Nordic Alliance
for Clinical
Genomics

WORKSHOP REPORT

NACG 8th Clinical Workshop
Oslo 19.-21. November 2019

About NACG

The Nordic Alliance for Clinical Genomics (NACG) is an independent, non-governmental, not-for-profit Nordic association. NACG gathers stakeholders in clinical genomics who collaborate to identify and address emerging challenges to the implementation of clinical genomics and precision medicine. NACG partners collaborate to identify and address emerging challenges to the implementation of clinical genomics and precision medicine. Learn more about the Nordic Alliance for Clinical Genomics at https://nordicclinicalgenomics.org/ or contact us at post@nordicclinicalgenomics.org.

Mission

NACG partners work together and learn from each other to lift performance standards. We aim at responsible sharing of trustworthy data for improved diagnosis and treatment, and as a resource for research.

Goals and activities

- Facilitate the responsible sharing of genomic data, bioinformatics tools, sequencing methods and best practices for interpretation of genomic data.
- Enhance quality of genomic data and processes and explore methodologies to provide assurance.
- Understand legal barriers to the implementation of personalized medicine and to engage with key stakeholders that influence these barriers
- Develop demonstration projects that challenge perceived legal barriers that limit responsible and ethical sharing of genomic and health data.
- Build bridges between research and clinical communities, technologies and practices to foster innovation

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Symbols

 Lecture / presentation

 Interactive workshop

Abbreviations

CNV	Copy number variation
FIMM	Institute for Molecular Medicine Finland
GE	Genomics England
GMC	Genomic Medicine Centre
GMS	Genomic Medicine Sweden / Genomic Medicine Service (England)
GWAS	Genome-wide association study
IVDR	In Vitro Diagnostic Regulations
LDT	Lab developed or in-house test
MDR	Medical Device Regulation
NACG	Nordic Alliance for Clinical Genomics
NGC	(Danish) National Genome Centre
NGS	Next-generation sequencing
OUS AMG	Oslo University Hospital, Department of Medical Genetics
SV	Structural variants
WES	Whole exome sequencing
WGS	Whole genome sequencing

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Executive summary

This report summarizes the Nordic Alliance for Clinical Genomics' (NACG) symposium and 8th workshop that took place at Høvik on the 19th – 21st November 2019. The events gathered 102 participants from 31 organizations in seven different countries (Table 1, Figure 1). The full list of participants is available in Appendix 4.

The objective of this workshop was to progress NACG work to share experiences, data and best practices relevant for the clinical implementation of genomics, and to collaboratively explore pain points in producing and using genomic data to the best of the patient (Figure 2).

Table 1 Summary of participation at NACG events November 2019

Country	Organisation	Number of participants
Denmark	Aarhus University Hospital	2
	CIFS	1
	Danish National Genome Center	3
	Rigshospitalet	8
	University of Copenhagen and NSHG-PM	1
	Vejle Hospital	1
Finland	HUSLAB	2
	University of Helsinki	4
Iceland	Landspitali - Univ. of Iceland	1
Norway	BigMed	1
	Legemiddelindustrien (LMI)	1
	Oslo University Hospital	40
	St. Olavs Hospital	1
	The Norwegian Directorate of Health	2
	Universitetet i Oslo	1
	University Hospital of North Norway	2
	University of Oslo	2
Sweden	Karolinska Institutet	1
	SciLifeLab	4
	Karolinska University Hospital	1
International	Agilent	1
	Astrazeneca Nordics	1
	DNV GL	12
	Illumina	2
	Limbus Medical Technologies GmbH	1
	NEC OncoImmunity	1
	Oxford Nanopore	1
	Roche Diagnostics	1
	Roche Norge AS	1
	Thermo Fisher Scientific	1
	Twist Bioscience	1

Figure 1 Participants at the 8th NACG clinical workshop

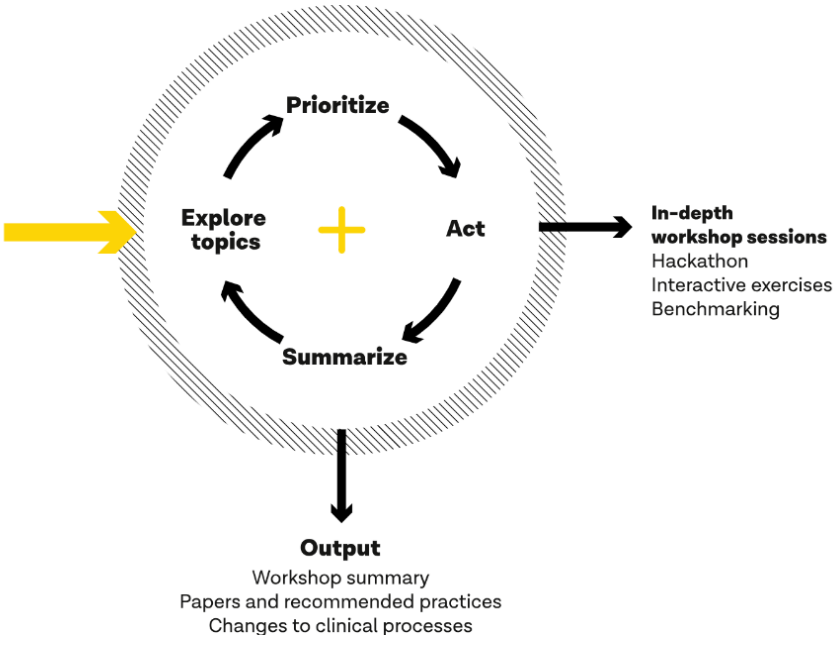


Figure 2 NACG members discuss and explore topics of interest to identify shared challenges and strategies for overcoming them. Prioritized topics are explored in in-depth interactive exercises. Findings and learnings are summarized in workshop summary reports and collaborative papers and contribute to lifting performance standards.

NACG event outline

The overall outline of the NACG symposium and workshops is provided in Table 2 and Table 3, detailed agendas are provided in Appendix 2 and 3. A pre-conference on the legal framework for personalised medicine was organized by the University of Oslo and the Oslo University Hospital, a separate conference report from this event will be made available through the NACG website.

Table 2 NACG event outline

	Mon 18. Nov	**Tue 19. Nov**	**Wed 20. Nov**	**Thu 21. Nov**
Morning	The legal framework for pers. med.	The legal framework for pers. med.	NACG symposium	NACG workshops
Afternoon	The legal framework for pers. med.	NACG symposium	NACG workshops	NACG workshops
Evening		Reception & Dinner		

Table 3 Outline of NACG workshops

	Wednesday 20. Nov		**Thursday 21. Nov**	
Morning			9:00 Consent (Room: Big Blue 1)	9:00 Structural variants (Room: Big Blue 2)
Lunch	12:00		12:00	
After-noon	13:00 NGS for cancer diagnostics (Room: Big Blue 1)	13:00 Structural variants (Room: Big Blue 2)	13:00 MDR and IVDR - how to address the upcoming regulations? 14:00 Next steps 15:00 End	

NACG Symposium

Figure 3 Dag Undlien, NACG chair, opening the NACG symposium.

Welcome and opening remarks

	Speakers:	Dag E. Undlien, OUS AMG & NACG steering committee chair Kenneth Vareide, CEO Digital Solutions, DNV GL Paul Chaffey, State Secretary to the Norwegian Minister of Digitalization
Dag Undlien	-	Dag introduced the NACG community and highlighted that it is open and including in welcoming new partners and sharing information through workshop reports and the organization's website. - NACG is based on Nordic commonalities and shared challenges, where joining forces and continuing the Nordic tradition of collaboration can contribute to advancing clinical genomics in the region. - NACG is growing; attracting more members and workshop participants. - Interdisciplinarity is key in overcoming challenges in clinical genomics, and Dag acknowledged the success of the PerMedLaw conference that preceded the 8th NACG event and welcomed the legal network into NACG.
Kenneth Vareide	-	Kenneth introduced DNV GL; the organisation's purpose of safeguarding life, property and the environment and the strategic focus on digitalization, with healthcare as a prioritized area. - Owned by an independent foundation, the company re-invest 5% of annual turnover into research and development.
Paul Chaffey	-	Paul discussed how digital technologies and collaboration are essential to face challenges associated with changing conditions such as older population, peoples' increasing expectations, renewable energies and climate change. - Referring OECD's Digital Government Review of Norway, Norway is well placed on the path to digital transformation, but still a need for: o Clearer responsibilities and better coordination o Improving ICT projects management o Better user-driven service delivery o Using data as a strategic asset

	- The Norwegian strategy for personalised medicine in healthcare highlights five strategic areas: Expertise and information, Quality and academic and clinical development, Health registries, Information and communication technology (ICT) and Research and innovation
	- Discussed new Norwegian digital strategy 2019-2025 that places focus on:
	  ○ Seamless services and a user-centric focus
	  ○ Increased data sharing and value creation
	  ○ Clear and digitalisation-friendly regulations
	  ○ A common ecosystem for national digital collaboration and service development
	  ○ Governance and coordination for more seamless public sector
	  ○ Enhanced cooperation with the private sector
	  ○ Increased digital competence in the public sector
	  ○ Cyber Security

National Initiatives: Denmark

	**Speaker:**	Bettina Lundgren, Director of the Danish National Genome Centre (CEO, MD, D.M.Sci)
	Objective:	Update on developments with the Danish National Genome Center
Key information:	**Personalised medicine for benefit of patients** • Bettina introduced the Danish National strategy for Personalised Medicine (2017-2020), including the National governance structure and the Danish National Genome Centre (NGC) and highlighted Danish strongholds: harmonized health registries, biobanks and databases, good IT infrastructure and high level of digitalisation, active research and life science industry and many relevant activities collaborating across healthcare and research. • The NGC is financed through national budget (2017-2020, 100 mio DKK), private foundation grants (990 mio DKK over 4.5 years), existing healthcare budgets and public research. • The NGC's mandate is defined by Act passed 29th May 2018. NGC is an institution under the Minister for Health, supporting the development of personalised medicine in collaboration with relevant stakeholders such as the Danish healthcare system, research institutions and patient organisations. • Bettina reviewed the infrastructure for personalised medicine in Denmark, as well as the governance for inclusion of new patient groups. • The working group for clinical use of WGS (NGC, Regions, LVS) is tasked to identify 60 000 patients to WGS in next five years, using five guiding principles: 1. Expertise and value to patient, 2. Access to fast and better treatment, 3. Economic considerations (short and long term), 4. Geographical equality, and 5. Broad effect in the Danish society.	
Discussion	Answers to questions include: Data is stored at NGC and accessible to staff and researchers. Results and interpretation in EPJ. Patients can consent to treatment and opt-out of inclusion in research. Patients have access to their own data, but NGC owns the data.	
Conclusions:	Denmark have reviewed other country genome sequencing initiatives, and international advisor reports to establish the Danish way 'for the patients.	

National Initiatives: Finland

Speaker: Aarno Palotie, Research director of the Human Genomics program at FIMM, Finland

Objective: Share information on initiatives within Finland

Key information:

- Aarno introduced the FinnGen project; a public-private partnership combining genome information with digital health data from national health registries.
- Government backing includes the National Genome Strategy, the Biobank Act, Secondary usage of register data and the National Genome Centre.
- Builds on existing infrastructure such as nationwide registries and biobanks.
- The Finnish Biobank Act addresses:
    - Registration of biobanks, wide consent and protection of participants
    - Transfer of existing sample and data collections to biobanks
    - Possibility to recontact
    - Possibility to collect samples and data from the health care
    - Collaboration with industry
- Infrastructure building blocks:
    - The FINGENIOUS® portal provides access to major biobanks.
    - FINDATA: data permit authority
    - FICAN: regional and national cancer centers
- FinnGen's existing sample collection include 200 000 Finns, and will include 300 000 new sample donors over the next 6 years
    - Legacy collections: 200 000
    - Prospective collections: 300 000
- Participation is voluntary, consent can be withdrawn. Samples are coded and identities not available to FinnGen. Genome data produced from biobank samples is owned by the Finnish biobanks.
- Arno provided examples of new loci discovered based on the Finnish population data and discussed the use of longitudinal data for predictions with public health impact, e.g. breast cancer screening.
- The importance of linking FinnGen with global biobanks and data repositories was discussed as a resource for identifying new loci where larger volumes of population data is needed.

