IMPRESS-Norway:

Improving public cancer care by implementing precision medicine in Norway

Proposed national Drug Rediscovery Protocol (DRUP)-like study for Norway

DRUP in the Netherlands and similar studies in US, Canada, the Nordics and other European countries ongoing or to start

DRUP
the Drug Rediscovery Protocol
Expanded use of existing anticancer drugs

TAPUR Targeted Agent and Profiling Utilization Registry Study | ASCO
American Society of Clinical Oncology

Canadian Profiling and Targeted Agent Utilization Trial (CAPTUR)

ProTarget
A Danish Nationwide Clinical Trial on Targeted Anti-Cancer Treatment based on Molecular Profiling

MEGALiT

IMPRESS NORWAY

FIN-DRUP
DRUG REDISCOVERY PROGRAM IN FINLAND

Why the interest in the DRUP-trial?

LETTER

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The Drug Rediscovery protocol facilitates the expanded use of existing anticancer drugs

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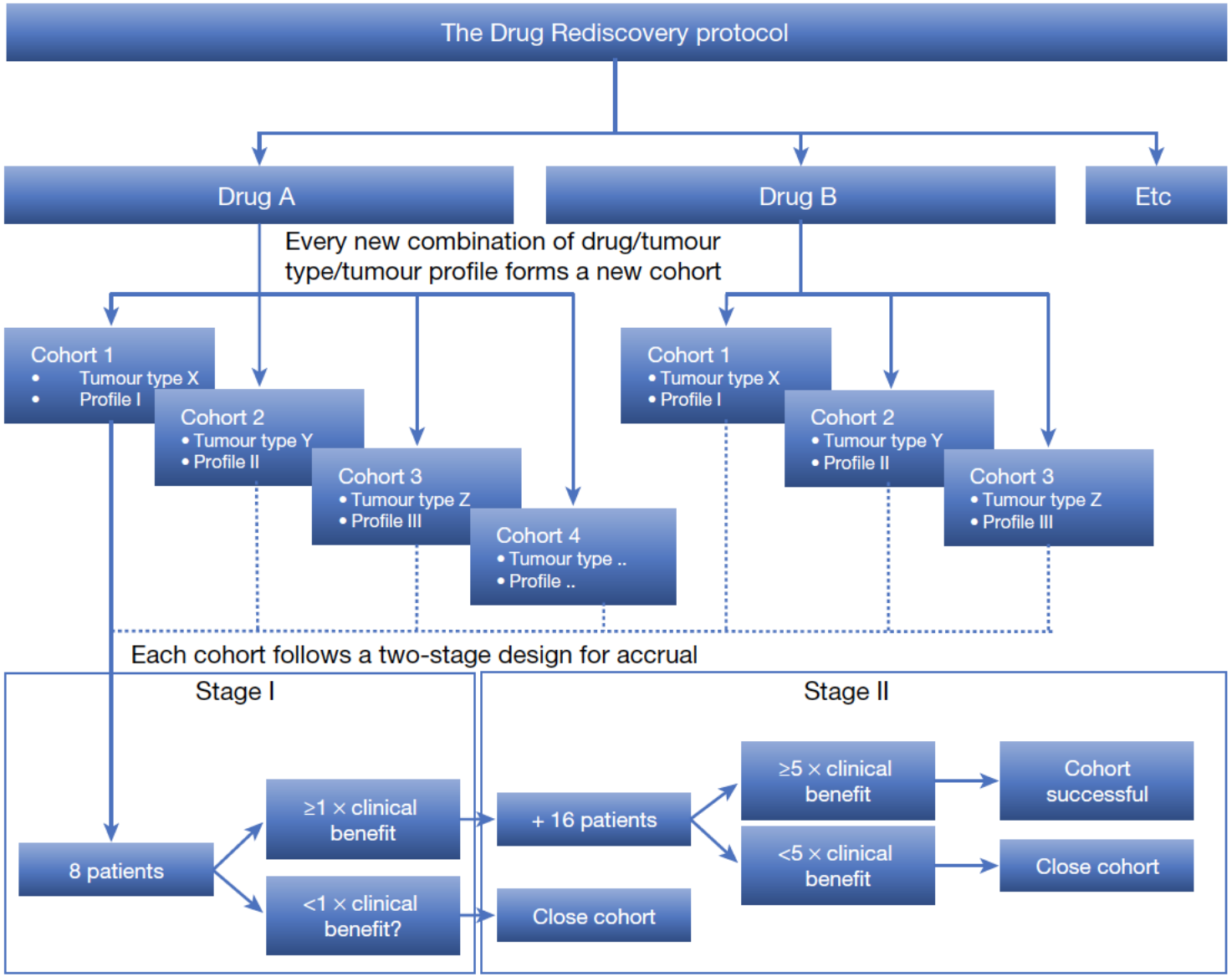
The large-scale genetic profiling of tumours can identify potentially actionable molecular variants for which approved anticancer drugs are available[1–3]. However, when patients with such variants are treated with drugs outside of their approved label, successes and failures of targeted therapy are not systematically collected or shared. We therefore initiated the Drug Rediscovery protocol, an adaptive, precision-oncology trial that aims to identify signals of activity in cohorts of patients, with defined tumour types and molecular variants, who are being treated with anticancer drugs outside of their approved label. To be eligible for the trial, patients have to have exhausted or declined standard therapies, and have malignancies with potentially actionable variants for which no approved anticancer drugs are available. Here we show an overall rate of clinical benefit—defined as complete or partial response, or as stable disease beyond 16 weeks—of 34% in 215 treated patients, comprising 136 patients who received targeted therapies and 79 patients who received immunotherapy. The overall median duration of clinical benefit was 9 months (95% confidence interval of 8–11 months), including 26 patients who were experiencing ongoing clinical benefit at data cut-off. The potential of the Drug Rediscovery protocol is illustrated by the identification of a successful cohort of patients with microsatellite instable tumours who received nivolumab (clinical benefit rate of 63%), and a cohort of patients with colorectal cancer with relatively low mutational load who experienced only limited clinical benefit from immunotherapy. The Drug Rediscovery protocol facilitates the defined use of approved drugs beyond their labels in rare subgroups of cancer, identifies early signals of activity in these subgroups, accelerates the clinical translation of new insights into the use of anticancer drugs outside of their approved label, and creates a publicly available repository of knowledge for future decision-making.

