enserink

Inst. for Immunologi, OUS

Ludvig A. Munthe

Dong Wang

Avd for Blodsykdommer, OUS

Geir E. Tjønnfjord

Fredrik Schjesvold

Oslo senter for biostatistikk og epidemiologi, UiO/OUS

Arnoldo Frigessi

Manuela Zucknick

NCMM

Centre for Molecular Medicine Norway

Nordic EMBL partnership for Molecular Medicine

From disease mechanisms to clinical practice