National Initiatives: Sweden

Speaker: Anna Lindstrand, Karolinska Institutet & Karolinska University Hospital

Objective: Share information on Genomic Medicine Sweden

Key information:

- Anna introduced the Swedish Life Sciences road map with its three identified prioritized areas to develop healthcare;
    - Utilization of digital health and health data
    - Precision medicine
    - Tomorrow's health and social care
- The Genomic Medicine Sweden is a nation-wide collaborative effort that aims to offer all patients equal care regardless of healthcare region by providing front edge diagnostics, precision medicine focus, a unique national research database and innovation & industry cooperation.

- The project is currently in the Implementation stage, after which the extension phase has a 5-10 years perspective.
- The initiative brings together 7 regional Genomic Medicine Centres (GMCs) and National infrastructures (Informatics, ELSI, Innovation & industry collaboration, HEOR and Education) with 7 work packages for diagnostics & therapy.
- Ongoing legislative work to improve data sharing in a responsible way, a new research and innovation bill will enter into force from 2021.
- Sweden is a signatory state to the 1+million Genome Initiative.
- GMC Karolinska focus areas;
    - Rare diseases: WGS, <2 000 samples per year, in 5 years 10-15 000 samples per year.
    - Cancer: solid tumours and leukaemia, expected to increase from 10 000 samples per year today to 50 000 samples per year in 5 years.
- Key challenges are related to ethical and legal aspects, IT informatics platform, access to drugs and clinical studies, competence provision (training), health economy, industry cooperation and long-term financing.

The European 1+ Million Genomes from a Norwegian perspective

Speaker: Grethe Synnøve Foss, project manager for the Norwegian Strategy for Personalised Medicine at the Directorate for Health and Care

Objective: Update on 1+Million Genomes initiative progress and fit with Norwegian progress in personalised medicine.

Key information:

- Norway is latest nation to join 1+ Million Genomes, signed in June 2019. The initiative now counts 21 countries.
- Aim: setting up a collaboration mechanism with the potential to improve disease prevention, allow for more personalised treatments and provide a sufficient scale for new clinically impactful research, by reaching at least 1 million sequenced genomes in the EU by 2022.
- Work is organised in 10 working groups, and Grethe focused on discussing WG2 on Ethical, Legal and Social Issues (ELSI).
- Matters to be discussed and decided include overall legal framework, territorial scope, activities, data contributions (healthcare, researchers, individuals, industry), data subjects, financing (investment for IT infrastructure, curation, operation costs) and access procedures (application form, decision criteria, administration).
- The Norwegian directorate of Health in WG1 Governance and WG2 ELSI, also to ensure alignment with National strategy for personalised medicine (2017-2021).
- Current work on the National strategy includes legal clarifications for sharing of genetic variants, ethical, legal, technical impacts of storing and sharing of genomic data, development of updated guidelines on cancer treatment and guidance to the laboratories on genetic testing, developing the financial systems for genetic analyses and providing information to the general public and professionals on personalised medicine. The guidance to laboratories on genetic testing will be released within EOY 2019, and updated later when clarifications on storing and sharing of genomic data are available.
- The Biotechnology act, regulating diagnostic and predictive genetic testing, is currently under revision.
- The Directorate's Board for personalised medicine is starting up December 2019, bringing together stakeholders from industry, healthcare, patient organisations, registries, professional organisations, research and

	governmental bodies and will be a vital mechanism to coordinate the implementation of the national strategy, ensure coordination with healthcare services and prioritisation of problems. • Public involvement and debate to ensure trust and consent will be key as sharing of Norwegian data into the 1+Million Genomes initiative is not covered by current consent process.

Nordic PerMedLaw initiative on the regulatory framework for personalised medicine

Speaker:	Gjertrud Bøhn Mageli, Oslo University Hospital
Objective:	Introduction to PerMedLaw

Key information:

- Gjertrud introduced the necessity for a legal network to identify and solve bottlenecks in implementation of precision medicine early.
- PerMedLaw started with and is a continuation from the BigMed legal work package.
- Example of BigMed legal work is recently release legal statement on sharing variant classifications.
- Further questions arise relating to genetic data with more variants and the incorporation of phenotype data.
- PerMedLaw hopes to gather legal professionals across the Nordic region and establish a discussion platform for precision medicine.
- Gjertrud encouraged hospital legal professionals to connect and engage in the discussion on legal issues to be prioritized and how to work together on the key issues.

Conclusions: There is a need for a cross-disciplinary approach to overcome the barriers to clinical genomics. With the inclusion of Nordic PerMedLaw in the NACG community, the ambition is to provide a forum for legal professionals in the Nordic to work together with clinicians and bioinformaticians to address key issues.

Experiences with Variant Exchange – practical cross-border sharing

Speaker:	Stephen McAdam, Digital Health Development Director, DNV GL
Objective:	Updates beta testing of the Variant Exchange that enables secure sharing of variant classifications and evidence between trusted partners.

Key information:

- Stephen introduced the Variant Exchange (https://variant-exchange.dnvgl.com/home) and its *raison d'être:* Sharing of variant classification data is key for patient safety and was identified as a priority at early NACG workshops.
- Needs identified included quality control and variant classification management, secure sharing with trusted partners of choice and discordance detection and alerts. Functional requirements included submit, search and access through API & GUI.
- A Data Privacy Impact Assessment (DPIA) and risk assessment were developed with support from BigMed partners (UiO, OUS), resulting in modifications such as free text options being removed to reduce risks of including person identifiable information to an acceptable level. The BigMed

	legal work package released a statement about the anonymous nature of classification data and the need to share, and the Directorate of Health in Norway is currently reviewing the issue of classification data and privacy risks. • Stephen provided a brief demonstration of the Variant Exchange and updated the forum on progress in beta testing with the Danish breast cancer variant classification group and Oslo University Hospital. Stephen also invited other groups to participate in the beta testing for Q1 in 2020.

Next generation sequencing of common and rare diseases in Iceland - interdisciplinarity

Speaker:	Patrick Sulem, Head of Clinical sequencing, deCODE genetics/Amgen, Iceland
Objective:	Share experience from deCode from the last twenty years, and WGS from last 8 years

Key information:

- Patrick introduced the deCODE genetics Sequencing project in Iceland (320 k inhabitants) over the last 20 years, where WGS of 60 k Icelanders has revealed >100 M variants.
- DeCode is a population based genetic research resource in context of rare disease. It contains information from de novo mutations, recessive diseases, trios and siblings.
- The last eight years: complex traits association with common and rare variants

Research output examples include:

- APP variant reducing risk / protects against Alzheimers and age-related cognitive decline.
- TREM2 variant associated with Alzheimer's (incomplete penetrance but high risk).
- LOF variants in ABCA7 confer risk of Alzheimer's.
- BRCA2 999del5 mutation carried by 0.7% of Icelandic population a high-risk mutation for breast and/or ovarian cancer (75%). A website has been set up to allow people to access information about their carrier status, which has been visited by ~29 000 women and ~10 000 men.

Discussion

Answers to questions include: Academic institutes and collaborations welcome, with limitations, GWAS interpreted data can be supplied. Data is stored locally in an isolated platform. Not connected to Beacon, but 2600 variants and annotation published on EGA archive.

Clinical genomics at scale; lessons from Illumina

Speaker:	Paul Jones, Head of Population Genomics, EMEA, Illumina
Objective:	Share learnings from collaboration with Genomics England (GE) on how to develop a partnership framework to support population genomics at scale

Key information:	• Paul introduced the challenges of population genetic that have been identified through the GE endeavor. These include issues relating to accelerating adoption, affordable population health, value calculations from genomics, cross-sector collaborative requirements, a learning health ecosystem, and prioritization on a global agenda. • Progress blockers were met by strategic responses to stimulate transformational rather than incremental change, focussing on minizing delivery risk, innovative commercial models, building and promoting international community for collaboration, including global industry actors and facilitating international research agenda through alignment of approaches (e.g. data fabric). • Stated the importance of clear governance of an initiative to achieve its potential; from defining and sharing vision, setting goals and targets, engaging stakeholders, identifying levers and barriers, evaluating options, building business case, extablishing funding mechanisms, creating entity, leadership and structure, agreeing governance to defining clear KPIs. • Summarized key choices and decisions to be made to implement a genomics enging at population scale and emphasized the importance of separating out the different industry agendas to achieve success: 1) pharma & biotech engagement, 2) integrating platform partners and 3) stimulating economic development.

Towards a regional and national strategy for clinical cancer genomics in Sweden

Speaker:	Valtteri Wirta, Director, Clinical Genomics facility, Science for Life Laboratory (SciLifeLab), Karolinska Institutet, KTH Royal Institute of Technology & Head of Operations, Genomic Medicine Center Karolinska, Karolinska University Hospital
Objective:	Introduce cancer focus in Genomic Medicine Sweden and Genomic Medicine Center – Karolinska, and set the stage to discuss further Nordic collaboration in clinical cancer genomics.

Key information	• Valtteri discussed the necessity of different sequencing strategies for cancer genomics, with a vision for joint infrastructure for research, clinical trials and diagnostics for improved patient outcome. • Summarizing the Swedish healthcare system, Valtteri introduced the 21 independent healthcare regions and 7 university health care regions, with their strong tradition of lab developed tests, and the balance between expectations of equal healthcare services while there is no direct governmental decision making on regional issues. • Cancer (solid tumors and leukemia) and rare diseases are current focus areas for the Genomic Medicine Sweden (GMS) initiative. The cancer samples per year in routine diagnostics is today 10 000 samples, expected to increase to 50 000 wihin the next 5 years. • Currently setting up broad project specific panel bases, data generation and bioinformatic workflows, including TWIST technology and SCOUT. • Highlighted opportunity for joint development in the BALSAMIC (Bioinformatic AnaLysis pipeline for SomAtic Mutations in Cancer) project: https://github.com/Clinical-Genomics/BALSAMIC. • As an example of GMS pilot project, Valtteri discussed WGS for pediatric cancer diagnostics where sequencing and analysis of 350 children per year in parallel with conventional standard-of-care-diagnostics has been initated

(https://www.barncancerfonden.se/barncancerrapporter/barncancerrapporten-2018/med-vilfred-mot-framtiden/).

- While the CancerCoreEurope collaboration partner includes seven European partners), the audience was encouraged to consider opportunities for a stronger Nordic collaboration.

Genomic medicine in clinical oncology

Speaker:	Kristoffer Rohrberg, Head of Phase I unit, Rigshospitalet, Copenhagen
Objective:	Update on progress in Denmark

Key information:

- Kristoffer reviewed the transition to tumour agnostic treatments in oncology as a paradigm shift, where the prerequisite is detailed biological understanding coupled with clinical data showing large magnitude and consistency of effect in patients with rare & refractory cancers, where there are limited therapeutic options.
- The heterogeneity in cancer was demonstrated in patients with adenocarcinoma of the lung, differentiated per driver oncogenes, heterogeneity within patients with EGFR mutations and heterogeneity in resistance mechanisms.
- A review of the Copenhagen Prospective Personanlized Oncology (CoPPO) was provided.
- Reviewed patient referral route to phase I unit, and consequent genomic strategy (Biopsy, WES, RNAseq, expression array, Germline seq) as well as outcome for included patients (actionable targets/progression).
- Genomic analysis for end-stage cancer patients is at different levels of implementations in the different Danish health regions. A national genomic tumourboard was recently launched to discuss genomic reports (virtually) and abberations that are actionable or open clinical trials that a patient can be enrolled in.
- A Danish nationwide clinical trial on targeted cancer treatment based on genomic profiling (ProTarget) has been introduced.
- Kristoffer proposed the potential for Nordic collaboration in cross-border referrals to trials (leading to more Nordic trials, treatment options and treatments for rare aberrations in trial), Nordic tumour board and Nordic investigator initiated trials.