is taken into consideration. However, with regards to drug sensitivity, the importance of a given genetic or molecular variant is usually tested in the subtype of cancer that most frequently contains this variant. The importance of the same variant in other cancers often remains unknown. Third, as drug development is challenging for rare subtypes of cancer, this can create inequality in care[12]. Finally, with growing pressure from society to increase the success rate of drug-development trials[13], there is hesitation amongst payers to reimburse large-scale sequencing efforts before they have proof that these efforts will make healthcare more sustainable. As a result, we are not using the full potential of rapidly expanding technological advances, knowledge of biomarkers and the spectrum of approved anticancer drugs for our patients.

The Center for Personalized Cancer Treatment was founded in 2010[14] to address these issues. In this network (which now connects 45 hospitals in the Netherlands), patients with all types of metastatic cancer are offered the opportunity to undergo a fresh tumour biopsy for whole-genome sequencing (WGS) before starting systemic anticancer treatment. The WGS results are combined with treatment outcomes in a national, centralized database for research purposes, and returned to the physician who is treating the patient for future planning of treatment. This initiative has contributed to the identification of potentially actionable variants in cancers that are not routinely tested for these variants. To provide treatment opportunities for patients in whom such variants were identified (while simultaneously collecting clinical outcomes), we began the Drug Rediscovery protocol (DRUP), in which we seek to expand the use of targeted therapies that have been approved by the European Medicines Agency (EMA) and/or US Food and Drug Administration (FDA) beyond the approved indications of these therapies.