Conclusions: There is potential for Nordic collaboration in cross-border referrals to trials (leading to more Nordic trials, treatment options and treatments for rare aberrations in trial), Nordic tumour board and Nordic investigator initiated trials.

Systems biomedicine for precision therapy in cancer

Speaker:	Caroline Heckman, Institute for Molecular Medicine Finland (FIMM)
Objective:	Update on progress in Finland

Key information:	• Caroline presented an overview of the functional precision medicine program for hematology in Finland with examples in multiple myeloma and acute myeloid leukemia, and expanding of the program to solid tumours with the iCAN flagship program. • According to the FDA less than 10% of US cancer patients benfit from genome-driven targeted treatment strategy (2018). Clinical application in real-time requires deep molecular profiling and profiling of ex vivo drug sensitivity and resistance testing to explore dependency on signalling and predict clinical response. • Presented the Finnish hematology registry and biobank with samples from patients with a hematological disease, where samplelogistics, processing and coding is done by the FRCBS and storage is at FIMM. Researchers (including pharma) apply to the FHRB board for use of samples, and data is regruned to the FHRB database (www.fhrb.fi). • Caroline described the multiple sequencing platforms and functional drug testing platform at FIMM, enabling pharmacopeia-wide drug sensitivity and resistance testing with dose-response curves for each drug. Examples of stratification of myeloma patients based on drug sensitivity profile was provided, where drug sensitivity defined myeloma subgroups showed different clinical outcomes. • Discussed extension of approach to solid tumours, using ovarian cancer as example. • The iCAN flagship programme was introduced, discussing the organisation of the digital precision cancer medicine platform and the four defined pilots (colon, breast, ovarian cancer as well as hematological malignancies) while new pilots will be defined.
Conclusion / summary:	• Functional platforms to assess drug effects on patients cells in real-time can facilitate identification of drugs that could be readily repurposed for patient care. • Integrating information from functional testing with genomic, transcriptomic and other molecular profiling data can help identify indicators of response. • However, validation of the functional testing platforms and the identified therapies is required through clinical studies. • Cross-comparison of different assays and standardization is also needed.

Genomic medicine in cancer and & precision drugs

Speaker: Per Barfod Andersen, Nordic diagnostic manager, AstraZeneca (AZ)

Objective: Update on AZ activities in cancer & precision drugs

Key information:	• Per introduced AstraZencas' current precision medicine portfolio of >30 diagnostic test approvals linked to 6 precision medicines and $230 million invested in diagnostic partnerships. • AZ's oncology precision medicine value cycle includes biomarker discovery, diagnostic development and commercial delivery. • FDA's new drug and biological approvals 2018: one-third of all new approvals were first in class offering a novel mechanism of action. • Need to balance biomarkers & efficacy to maximize patient benefit; all-comer drug approach is not future-feasible (efficacy and price would not be appropriate). • Drug approval go through an EU central medicine authorization, and then local process including review and prizing.

	• Reviewed standardization problems as NGS panels differ in content and breadth across partners, highlighting the necessity for building own specific panels.
Conclusions:	Leading pharmaceutical companies are very interested in actionable targets identified in WGS for precision medicine and invest in their research and diagnostic portfolio through partnerships and other licensing strategies.

Models to drive innovation through targeted treatment approaches

Speaker:	Duarte Marchand, Country Manager for Takeda Norway
Objective:	Update on Takeda activities and models to drive innovation through targeted treatment approaches
Key information:	• Duarte introduced Takedas' history, modality diverse partnership models and focus on innovation through targeted treatment approaches, specifically in Oncology. Vision: strive towards better health and a brighter future for people worldwide through leading innovation in medicine. • Reviewed pharma industries growing interest in smaller patient groups where targeted treatments can yield result; accelerated oncology drug approvals are driving more solutions for targeted patients becoming available. • Competing pharma strategies to accelerate discovery, Takeda has prioritized to focus on modality diverse TA and multiple partnerships (200+) to increase likelihood of success by maximizing therapeutic options. • Takeda has a diverse pipeline portfolio; two late stage pipelines in oncology that are targeting specific small patient population groups. • Takeda has a virtual Center of Excellence for Evidence Generation that partners with local bodies (academia and clinicians).
Conclusions:	The unprecedented increase in number of NME since 2001 is driven by more targeted approach. To sustain the pace of drug discovery, key choices need to be made in strategic approach to R&D. Takeda believes that their unique approach towards partnerships will yield better results moving forwards.

Figure 4 Panel guests (L-R; Per Barfod Andersen, Nordic diagnostic manager, AstraZeneca, Caroline Heckman, Institute for Molecular Medicine Finland (FIMM), Duarte Marchand, Country Manager for Takeda, Kristoffer Rohrberg, Head of Phase I unit, Rigshospitalet, Copenhagen))

Opportunities for Nordic collaboration in clinical oncology – panel discussion

Session lead:	Valtteri Wirta, Director, Clinical Genomics facility, Science for Life Laboratory (SciLifeLab), Karolinska Institutet, KTH Royal Institute of Technology & Head of Operations, Genomic Medicine Center Karolinska, Karolinska University Hospital
Objective:	Discuss opportunities for Nordic collaboration in clinical oncology
Panel participants:	- Kristoffer Rohrberg, Head of Phase I unit, Rigshospitalet, Copenhagen - Caroline Heckman, Institute for Molecular Medicine Finland (FIMM) - Per Barfod Andersen, Nordic diagnostic manager, AstraZeneca (AZ) - Duarte Marchand, Country Manager for Takeda

Key information:

- The pooling of patient data is highlighted as attractive for pharma companies, however the lack of harmonization within a country and across the Nordics, as well as different regulatory bodies and financing agreements in each country, is prohibitive to initiating clinical studies that require high numbers of patients.
- Unique data commodity in Nordics offers value, but doubt cast on value maximization from this. Access applications take 9 months to process, cross database use is difficult (ehealth initiative to simplify). Needs industry collaboration, and 'true partnerships' as opposed to investigator-initiated trials, to improve landscape.
- Health data and registries must be linked to biobanks in a streamlined fashion.
- Requirement for paradigm shift. Necessary to feed new technology into a new system (eg digitalization) rather than trying to use the old one.

	• Cancer field therapeutics offer pharma the best 'money-makers' in their pipeline, but how development of these is prioritized is an ethical and economical consideration (5th 6th stage of treatment in a larger patient group or unmet need in micro patient population).
Conclusions:	The Nordics can gain a competitive advantage on access to pharma pipeline drugs for precision medicine clinical trials through collaboration and pooling of patient registries and biobanks. The unique breadth and accessibility of Nordic health data offers an advantage in applications for innovation funding, but this is amplified if larger collaborations are formed to compete with those offered across Europe.

Symposium closing remarks

	**Speaker:**	Dag E. Undlien, OUS, NACG chair
	Objective:	Conclude symposium and update from steering committee meeting 20th Nov.
NACG membership	Dag welcomed two new members to NACG: • Aarhus University hospital • Helsinki University Hospital	
NACG steering committee	During the NACG Steering committee meeting 20. Nov 2019, steering committee elections were carried out based on nominations from the membership and as previously communicated to the membership. The new steering committee composition is provided in Table 4. Three members were thanked for their contributions to the board as their serving time has come to an end: - Karin Wadt, - Maria Rossing - Joachim Lundeberg	
Next NACG workshop	The 9th workshop will take place in Reykjavik 11th-12th May 2020.	

Table 4 NACG steering committee per Nov 2019 election

Role	Name	Institution	Expiry of new SC-period
Chair	Dag E. Undlien	Oslo University Hospital	Nov 2022
Vice chair	Valtteri Wirta	Karolinska Institutet/ SciLifeLab	Nov 2020
Vice chair	Morten Dunø	Rigshospitalet	Nov 2022
Member	Stephen McAdam	DNV GL	Nov 2020
Member	Jón Jóhannes Jónsson	Landspitali – National University Hospital	Nov 2020
Member	Janna Saarela	FIMM	Nov 2020
Member	Ane Yde Schmidt	Rigshospitalet, Center for Genomic Medicine	Nov 2022
Member	Kasper Thorsen	Danish Genome Centre	Nov 2022
Member	Gjertrud Bøhn Mageli	OUS legal, representative for Legal network	Nov 2022

Figure 5 Presenters from symposium and workshop

NACG Workshops

The workshop was organized as illustrated in Figure 6, detailed agenda is available in Appendix 1.

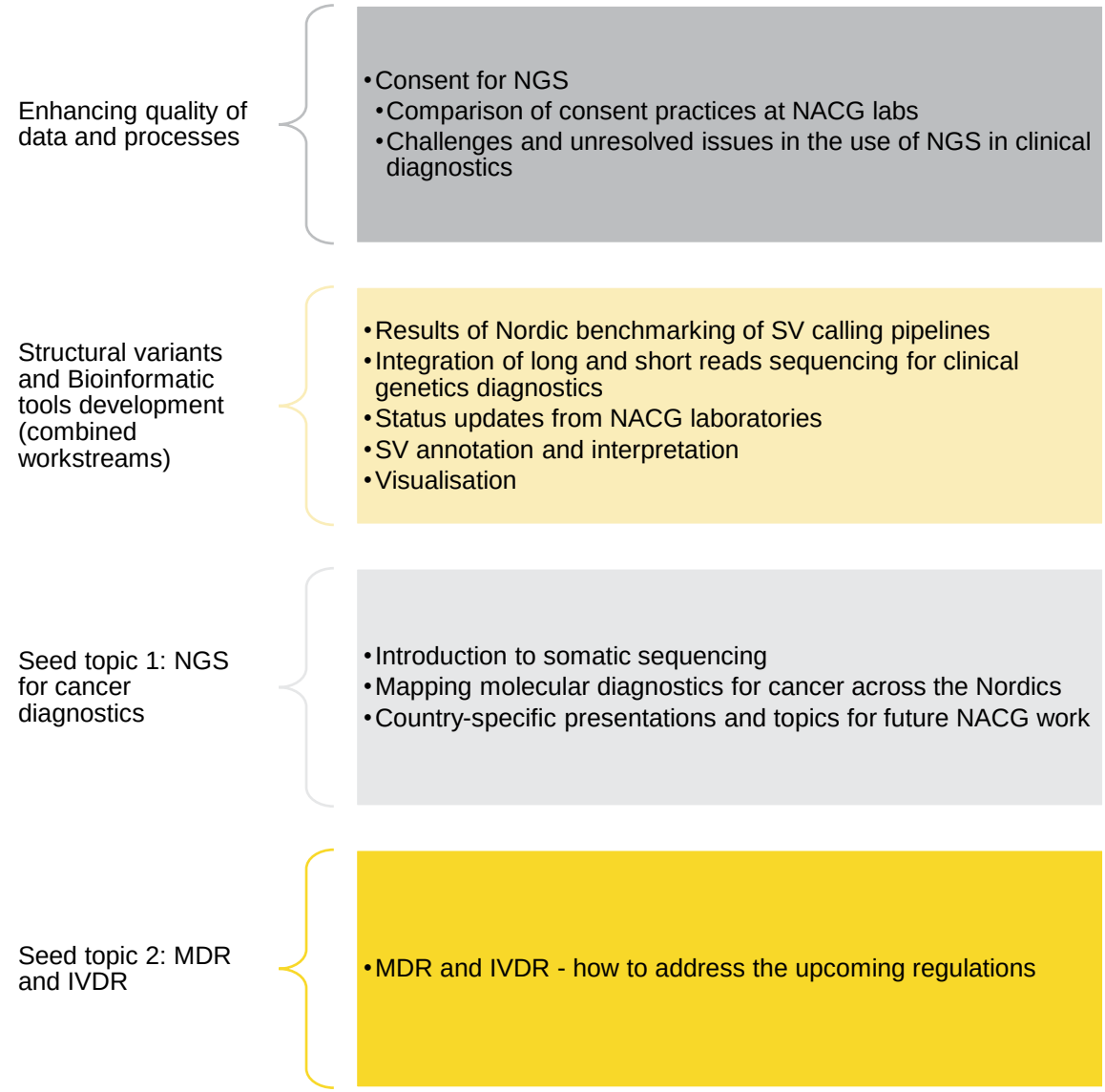


Figure 6 Workshop outline

Consent for NGS

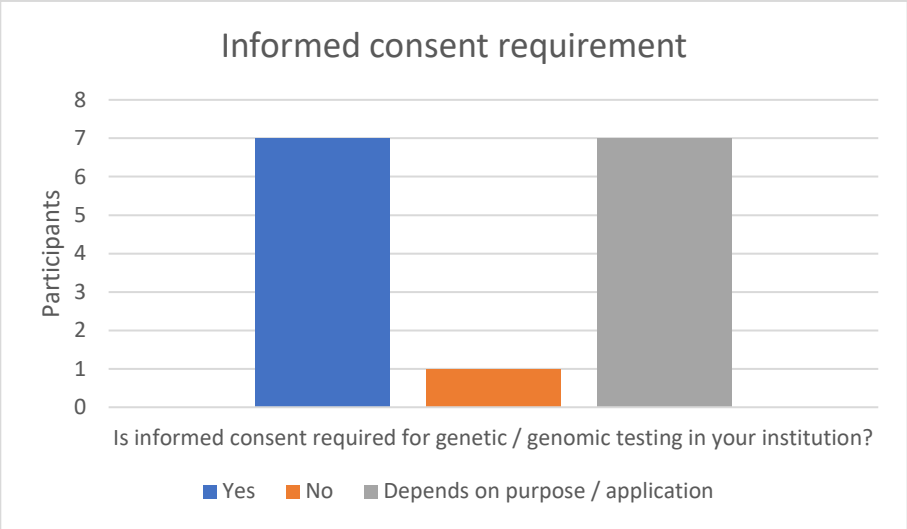
Working group lead: Sharmini Alagaratnam, DNV GL & Kaisa Kettunen, HUSLAB & FIMM

Enhancing quality of data and processes

- Consent for NGS
- Comparison of consent practices at NACG labs
- Challenges and unresolved issues in the use of NGS in clinical diagnostics

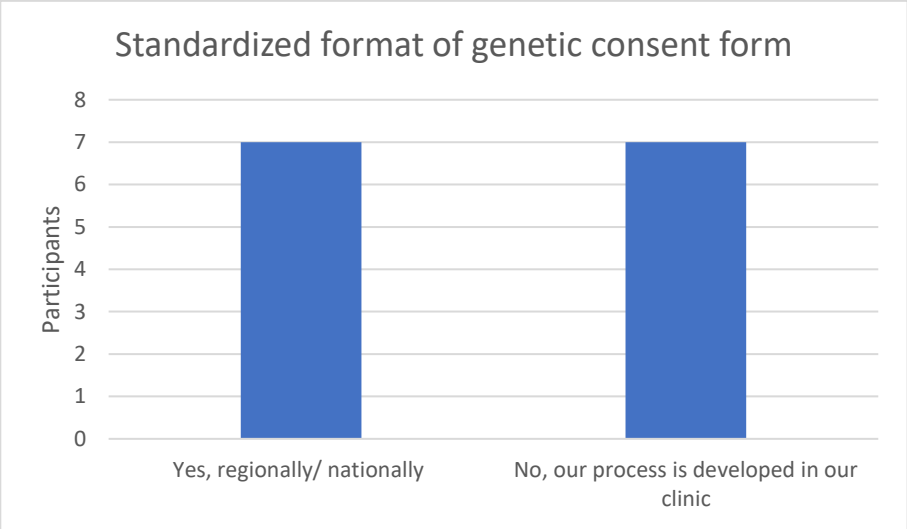
Introduction to consent requirements

	Speaker:	- Line Borgwardt and , Centre for Genomic Medicine, Rigshospitalet - Christina Westmose Yde, Centre for Genomic Medicine, Rigshospitalet
	Objective:	Understanding informed consent procedures in genomic testing and reviewing forms, policies and systems across the world
Introduction	Sharmini and Kaisa first introduced the modus operandi of the working group, past topics and the relevance of consent in clinical genomics.	
Setting the stage	Informed consent as a tool in genomic testing - Legal requirements - Content of consent - Process of consent Most important - Consent to secondary findings being returned - What happens to the data; can it be used for research? - Where is the data kept? DK NGC: common national consent; harmonized across Denmark	
Expectations	Workshop expectations focused mainly on understanding the systems and consent forms set up in the different countries and if / which electronic platforms are in use.	
Baseline for workshop	Baseline for the workshop was established through the following Menti poll questions and follow-up discussions on consent practices.	

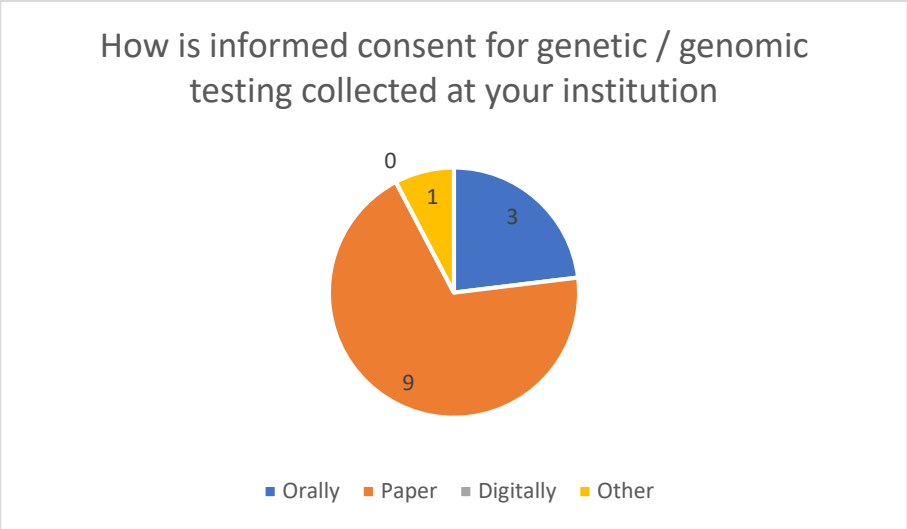


- Norway: implicit consent is widely used; medical records often only document that the patient has been informed.
- DK: Always implied; more focused on information transfer. Consent is now being more formalized
- FI: Patients are informed, but do not usually sign. In the case of exome sequencing then written consent is secured.

Audience question and discussion on genetic exceptionalism: Introducing consent makes the patient concerned when not used to it in other forms of medical testing.



- DK: Harmonized through new law, even if guidelines were also previously available



How is informed consent important / relevant for your work
- For recontacting patients (data is stored) - What to do with the secondary findings? - To know patient preferences; e.g on return of results of secondary findings, reanalysis would be useful - Secondary findings and research use of data - Important for knowing what results can be given to the patient. - For research purpose and ethical approval issues - Secondary findings - If I see a secondary fiinding - Can't release data without - Very important! To give the right information to the patient - To have the possibility to share data - It is necessary condition for doing our work and to progress ahead - Ensure that the info about the test has been given and is understood by the patient - Necessary for research unless get exception from REC. - Because we are considering building "Consent as a service" pilot

Conclusions	Discrepancies exist between method of obtaining, structure and content of consent forms across the Nordics. The process of requesting consent can be intimidating to patients.

Consent regulation and practice in Denmark

	**Session lead:**	Peter Johansen, Denmark National Genome Centre
	Objective:	Familiarization with the new law covering genomics and consent in Denmark
Presentation	Recent law announcement (4th April 2019) - Consent to receiving treatment (diagnosis, treatment, maternity care, rehabilitation, health care as well as prevention and health promotion in relation to the individual. - Information to the patient is given verbally and handed out in writing. - The patient has the right to decline information about his current health and treatment. - Data storage is a prerequisite for receiving treatment/diagnosis, as such consent is NOT obtained for this purpose. - Right to revoke consent at any time, although how to implement this in practice not yet determined. - Written consent must be collected for but is not limited to the following analyses: WGS, WES, Total RNA seq and GWAS with extensive mapping of rare variants. - Genomic data is stored at the National Genome Center (mandatory by law). - Data can be used for research unless the patient opts out. Written consent form (National Genome Center) covers agreement for treatment, sharing of incidental findings with participant, information storage at the NGC, the possibility of contact later in life if new knowledge is discovered and information on the possibility that data may be used for research.	
Discussion	Access to genomic data for research purposes is approved by ethics committee. Individuals who wish to opt out of research inclusion will be flagged and their data kept in a separate repository. The sharing of data is not explicitly mentioned in consent forms. Wording in law often includes a passage that delivery of information on genome sequencing and collecting of consent should be separated in time. Consent is required for the NGC to return the data to the requisitioning clinic. Clear and official clarification on practical implementation issues related to consent are resolved by contact point at NGC. In instances of trio testing, consent is required from all three individuals undergoing seqencing.	
Conclusions	Standardization of consent protocols in Denmark has been enforced following introduction of a new legal precedent in April 2019. Following the giving of verbal and written information, written (paper) consent must be obtained prior to clinical inclusion. Inclusion of data in research is synonymous with clinical consent; opt-out is required for exclusion. A digital solution for management of consent is being developed.	

Consent documents from around the world

	Session lead:	- Sharmini Alagaratnam, DNV GL - Kaisa Kettunen, HUSLAB & FIMM
	Objective:	Review consent documents from six institutions/countries
	Workshop outline:	Identify likes and dislikes from consent documents and used this to consider how to address issues relating to data storage and sharing, secondary findings, scope, design of information and process, re-analysis and re-contacting and research within the consent documents.
		Consent documents from Genetics England, Australian genomics, Denmark (NGC), Iceland (Landspitali), Oslo (OUS) and Sweden (Sockholm) (Figure 7) were reviewed, focussing on selected key topics. See Table 5 for summarized results.
		Jon J. Jonsson (Landspitali - Univ. of Iceland) introduced the WMA Declaration of Reykjavik – Ethical considerations regarding the use of genetics in health care and the specific points relevant to consent contained in this document including informed consent, additional findings, confidentiality, third parties and potential gene therapies.
Conclusions		Discussions on important consent issues, solutions, suggested elements and specific dislikes were identified. These elements are summarized in Table 5.

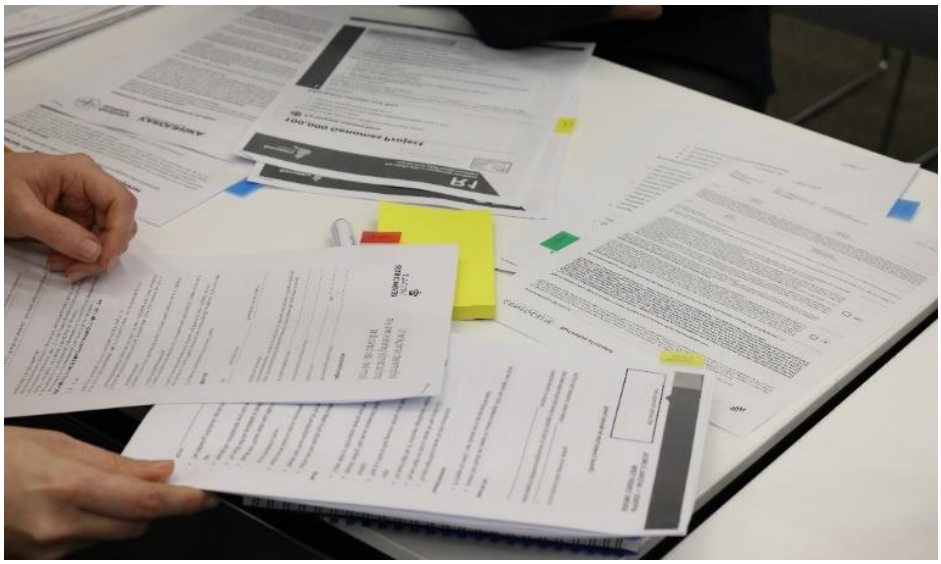


Figure 7 Consent documents for consideration from Genomics England, Australia Genomics, Centogene, Denmark, Landspitali (Iceland) and Karolinska University Hospital (Stockholm).