The DRUP is an ongoing, prospective multi-drug and pan-cancer

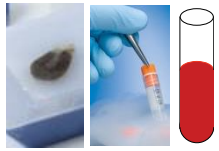
- Included 46% of patients referred to a national molecular tumor board
- Reports clinical benefit by defined criteria in 34% of included patients
- Both better than any other genomic medicine / precision cancer medicine trial so far


The Drug Rediscovery protocol
Drug A
Drug B
Etc
Every new combination of drug/tumour type/tumour profile forms a new cohort
Cohort 1
• Tumour type X
• Profile I
Cohort 2
• Tumour type Y
• Profile II
Cohort 3
• Tumour type Z
• Profile III
Cohort 4
• Tumour type ..
• Profile ..
Cohort 1
• Tumour type X
• Profile I
Cohort 2
• Tumour type Y
• Profile II
Cohort 3
• Tumour type Z
• Profile III
Each cohort follows a two-stage design for accrual
Stage I
8 patients
≥1 × clinical benefit
<1 × clinical benefit?
Stage II
+ 16 patients
≥5 × clinical benefit
<5 × clinical benefit
Cohort successful
Close cohort
Close cohort

National Infrastructure for Precision Diagnostics (InPreD)

- for cancer patients where experimental treatment/clinical trial inclusion is an option

Informed consent
Molecular profiling



Sampling tissue/blood, existing biopsies

Molecular analyses

Data-analysis

Molecular Report

Interpretation, Integration with clinical information

MTB meeting: Assessment for biomarker-trial match

No biomarker or not eligible for trial
Back to ordinary treatment program with survival follow-up

1) Selected to **biomarker defined trial -** **Informed consent**

2) Biomarker present but no trial available

Inclusion in IMPRESs-Norway

Whole Genome sequencing, Sequential biopsies, additional sampling for **translational research**
- **Informed consent**

National Molecular Tumor Board (MTB):

- Weekly Virtual meetings
- A core group with broad competence: pathology, oncology, hematology, molecular biology, bioinformatics, ++
- Referring clinician
- Others (e.g. trial coordinators, local clinicians/pathologists)

Dynamic protocol

- Patients with advanced disease
  - Solid tumors and hematological indications
- DRUP-like combined umbrella / basket design with Simon two-stage model of expanding cohorts
- Close collaboration and and coordination with DRUP-network trials in Europe and beyond:
  - Negative cohorts from other countries not to open in Norway
  - Data aggregation across studies for slowly accruing cohorts (details being defined)