Table 5 Aggregated topics

	What's good/bad about the forms reviewed?	Suggested elements and solutions	Dislikes: What don't you want?
Data storage and sharing: Do patients understand how data is used / stored after consenting?	- Centogene: not tested if do not consent to data sharing? - DK: Data storage limited to the one server. Sometimes need to download. Change workding to limit to "healthcare system"? - OUS: No data sharing with insurance companies - Data sharing & reuse of data for future patients Do patients understand how data is used/ stored after consenting? - Data sharing & reuse of data for future patients often missing - Use of data for QC in NGS lab - Data sharing for different purposes: o Research o Diagnostic o QA	- Need to share data for diagnostics (help the next patient) - Need to share data for QA o "Legal issue" o Opt out o National QA database (implied consent) - Research: split between own disease and general - Explain what data is shared and what that means - Need to share genomic + phenotype information - Patient control by having access to consent & withdrawal (-research)	- Don't include too specific information on databases for sharing because this can changes over time - Do not want to reconsent for "everything" - Do not want unrestricted sharing of personal data (unless consented) - - Do not want to lose patient trust
Secondary findings: Which secondary findings to report, what do patients expect?	- DK: No defined list of which incidental findings need to be reported back - Australia: Should split between actionable and not for incidental findings, opt out - Unexpected non-paternity - Centogene: Risk of family relationship findings not included - What do patients expect? - Active or passive? - Genomics England's formulation indicates actively seeking additional finding - - DK NGC Question: what are the patient expectations on non-actionable secondary findings?	- Terminology secondary / incidental fidnings - Shared definitions - Education/information about findings - Limitations - General list of SF for patients - - Way for lab/test to react to SF wishes, i.e. run a duo, rather than do not test	Revealing SF without - Counselling - Understanding & consenting Specific list of SF for patients: "we have looked for these"
Scope: What is the breadth of consent obtained?	- DK: Unclear definition of when consent is needed or not, currently technology based. - How to manage resources to prioritize main illness instead of managing secondary findings - - Are people consenting to things where they do not really have a choice? Misleading.	- What do we need formal consent vs verbal consent for? o Formal written consent, omics or predictive o Not practical to inform / obtain consent when patient (patient family) is exhausted o Iceland: no rules to regulate storage of raw data - Do we need to ask or just inform about actionable findings? - No to actionable: consents for family members - Inform about data sharing (opt out) - Inform for recontacting - Risk of identifying nonpaternity	Clinical setting: do not ask the patient if they do not have a choice

Information and process: Is the information accessible?	- Design and phrasing of form important for conveying information to patients:
	  ○ Genomics England simple, divided into sections, plain language used
	  ○ Australian Genomics: Long, should the clinician spend so much time on the marginal questions?
	- Lack of contact information through the process
	- How to communicate uncertainty without compromising trust
	- Tailoring of information for different patients
	- Clear language needed
	- Understanding background; need for translation of information provided to patient?
	- Non-findings vs negative findings
	- Requirement for written information
	- - Shared decision making
		- Ask the patients!
		- Understandable language is important
		- Divide into subjects
		- Highlight the most important
		- Information sections
		- Different levels of information, dynamic for patients interested in learning more (need to know vs. nice to know levels)
		  ○ Link to videos
		  ○ Optional extra information
		  ○ Phrasing: I understand…., I agree…
		- Consent part:
		  ○ Clear separate section,
		  ○ Phrasing: Yes, I want…, No, I do not want…
			No go: risk of filling out wrong!
			- Forms needs to be fail-safe
			- Unclear phrasing
			- Small fonts that are unreadable
			- - Too much information in consent part

Reanalysis & re-contacting	Information on reanalysis / recontacting often missing	Communication of uncertainties without impacting trust Consent scope - Legal requirement to document - Do we need to store all this data? (for what purpose? □ national discussion) - - Unclear definition of when consent is needed or not (DK). Technology as a qualifier	

Research: Consent for Inclusion of data in research?	- Research vs clinical
	- Broad vs specific (my disease or similar disease) research consent
	- Karolinska:
	  ○ Consent is only for participation in research?
	  ○ No opt out option?
	  ○ No diagnosis without consent?
	Research vs. diagnostic
	- Clarity of what the difference is
		- Separate research and diagnostics or opt out the research
		- Digital consent (Norway:minhelse.no?)
		  ○ Should be electronic while requisitioning
		  ○ Both consent and requisitioning is today on paper
		- Norway: different laws regulate research and diagnostics
		  ○ Norway: NGS quickly bridges to research, and different demands to clinic and research is confusing
		  ○ Research triggers need to inform the patient about how long the data will be stored
		  ○ Clinic: data storage needed for mandatory documentation	

Structural variants & Bioinformatic toos development

Structural variants and Bioinformatic tools development (combined workstreams)

- Results of Nordic benchmarking of SV calling pipelines
- Integration of long and short reads sequencing for clinical genetics diagnostics
- Status updates from NACG laboratories
- SV annotation and interpretation
- Visualisation

Session lead:	- Tony Håndstad, AMG, Oslo University Hospital - Oleg Agafonov, DNV GL, - Rasmus Lykke Marvig, Rigshospitalet
Objective:	Share experiences in using SVs for clinical diagnostics, examine SV-calling methodology, and discuss benchmarking results of SV calling pipelines from the NACG laboratories. Discuss a detailed overview of downstream processing, including tools and strategies for merging results of multiple callers, annotation visualization.
Workshop outline:	1) Results of Nordic benchmarking of SV calling pipelines 2) Talk: Integration of long and short reads sequencing for clinical genetics diagnostics. Anna Lindstrand 3) Status updates from NACG laboratories 4) SV annotation and interpretation 5) Visualisation of SV: tools and best practices

Results of Nordic benchmarking of SV calling pipelines

Session lead & facilitator:	Oleg Agafonov, Senior Researcher, DNV GL
Objective:	Present and discuss results of Nordic benchmarking of SV calling pipelines

Results from benchmarking

Benchmarking was performed for raw variant sets received from three laboratories. In addition we supplemented a callset from Manta variant caller executed on BaseSpace cloud platform.

- Benchmarking was performed with GIAB SV 0.6 callset (Ashkenazi trio: Zook *et al* 2019) and Truvari, a Structural variant comparison tool (https://github.com/spiralgenetics/truvari). Resulting metrics - precision, recall and F1 score were compared between the laboratories, Figure 8.

- Participants of the benchmarking discussed that in order to achieve high sensitivity, one need to merge results from several callers. Various callers were shown to have high performance for different variant types. However, merger of variants from multiple callers can add noise, although this can be reduced through filtering, potentially prior to clinical use. Some callers e.g. Manta utilize a variety of algorithms for detecting variants and are undergoing development to become a universal caller, however, this process takes time.

GAIB 0.6 SV callset is limited to insertions, deletions and tandem duplications, and excludes other types of variants. To overcome limitations of the benchmarking with GIAB callset, it is possible to develop a complementing artificial set of variants, or a collection of real varains injected in a sample.

Panel discussion

First, participants of the workshop were asked to discuss in small groups challenges, experiences and solutions regarding calling structural variants and benchmarking of variant calling pipelines. Each group had a task to formulate 3 questions, which they would like to be discussed in a panel. These questions were entered to slido, and up/downvoted by the participants. Questions receiving the highest number of votes were addressed to the panel. The panel discussion is summarized in Table 6 below.

Participants of the panel:

- **Henrik Stranneheim,** Head of Bioinformatics, Clinical Genomics, Scilifelab, Stockholm
  Senior bioinformatician, Centre for inherited metabolic diseases
- **Rasmus Marvig**, Head of bioinformatics, Center of Genomic Medicine, Rigshospitalet, Copenhagen
- **Tony Håndstad,** Bioinformatician (coordinator of diagnostics bioinformatics), Department of Medical Genetics, Oslo University Hospital, Oslo
- **Anna Lindstrand,** Head of the Clinical Genetics diagnostic laboratory, Karolinska University Hospital
  Group leader for Rare Diseases research group, Department of Molecular Medicine and Surgery (Karolinska Institutet), Stockholm

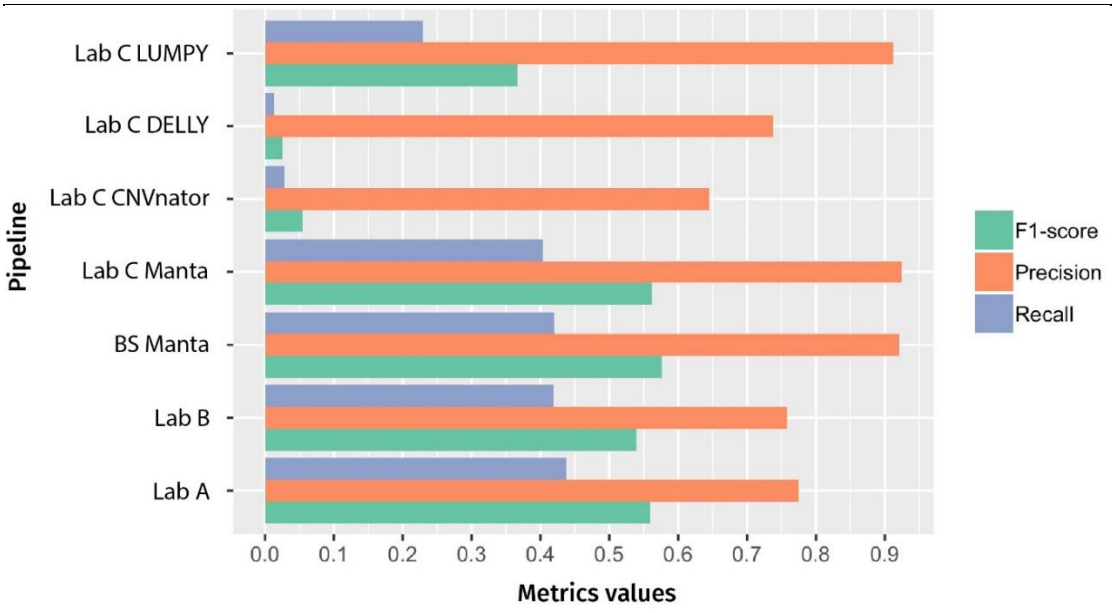


Figure 8 Performance of tested variant calling pipelines and tools over insertions (including tandem duplications) and deletions. Two complete pipelines (with combined outputs from multiple tools) from Lab A and Lab B were benchmarked, along with results from individual variant callers provided by Lab C (Lab C LUMPY, Lab C DELLY, Lab C CNVnator, Lab C Manta). In addition, results from Manta executed on BaseSpace cloud platform (BS Manta) are presented.

Table 6 Summary of panel discussion on SV calling benchmarking

Question	Answer
What is the benefit of using linked reads compared to long reads? What does one gain?	Linked reads add resolution specificity, gain in precision. It allows to bridge repeat elements or to phase data.
Should we only call variants in regions we can interpret?	Inversions can be quite large, too many genes, need to be able to relate to the clinical analysis – but they may have additional information that could aid analysis. Everything should be called in coordination with databases and *in silco* panels afterwards to decipher importance.
Should reported CNV calls always be confirmed by alternative methods? Is this practical in all sorts of regions?	SV calling is still pioneering, therefore we should use orthogonal methods for confirmation. For SNVs this may not be necessary if there is a good quality call that fulfils criteria, but CNVs should be verified. This differs from case to case, often there is a necessity to do PCR across the breakpoint
Can we realistically share actual patient (verified) variants (and fastq files)?	This can be done under the right circumstances. SNPs are shared, so if legal precedent can be determined this should be done. FASTQ sharing depends on the region etc. Possibly we will move away from data sharing and more likely to do portable pipeline, or solutions similar to 'Beacon'.
How many labs are using WGS for SV calling today?	SciLifeLab has implemented that. Overall, there is an agreement in the field to move in this direction.
Do we need multiple callers and why?	Different callers vary in their ability to detect different types and sizes of variants. Publications call for multiple callers, some are more accurate than others and integrate more types of signals into the algorithm. It is possible to get some boost in the recall by using multiple callers. Additionally, we need read depth caller to get breakpoints (CNVnator – internal quality checks included, variants greater than 5 kb, not good for small variants). Manual curation is still a necessity. Mobile element callers should also be considered.
Access to pipelines is not easy, this makes it hard to insert data, why is this the case?	Bioinformatics lack some usability. The software can be portable, however, pipelines are more complex. Online access would be helpful. An agreement that incorporating databases into a package for download would be helpful. SciLifeLab: Not easy but not that difficult to use – doable and will help. A problem is that the run time environments (e.g. the compute clusters) all have slightly different quirks and requirements, so even the use of frameworks like Nextflow and Singularity must be customized to each site to some degree. No control over pipeline when changes are made.
What are problems with VCF representations of SVs? How can we solve them?	Most callers do not follow the same standard, so adjustments are needed for combining variants form multiple callers, and this is where errors often arise. Standardization for VCF tags used for SVs would also be beneficial.

Reference graphs; how to improve?	Reference graphs lack standardisation. Truvari not able to handle in a good manner, there is a necessity to harmonise. VCF classification is too loose and not all adhere to the standard. The community should apply pressure to try and enforce this. Ultimately if they are not good they will not be used and will fall out of favour. VCF has a standard for tags and users should be encouraged to use them.
What are the limitations of the GIAB SV callset?	GIAB only contains insertions, deletions and tandem duplications that represent relatively short SVs; tools that benchmark against this are overfitted (not real data). Performance depends on a dataset; just using one is suboptimal and gives the wrong impression. Synthetic datasets for benchmarking struggle to reflect reality, with too many biases messing up the calling. It would be more ideal to use real data where we know the variants are; practically in clinical pipelines, this would mean having confirmatory data sets.
Should we only trust variants identified by more than one caller?	Need to ensure that we do not discard SVs just because it has not been called by multiple callers. However, it is impossible to report a large number of variants so filtering must occur.
Individual labs with own validation sets; can we share variants? Can we package the pipeline into a singularity to be run on that facilities' standard datasets?	It is not technically difficult to package single tools into singularity images to make sharing easier. Complex pipelines could be more challenging for packaging into a single container. Also, there is a concern that benchmarks can take them out of context (removes down- and up-stream).

Integration of long and short reads for sequencing for clinical genetics diagnostics

	**Session lead:**	Anna Lindstrand
	Objective:	Share learnings from the use of WGS and long-read technologies to resolve structural variants for diagnostics of rare diseases.

Key information

Balanced SVs may pinpoint human disease genes and represent missing heritability.

FindSV was developed as a wrapper for SV calling and filtering which showed high accuracy, sensitivity and precision in evaluation in samples with known SVs. Implementation of WGS-SV calling in monogenic rare diseases has increased the diagnostic yield.

Clinical examples reported:

- A founder duplication in LAMA2 causing neuromuscular disease with complimentary IHC staining of merosin confirming LOF mutation
- Complex intrachromosomal rearrangement disrupting three epilepsy genes

Clinically relevant SVs are detected in 6.5 % of monogenic WGS panels. A study of comprehensive WGS analysis in 100 cases referred for chromosomal microarray analysis and 30x PE-WGS resulted in the identification of 10 large CNVs which were detected with both CMA and WGS. Vcf2cytosure was

developed and used to export SV vcf to cgh file for uploading into the array analysis software. Analysis of WGS reveals the presence of derivative chromosomes and solves their genomic structure, detects two small CNVs not seen by array and detects repeat expansions. SNVs detected in a panel of 887 genes; 13 pathogenic/likely pathogenic variants and one case of maternal UPD detected. Limitations of short-read WGS SV analysis:

- balanced rearrangement detection rate 70-90% depending on cohort and data quality
- positioning of duplicates can be tandem/intersperse
- Phasing of SV and SNV, compound heterozygotes and complex rearrangements.

Complimentary WGS technologies to decipher SVs include 10X genomics, Bionano optical maps and Oxford nanopore. Chromosomal rearrangements with WGS are challenging to decipher. There is a necessity for complementary technologies alongside short-read WGS for determining balanced breakpoints located in repeats and multiple structural variants *in cis*. In addition to this, better analytical tools (callers and databases) are desired for solving complex rearrangements and screening linked and long reads. The reference genome is also a limiting factor.

Status updates from NACG laboratories on SV related work

Session lead: Oleg Agafonov

Objective: Status updates from NACG laboratories working on the implementation of SV pipelines in clinical diagnostics

Rasmus Lykke Marvig, Rigshospitalet

Started out testing using 11 tools for CNV (DEL+DUP) calling, WGS carried out on 44 in-house samples and NA12878

Sample	No. of samples	Reference call
NA12878	1 (2,076 CNVs)	Haraksingh et al. 2017; Sudmant et al. 2015
In-house samples	38 (median 7 CNV per sample)	CytoScan HD array
In-house samples	6 (1 CNV per sample)	MLPA

- No tool was found to be perfect. Precision was difficult to assess as we used a known truth set for NA12878 with only 2,076 CNVs (probably less than complete set of CNVs) and known truth for in-house WGS was Cytoscan HD microarray with only few CNVs per sample. Some tools did well in recall. We moved on with four tools into production pipeline: DELLY, Lumpy, CNVnator and Manta. Manta, DELLY, and Lumpy are recommended by Kosugi et al. 2019 for certain types of SVs.
- Filtered against gnomAD-SV and 70 in house WGS (uses SVDB)
- Calls of the same type that fulfil overlap (0.1) and breakpoint (1000 nt) criteria are filtered if prevalence in in-house WGS is >20% and gnomAD-SV is >5%
- SV pipeline accessible by all WGS to these callers, but rules are separate and additional output merging steps are required

SVs are a diverse group and multiple approaches are required to call from short reads. SV calling tools offer improved precision and recall for reference samples that have been used to develop callers, compared to real data.

Piotr Starnawski, Department of Molecular Medicine, Denmark (MOMA)	The majority of panels performed (approximately 100 genes) are carried out on clinical diagnostic cases related to cancer or heart disease - For WGS use Manta and Delly2 - For WES use ExomeDepth and Delly2 - Interpreters are happy with breakpoints for both - Combine results to a single vcf file. Interpreters use IGV to validate reports. Look at frequencies and occurrences to help filter false positives Utilize non-standard pipelines (not accredited, projects for terminal patients, borderline research projects) for somatic sequencing - For somatic cancer – Svaba, Delly2, CNVkit For mRNA pipeline – STAR-fusion, TopHat-fusion and Arriba
Henrik Stranneheim, SciLifeLab	SciLifeLab runs a comprehensive (SNV, INDEL, CNV, SV, repeat expansion, uniparental disomy, mitochondrial genome), rapid (5-14 days) rare disease diagnostic workflow. Large scale implementation >120 samples per month and 15 patient categories. - Scout SV view development tool utilised for gene panels. Filtering is required for use in the clinic - Short tandem repeats study verified in 9 samples with pathological expansions and screened on a set of 100 ID patients and a set of selected cases (n=32). Nucleotide expansion and colour code for pathogenic variants viewed in Scout. - Utilising chromograph (integrated into Scout) to visualise (PNG images) WGS and WES calls from trios and uniparental disomy - Carried out RNAseq pilot before summer for use in the clinic. Working on validating pipeline, plan to build database tools from the incorporation of new patients. Uniform DNA and RNA level and then use scout. Focus on custom developed informatics tools and solutions.
Tom Egil Sørlie, OUS	- OUS, DMG tested Parliament2 – complexity/safety concerns; docker packaging not supported in the computing cluster – ended up discarding Parliament2 and instead wrote own SV calling pipeline in Nextflow based on many of the same tools - Infrastructure challenges – time-consuming, 8x more data to process - Split pipeline to allow reanalysis of the same data Dragen pipeline is almost ready to be used, including Manta and Canvas (depth-based caller from Illumina). Nevertheless, it is not clear if this will work for all WGS.
Wrap up discussion	The development of a synthetic benchmark dataset was discussed. Participants favouring the inclusion of inversions and translocations. SciLifeLab postulated that they are working on the development of an open-source tool for the creation of a synthetic dataset. Results from the current benchmark study should form a small report, as documentation that benchmarking is occurring is valuable. As an alternative to developing a synthetic benchmark, using NA12878 control samples and other available benchmarks was highlighted as an alternative option.

SV annotation and interpretation

	**Session lead:**	Tony Håndstad
	Objective:	Share knowledge and resources for annotation, clinical evaluation and interpretation of SVs
Bioinformatic tools: Points to consider - Tony Håndstad, OUS	There is an agreement that multiple calling algorithms are required to capture all types/lengths of SVs accurately, but which ones? Consolidating multiple call sets to one unique set can be problematic: interpreters want to only see each variant listed once, how is this done? How do we keep track and annotate variants with in-house variant frequencies? Do we still need to improve the process for interpretation and develop tools/visualization methods?	
SVDB tool annotation and frequency – Jesper Eisfeldt, SciLifeLab	- WGS SV databases - Create database – do SV calling, filter and quality control - SV merging to determine which calls represent the same variant, many methods (reciprocal overall, wriggle, cluster analysis, machine learning, and Tools). - SVDB – DBScan – cluster based on breakpoint distance - subclustering based on overlap - Seven bridges graph genome suite - Vcfanno, SVDB or NIRVANA (Illumina) tools - Nirvana – lots of information including SV effects (.Net appliance) - LoqusDB observation count database – clustering in clinical genomics (faster and less exact) - *Public databases* - Available as VCF files – variants and frequencies - Large public databases with VCF file resources include 1000genome, SweFreq, GnomAD (15000 individuals), and Genome of the Netherlands (250 trios, 750 individuals). - Gnomad.broadinstitute.org offers a resource that aggregates and harmonizes WES and WGS data from large-scale sequencing projects, with summary data available for the scientific community - Different populations cause problems in the local self-built Nordic database (they cluster differently), then the global tools are more representative for SVs There is a necessity to re-create database when you make small changes to the pipeline.	
ACMG guidelines for CNV interpretations – Morten Eike, OUS	ACMG and ClinGen released new guidelines for interpretation of CNVs in Nov 2019. The purpose is both to increase consistency and transparency of CNV interpretations, and to better align SNV and CNV interpretation guidelines. The new guidelines are meant as a thorough but not exhaustive educational resource, apply to dominant Mendelian disorders and assumes true variants. Consistency is urged between patients, meaning a classification should not be downgraded only based on the absence of a specific phenotype in your particular patient. The CNV guidelines introduce a semi-quantitative, evidence-based scoring framework, primarily designed for single copy gains or losses (although they may be relevant to other types of CNVs). The criteria for assigning point values are split into five sections, separately for CNV gains and losses: 1. Genomic content, 2. Overlap with established (see supplementary material for useful examples), 3. Gene number, 4. External case review, 5. Inheritance/family history. The categorical strengths in the framework are similar to SNV guidelines, and sets point values -1 (benign) to 1 (pathogenic). Many criteria can be adjusted	

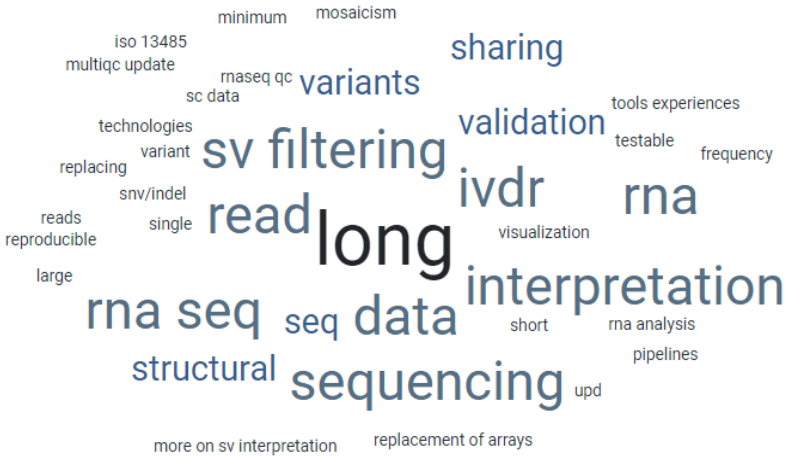
	within a suggested range, where score 0 is used for poor evidence. Adjustments are made in 0.05 increments (up to 20 choices) and deviations from the default value must be documented. - The final point value (min -1, max 1) decides the classification of the variant, using the same 5-tier classification scheme as for SNVs. An online calculator is available at cnvcalc.clinicalgenome.org.