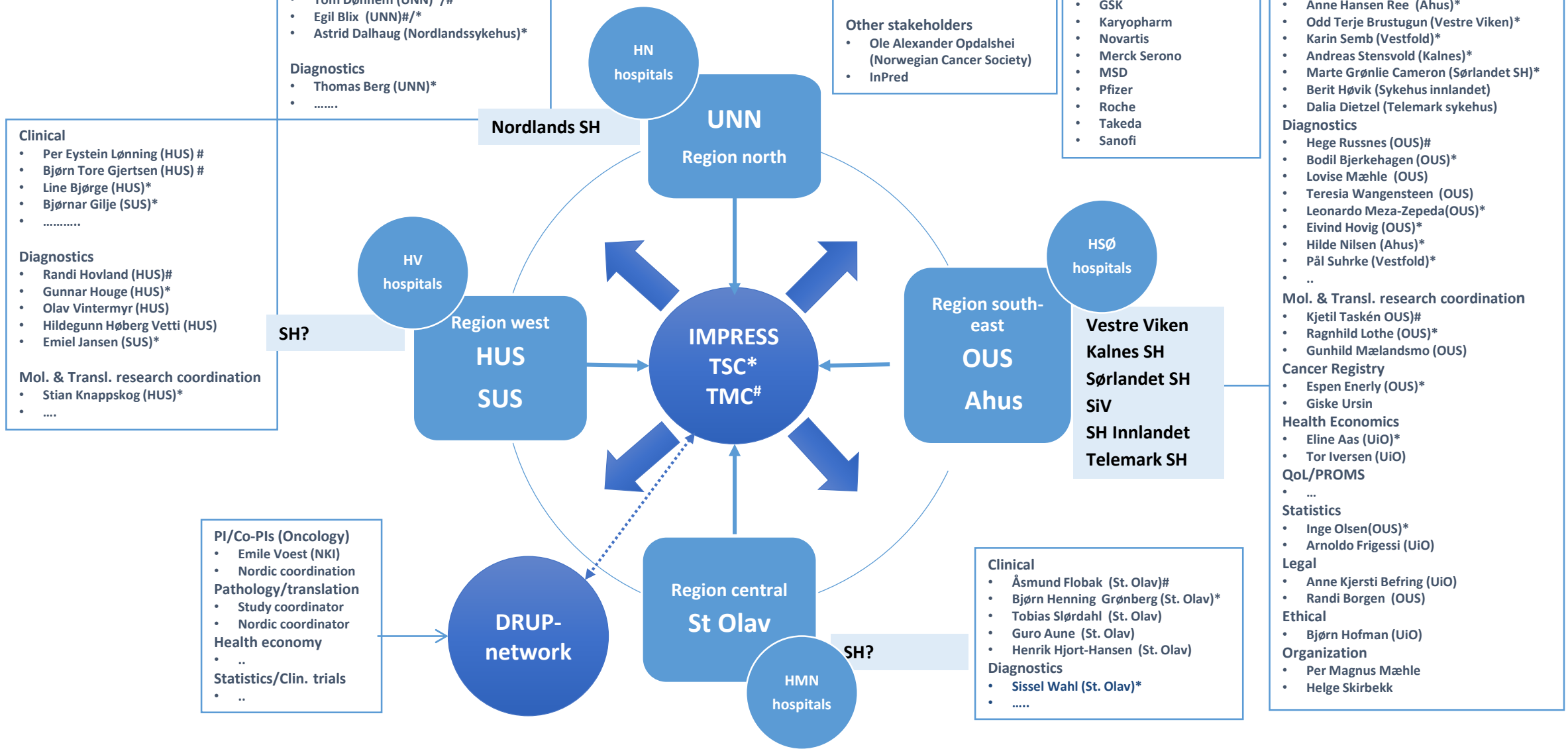
Approach - Use of approved drugs

- Approved (FDA/EMA) drugs (incl. approved combinations)
  - Known safety-profile, off-label use
  - Small molecule substances, monoclonal antibodies, immunotherapy
- Pharma partners provide defined number of treatment slots per drug
  - 17 companies
- Hands-on experience via patient treatment in local hospitals supported via National Tumor Board
- Health care system gets systematic data collection for knowledge base on National level
- Coupling to Norwegian Cancer Registry and the INSPIRE project
- Coupling to excellent translational research milieus across Norway

IMPRESS-NORWAY: Advancing Cancer Precision Medicine and Translational Research

- Growing DRUP-based trial network: opportunity to scale and aggregate data in Europe
- Leverage strong Nordic networks for certain indications with DRUP-initiatives in SWE, DEN, FIN
- 500+ gene panel for nation-wide initial testing: broader basis for decision on patient inclusion
- Implementation of National Tumor Board
- Integration of data into National Cancer Registry: opportunity for long-term follow-up and broader data integration, real-world evidence
- In-depth analysis and research for specific cohorts (to be defined jointly with industry partners)
- National Testing Infrastructure: benchmarking and testing opportunities for diagnostic tests
- Norway's highly digitized population: opportunity to pilot digital solutions for patient recruitment and follow-up (patient reported outcomes)