Visualization of SV: tools and best practices

	Session lead: Rasmus Lykke Marvig **Objective:** Share knowledge of best practices of SVs visual inspection
SV visualisation – Rasmus Lykke Marvig, Rigshospitalet	A comprehensive survey of 35 visualisation tools has been published in 2019 in J. Hum. Genet. by Yokoyama and Kasahara. - Linear genome browser is good at showing short-read alignments - Dot plots are valuable for drawing alignments between two assembled genome sequences - Scatter plot works well for quickly capturing a genome-wide distribution of CNVs - Tables with SV details are good for getting an overview of candidate SVs and can be combined with filter functions - Circos plots; where chromosomes are arranged as arcs of a circle and SVs are represented by curves, allow visualization for a small number of large SVs - Graph Genome has value for visualising complex/nested SVs, e.g. when alleles differ in the sequence not present in the reference genome - Multi-way views allow multiple genome regions or samples in a single panel - Population view offers a tool to compile information from 100s or 1000s of WGS CGM uses IGV to visualize SVs with three tracks to help clinical analysts: 1. Read coverage in 10 kb bins 2. Discordantly mapped reads (coloured according to chromosome) 3. Reads with split alignments (coloured according to chromosome). Variants are coded as BEDs to make it easier to configure the appearance in IGV (breakpoint positions – INV and TRANS - with bold line, DEL and DUP by a thin line).
SV Visualisation - Jesper Eisfeldt, SciLifeLab	SVs are diverse – indels of 50 bp, affecting the entire chromosome in balanced and unbalanced ways - Different signatures and read depth: CNV, Precise versus imprecise - Visualisation relies on calling and filtering to give <100 variants. In clinical genomics use: Scout - Excel files for an overview - The clinic uses VCF2Cytosure which converts SV vcf to cytosure format - WIG track in IGV – convenient tool for scanning CVs - Scatterplots allow users to visualize read depth - IGV optimum for looking at the raw data - Circos plot good for big variants - Flowcharts: in research Draw.io (online flowchart editor) WGS to Karyotype/FISH

Wrap up and further planning of SV activities in NACG

	Session lead:	Oleg Agafonov, Senior Researcher, DNV GL
	Objective:	Discuss future NACG activities in the field of SV
Wrap up discussion	Participants were asked to nominate topics of interest for future SV sessions in slido. A word cloud was produced for these topics.	
Conclusions / actions	Multiple callers are required for calling of SVs, and further optimization is still needed. We lack a single tool suitable for visualization, nevertheless, a combination of tools works well. IGV is a tool of choice for a quality assessment. Participants have also discussed annotation of variants with frequencies from local databases, and a requirement to re-create a database when one modifies an SV calling pipeline.	



NGS for cancer diagnostics

Seed topic 1: NGS for cancer diagnostics

- Introduction to somatic sequencing
- Mapping molecular diagnostics for cancer across the Nordics
- Country-specific presentations and topics for future NACG work

Session lead:	- Vibeke Binz Vallevik, DNV GL, - Courtney Nadeau, DNV GL
Objective:	Provide an overview of routine somatic sequencing in the different countries and to identify important topics to address through the NACG forum
Workshop outline:	Patient pathways, guidelines and technical pipelines for somatic sequencing in the Nordics. Preliminary data from the BigMed project. Mapping cancer MDx and stakeholders.

Figure 9 NGS routine somatic sequencing in NACG

Introduction to somatic sequencing

	Speaker: - Vibeke Binz Vallevik, DNV GL, - Courtney Nadeau, DNV GL - Ane Yde Schimidt, Center for Genomic Medicine, Rigshospitalet
	Objective: Map participants, set stage, gather expectations, and present preliminary findings from Rigshospitalet and the BigMed cancer project.
Introduction	Courtney and Vibeke introduced the workshop, the NACG working method, and the goals for the event.
Who is here?	Activity to map the segments of the NGS pipeline workshop participants are actively involved in. Participants identified what they work with and results indicated: • Refer patients for testing or trials (0) • Preanalytics: logistics and sample accessioning (4) • Histology and sectioning (2) • DNA / RNA extraction & QC (9) • Immunohistochemistry, PCR testing, Arrays, or Sanger Sequencing (7) • NGS wetlab: library prep through sequencing(10) • Bioinformatics: alignment through variant annotation (9) • Variant interpretation (20) • Issue reports (15) • Participate in MDT or Tumour board (9) • Contribute to clinical guidelines (1) • Counsel patients (6) Participants also indicated under a category “anything else”: validation, quality assurance, AI, method development, head of MD ding, Quality control, facilitate, validate clinical lab assays, validation, admin, and IF systems infrastructure that support the workflow LIMS, pipelines. Conclusions: Team is heavily involved in wet-lab work, bioinformatics, and variant interpretation and reporting, but not in medical or pathology activities.
Expectations	Expectations from participants: - Overview of Nordic NGS in cancer - How to collaborate? - Identify groups to recruit - How to migrate research in to routine diagnostics - Best practices - Status of what is research and what is done in routine diagnostics - Contacts
BigMed Cancer Mapping Project	Courtney gave an overview of BigMed work package focusing on the mapping of molecular diagnostics in cancer. Work methodology presented with emphasis to understand “what is working and what is not” as well as identifying common challenges. Ane Yde from the Center for Genomic Medicine at Rigshospitalet presented a high-level overview of their somatic workflow, which started in 2014 and is used in a clinical trials setting. Courtney presented initial findings from BigMed:

- All settings demonstrate technically capable as in general, equipment and expertise can be found.
- In practice, what happens depends on organizational factors. Pre-existing patient algorithms impact patient depending on their …, established systems that work well within a certain context
- Isolated islands functioning well: communication between islands are difficult. Taking learnings to smaller regions poses challenges.
- Several areas non-standardized. For example, clinical guidelines for treating a disease, who writes the guidelines (e.g., question of who should be on the committees); reimbursement in a way that makes sense; and transfer of technology in terms of the system creating a robust system for scaling up (e.g., information package for onboarding).

Questions:

- To CDN: How will results be used?
    - Major take-aways after NACG and mapping more hospitals will be summarized, and a report aimed at broad stakeholders in healthcare will be issued in 2020. After mapping, labs get an interactive map from the process, which may or may not make it in to the final report as an appendix. Participants will get a chance to review prior to publication.
- To CDN: How much is the lack of interaction (e.g., between regions) driven by conflict?
    - Mapping seems to show as a general rule that territorial attitudes and organisational issues compose major bottlenecks moreso than issues surrounding technology
- To AYS: Is the CGM process certified?
    - Hard to assess and demonstrate compliance for certification, this is a recent launch and thus under development.

Figure 10 Discussion of routine NGS diagnostics.

Mapping molecular diagnostics for cancer across the Nordics

	**Speaker:**	- Vibeke Binz Vallevik, DNV GL, - Courtney Nadeau, DNV GL
	Objective:	Build an overview of the actors in cancer sequencing in the various countries, along with core activities and NACG involvement.
Method	Courtney and Vibeke explained the workshop process. Participants were divided into 5 groups, and each addressed 5 topics and 2-3 subtopics sequentially. These topis were: • Routine IHC, Arrays, PCR, and other MDx for (a) solid tumours, (b) hematological cancer, or (c) hereditary cancer • Routine NGS for (a) solid tumours, (b) hematological cancer, or (c) hereditary cancer • NGS supporting (a) cancer-focused clinical trials or (b) broad screening • Technology development, specifically (a) methods testing, verification and validation or (b) transfer of methods to other units • Contributions to clinical local, national, or international clinical guidelines Participants were first asked to cycle through topics and identify topics where their labs were actively working, or had ambitions to work in. In a second round, participants identified other units in their countries that were actively working on these topics. Participants were then given time to discuss each topic in depth, and add specific clarifying notes, questions, or issues and other topics. The mapping is summarized in Table 7 to Table 11 below.	

Table 7 Topic 1: Routine IHC, Arrays, PCR etc

		Sweden	Finland	Iceland	Denmark	Norway
Solid tumors	Yellow (want to do)					OUS Mol Pat, UNN, UIT (IKM)
	Green (are doing)	Karolinska IHC, PCR, ++ FISH	HUS LAB: Arrays	Landspat. IHI, PCR, NGS	GMC: array for phase 1	OUS Mol Pat, UNN
	Orange (someone else doing this)	KS, Ki Patologi, Felix Hagland, Mathlx			Dept. Pathology Aahus, Pathology dept and CPH Uni	MPX-IHC IMM Cyt
	Pink (Specifics)	A lot of diff. assays. Not my area of expertise. Helathcare	Brain tumors Sarcoma	IHC - several PCR-several NGS- breast cancer	none	<u>OUS-patologi:</u> -immunohistokjemi for alle krefttyper PCR for NRAS, KRAS, BRAF -Refusjon: JA
	Issues (Blue)				Primary tumor often in formalin (FFPE)	Formalin? (CfDNA, RNA, other ways?)
Hematology	Yellow (want to do)			Landspat. IHC, PCR		OUS MAL, Sanger, PCR, ddPCR,
	Green (are doing)	Karolinska ddPCR, FPIR, FISH, Flow cyt	HUS LAB dd, PCR, qPCR			Sanger, qPCR, RT, qPCRm Fragment, ddpcr, (FISH) OUS Mol Pat

	Orange (someone else doing this)					Hem avd. 1 /two weeks Haukeland, genetic avd. Blood monitoring OUS
	Pink (Specifics)	FISH, array, sanger Healthcare	ALL AML Myeloma	AML ILLUMINA MYELOVD PANEL		<u>OUS patologi</u>: -immunohistokjemi for lymfomer AML MDS MDN myelonatese PCR for -lymfomer (kloralitet, MYD88) -AML CEBPA, NDMI, EUI-1/MECOM, WTI/PRAME, FLT3, fusjonstranskripsjoner -MPN JAK2 V617F,JAK2exon12,MLP,CALR -KLL-VH-mut.analyse -ALL fusjonstranskripter klonalitet -MRD-analyser for ALL og AML, KML -KML-BUR-ABL1 ABL1 mutasjoner Refusjon: JA
	Issues (Blue)					
Hereditary cancer	Yellow (want to do)			Landspat. NGS		OUS Mol Pat
	Green (are doing)	Karolinska sanger, MLPA	HUS LAB MLPA, PCR			OUS Medical Genetics

	Orange (someone else doing this)	KS, Ki genetic,			Pathology monthly or yearly and CPH uni	All med gent. Avd. w/ skien Med gen, UNN /week
	Pink (Specifics)	FULGENT 300 Sophia genetic cancer panel		BRCA1+2 (urgent samples) PMS2 other cancer genes not on HTS MLPA Sanger sequencing RNA (BRCA1+2) BREAST Eggstokkreft MELAMOLLA(?)		Breast cancer Colorectal cancer
	Issues (Blue)			A few genes Sanger/MLPA RNAseq&DNAseq? Sample ntrl.(?)		