IMPRESS-Norway: Overview organization per 04.08.20



Public partners
- Øyvind Melien (FHI)
- Grethe Foss (Hdir)

Patients advocates
- Kari Grønås
- Ann-Charlotte Iversen

Other stakeholders
- Ole Alexander Opdalshei (Norwegian Cancer Society)
- InPred

Industry (TBC)
- AbbVie
- Amgen
- Astra Zeneca
- Bayer
- Blueprint Medicines
- BMS
- GSK
- Karyopharm
- Novartis
- Merck Serono
- MSD
- Pfizer
- Roche
- Takeda
- Sanofi

Clinical
- Tom Dønnem (UNN)*/#
- Egil Blix (UNN)#/*
- Astrid Dalhaug (Nordlandssykehus)*

Diagnostics
- Thomas Berg (UNN)*
- …….

Clinical
- Per Eystein Lønning (HUS) #
- Bjørn Tore Gjertsen (HUS) #
- Line Bjørge (HUS)*
- Bjørnar Gilje (SUS)*
- ……..

Diagnostics
- Randi Hovland (HUS)#
- Gunnar Houge (HUS)*
- Olav Vintermyr (HUS)
- Hildegunn Høberg Vetti (HUS)
- Emiel Jansen (SUS)*

Mol. & Transl. research coordination
- Stian Knappskog (HUS)*
- ….

PI/Co-PIs (Oncology)
- Emile Voest (NKI)
- Nordic coordination

Pathology/translation
- Study coordinator
- Nordic coordinator

Health economy
- ..

Statistics/Clin. trials
- ..

Clinical
- Åsmund Flobak (St. Olav)#
- Bjørn Henning Grønberg (St. Olav)*
- Tobias Slørdahl (St. Olav)
- Guro Aune (St. Olav)
- Henrik Hjort-Hansen (St. Olav)

Diagnostics
- Sissel Wahl (St. Olav)*
- …..

Clinical
- Åslaug Helland National PI(OUS)#
- Jon Amund Kyte (OUS)#
- Geir Tjønnfjord (OUS)*
- Kristina Lindemann (OUS)
- Monica Cheng Munthe-Kaas (barneonkologi, OUS)*
- Anne Hansen Ree (Ahus)*
- Odd Terje Brustugun (Vestre Viken)*
- Karin Semb (Vestfold)*
- Andreas Stensvold (Kalnes)*
- Marte Grønlie Cameron (Sørlandet SH)*
- Berit Høvik (Sykehus innlandet)
- Dalia Dietzel (Telemark sykehus)

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- Hege Russnes (OUS)#
- Bodil Bjerkehagen (OUS)*
- Lovise Mæhle (OUS)
- Teresia Wangensteen (OUS)
- Leonardo Meza-Zepeda(OUS)*
- Eivind Hovig (OUS)*
- Hilde Nilsen (Ahus)*
- Pål Suhrke (Vestfold)*
- ..

Mol. & Transl. research coordination
- Kjetil Taskén OUS)#
- Ragnhild Lothe (OUS)*
- Gunhild Mælandsmo (OUS)

Cancer Registry
- Espen Enerly (OUS)*
- Giske Ursin

Health Economics
- Eline Aas (UiO)*
- Tor Iversen (UiO)

QoL/PROMS
- …

Statistics
- Inge Olsen(OUS)*
- Arnoldo Frigessi (UiO)

Legal
- Anne Kjersti Befring (UiO)
- Randi Borgen (OUS)

Ethical
- Bjørn Hofman (UiO)

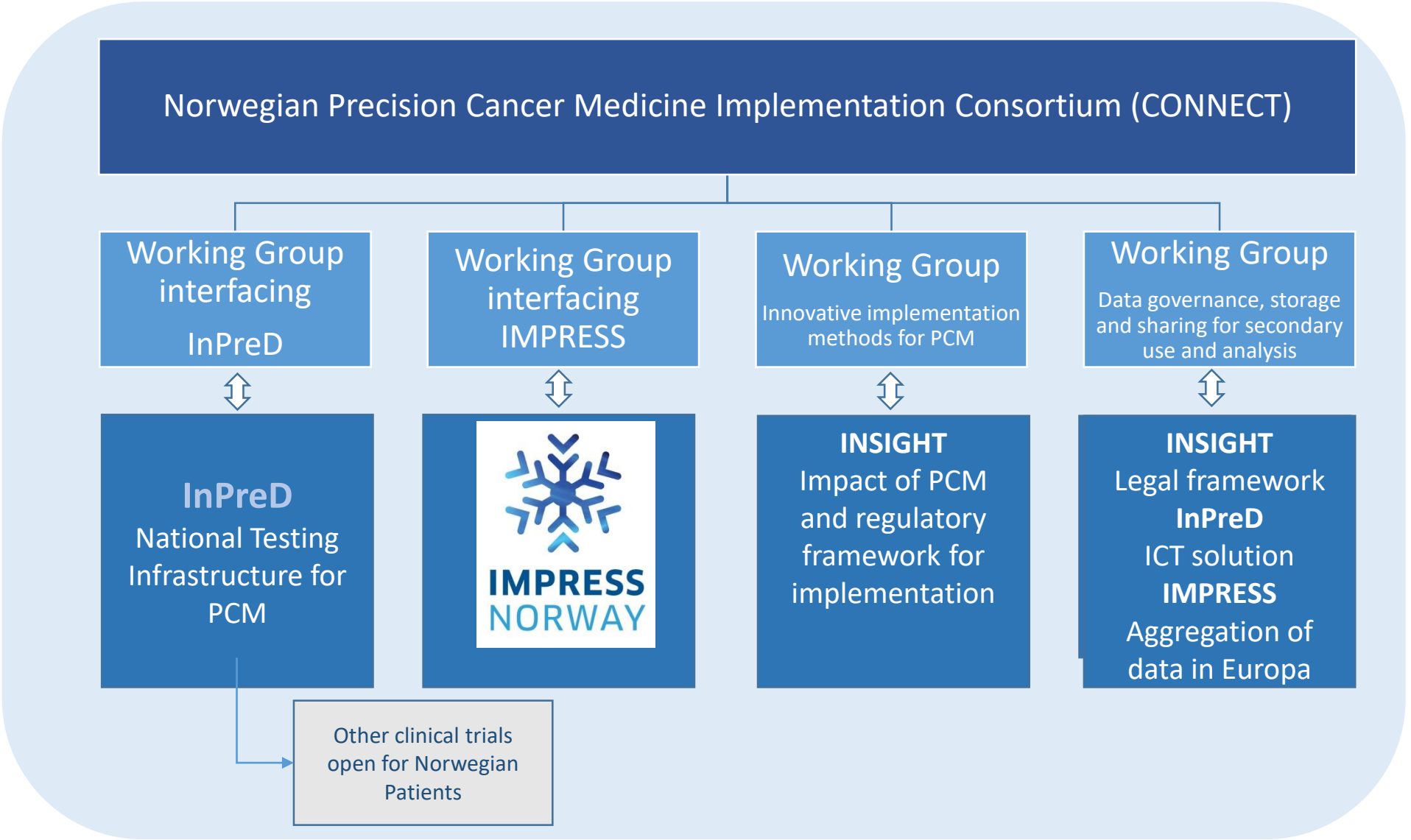
Organization
- Per Magnus Mæhle
- Helge Skirbekk

**Trial Steering Committee (TSC) members are marked with **

#Trial Managment Committee (TMC) members marked with # (also TSC members)

Public-Private Partnership for PCM Implementation in Norway:

Norwegian Precision Cancer Medicine Implementation Consortium (CONNECT)



IntPreD and IMPRESs with own Steering Structures and budget. Intimately linked to but separate from CONNECT.