Table 8 Topic 2: Routine NGS Diagnostics for:

		Sweden	Finland	Iceland	Denmark	Norway
Solid tumors	Yellow (want to do)					- OUS, AMG
	Green (are doing)	Many University hospitals, including Karolinska + some regional hospitals	HUSLAB FICAN (national)	Landspitali, (do)	- Genomic medicine DK MOMA DK	- OUS pathology - UNN
	Orange (someone else doing this)	Karolinska hospital, clinical pathology, monthly	daily		- Department of pathology Aarhus; - GM, DK: contacts:	- St. Olavs, once a month - Ahus, every second month - Vestfold, once a month - Stavanger? - Haukeland AMG, when needed
	Pink (Specifics)	- Sarcoma, RNA-SER, healthcare budget - Lung cancer (and some others), Thermo 22-gene panel, healthcare	High risk solid tumors - Pan cancer NGS panel - Hospital budget Sarcoma - RNA seq / fusion genes - Lung cancer Gene panels - Breast - CRC		Genomic medicine - All solid tumors (phase I): WES/ RNASeq/ array, NEXT/ Regions/ Innovation Fund - Ovarian cancer: NGS BRCA testing, Regions(hospital), for PARPi - Sarcoma: NGS RNASeq (fusions), Regions / hospitals MOMA: - All solid tumors, NGS (exm, HSG panel, RNA Seq), Region, NEXT	- Ovarian cancer, BRCA1/2, NGS/ targeted genet panel
	Issues (Blue)	- Pre-NGS sample handling		RNA seq - Interpretation - Reporting	- Where are the Nordic contacts?	Sample handling; FFPE / fresh frozen, need for

		- Path labs have limited experience of working with large scale NGS data - Interpretation				manual inspection before DNA extraction?? Ovarian cancer: - Complicated sample flow - Sample material quality - Independent verification of the variant DNA / RNA Reimbursement cancer pat.
Hematology	Yellow (want to do)			Landspitali (want to)		- UNN
	Green (are doing)	Some university hospitals including Karolinska	HUSLAB FICAN (national)		- Genomic medicine (benign) -GM (cancer)	- OUS Molecular pathology
	Orange (someone else doing)		HUSLAB, not often / daily		- Dept. clinical genetic, Rigshospitalet, monthly/ yearly	- Haukeland? - OUS AMG, when needed
	Pink (Specifics)	- Myel+lymph, throughsight panles (50 genes), healthcare, moving to bigger panels	Gene panel + fusion genes; myeloma, AML, ALL AML, MDS, MPN: - Myeloid gene panel, hospital budget	AML		OUS Molpat - Lemanom - Lunge / ion torrent - Colon / not enough - Neuro / routine - GIST OUS mol pat - Myeloid panel for CTSM (illumine) - AML - MDS - KLL - MPN Reimbursement : yes
	Issues (Blue)		RNA seq - Interpretation - reporting		-	- Accreditation standards OUS mol pat - Quantity and quality of samples

						- Reports - bioinformatics
Hereditary cancer	Yellow (want to do)				-	
	Green (are doing)	All university hospitals with Clinical Genetics	HUSLAB FICAN (national)	Landspitali (do)	- MOMA, DK Genomic Medicine	- OUS AMG
	Orange (someone else doing this)	Karolinska hospital, clinical genomics, weekly	weekly			- Haukeland medical genetics - St. Olavs
	Pink (Specifics)	Small panels (10 genes) + sometimes WGS, healthcare	Rare diseases - NGS outcourced to Blueprint Genetics - Hospital budget Panels - Breast - CRC	Fulgent – 300, Sophia genetics	MOMA - Colon Breast,… - Cancerpanel V3 – 107 genes (costum??) Genomic medicine - Breast, colon, melanoma, ovarian, etc. - NGS panel (costum?? Custom??) - Region / hospital	- Colon, breast, ovarian, pancreas, RB, endcrine, svulster, xxxx barnekreft, +++, - targeted NGS + exome
	Issues (Blue)					- CNV, - pseudogenes, - data sharing - Contamination problem - Relevant clinical information for variant interpreters - PMS2 on HTS and CNV

Table 9 Topic 3: NGS for cancer trials / screening programs

		Sweden	Finland	Iceland	Denmark	Norway
Diagnostics supporting trials	Yellow (want to do)	Karolinska Scilifelab	FIMM	Landspat.	MOMA Genomic Medicine Copnehagen phase 1	
	Green (are doing)					OUS mol pat, specialization UNN mol.pat.
	Orange (someone else doing this)	KI, Clinseq program / weekly			Phase 1 unit: RH Clin genetics MOMA	Pathology (OUS) 2-3 week
	Pink (Specifics)	CRC Trial, Panel (GMCK solid), Grant, 3000+ samples aim Pancreas Cancer Trial, WES, GRANT, 100 samples aim Metastatic Cancers ctDNA pilot, GMCK custom of DNA pilot, Foundation Grant, 100 Lyphoma pilot, Trusight & GMS panel, Healthcare, 100 pat Breast &Lung cancer T/N pilots, GMCK solid panel, Healthcare, 100 + 100 patients		Lung cancer, AML, Breast, Fulgent 300, Sophia Genetics	All solid tumours, NGS (RNA, EXM, panels), GM/MOMA	Lung Cancer, Immunoscore, TNM-I (UNN) Lung, NGS, Breast, Nanostring, Grants and core funding (Genomic core OUS yellow) All cancers, TSO 500, WGS, RNA-seq
	Issues (Blue)		Need and costs for accreditation		No standards for analysis/reporting Harmonization of broad cancer panels No standards for analysis No national / Nordic Standard for reporting	Variant interpretation workshops / benchmarking Reimbursement / financing models Collaboration between clinic and diagnostic units

						Panel standardization at Nordic level – lab and analysis
Patient screening	Yellow (want to do)		FIMM		Genomics Med, CPH (germline9 BRCA2	University of Tromsø IKM, OUS pathology Oncoimmunity, terapeutic
	Green (are doing)		National programs (breast cancer)	Landspat. Inherited cancer panels	MOMA germline BRCA 1 / 2 on OPRA pt	UNN mol pat. OUS med genetic CVS Molpat
	Orange (someone else doing this)					UNN med gen., 1 / week
	Pink (Specifics)					BRCA ½, HTS, Nasjonale takster, Diagnostikk
	Issues (Blue)					

Table 10 Topic 4: technology development

		Sweden	Finland	Iceland	Denmark	Norway
Transfer of methods to units	Yellow (want to do)	Karolinka & Scilifelab				OUS-pool – pat: we don't' do it
	Green (are doing)		FIMM to HUSLAB			Medical genetics OUS, Inst of cancerOUS, Genomic Core Onco…. R&D adoption, product qualification, QC validation
	Orange (someone else doing this)		weekly FIMM			Med genn UNN 2x Months
	Pink (Specifics)		Hematology, WES/WGS – FIMM → HUSLAB, Budget	Landspitalet, Northern Lights Assay		AMG, OUS, Bioinformatic tools
	Issues (Blue)		Standardizing analytical pipelines		No reimbursement for validation Legal issues with exchange of samples for validation	Gap between research & diagnostics Asking for help, reinventing the wheel
Methods, testing, verification, and validation	Yellow (want to do)	Scilifelab + collab. w/ clinics of karolinska				
	Green (are doing)		HUSLAB FIMM	Lanspat.	GM, DK: accredidate more and more analysis MOMA, DK	Medical genetics OUS, Inst of cancerOUS, Genomic Core Molecular Pat., OUS Molecular Pat, UNN

	Orange (someone else doing this)				GM, contacts,	Skien, Haukeland St. Olavs (Mol. Pat UNN)
	Pink (Specifics)	Myeloid 200-g panel, Lymphoid 250-g panel, TWIST, GMS National panel Solid tumor 370-panel, Twist custom, GMCK, Regional, Cf DNA panels, TWIST Custom, GMCK, Regional WGS for pediatric & acute leukemia, sponsors, incl childhood cancer fund	Cf DNA panels Somatic WES/WGS	General, Northern Lights Assay	All sollid tumors, MSK/EXM/RNAseq, new test → fusions, new test → ct DNA Update all tests , accreditate methods	All cancers, Targeted DNA and RNA, Fusions, WGS – low pass, liquid biopsies PMS2 on HTS, (NU Nexterm flex lab prep, Miseq -> NextSeq -> Highseq Up escalating from 48 to 96 samples
	Issues (Blue)	Legal issues for sample exchange for validations No good standard samples or data	Limited funding, Limited human resources		Lack of good standards (somatic control ref) Difficulties for exchange of data/ materials Somatic QC programs, good controls	Data sharing, IT infrastructure Sending of possible controls between countries/labs True variants data set Control samples Lack of standard Validation of panels Lack kof validation cohorts No of available samples Bioinformatician capacity, large amounts of data → many possibilities BUT lack of using these Reimbursement

Table 11 Topic 5: Clinical Guidelines:

		Sweden	Finland	Iceland	Denmark	Norway
Contributes to guidelines	Yellow (want to do)	- National guidelines more specific for molecular assays -	- National guidelines	- Landspitali - Yes	- Genomic Medicine Copenhagen	- National guidelines - OUS pathology
	Green (are doing)	-	- University hospital guidelines - Laboratory guidelines	-	-	-
	Orange (someone else doing this)	- Klinisk Genetik (hematology) Weekly -	- Hematology HUS, daily - weekly	-	- Clinical genetic department Copenhagen University Hospital weekly	- Oncologists, UNN, every 14 days - Directorate of health and care - Pathologists, daily
	Pink (Specifics)	-	-	- NIPT - Molecular tumor	-	OUS molecular pathology Action plan - Pathologist participate in methodology chapter in action plan for maligne blodsykdommer - Nobody from our group participate in action plan for lymphoma.
	Issues (Blue)	- More molecular details into guidelines	- National guidelines for using NGS based tests. Coordinate with national guidelines for treatment	-	-	- Outdated guidelines - Collaborative vs non-collaborative people - subjective

Country-specific presentations and topics for future NACG work

	**Speaker:**	All participants
	Objective:	Discuss learnings from countries and identify future topics
Method	Participants were divided into groups, but now based on country. They summarized discussions they had had throughout the course of the day, came up with country-specific findings, and presented these to the group.	

Denmark	• Lack of standardisation (concerns analysis, clinical reports)
	• Inclusion of patients is challenging (not everybody gets the same analysis done). Different criteria for getting the analysis across the country). Better national collaboration needed. (try to exchange material between regions: Århus and Copenhagen)
	• Data sharing
	• Different systems for e-journals. EPJ, Sundhetsplatformen etc. Do not have access to all information on patients
	• National guidelines (Next. National experimental therapeutic partnership)
	• Bioinformatics
	  ○ Somatic : working group for variant interpretation just started. The clinical report is one of the themes
	  ○ Need some guidelines for the whole process from patient to report
	  ▪ Standardized QC	

Sweden	Positive
	• Many big plans, several pilots
	• Several clinical trials and prospective studies in place. Build up knowledge and learn from these.
	• National level: nice harmonization between labs. Chemistry and the sequencing platform (solid tumors and hematology)
	
	Challenges
	• Lack of collaboration between diagnostic disciplines (genetics and pathology)
	  ○ One joint function or other solution
	  ○ Current organization is not sustainable
	• Interpretation. Due to lack of largescale testing in pathology
	• Validation: very tricky to share data and samples
	• Lack of harmonization in bioinformatics
	  ○ Don’t trust other’s pipelines
	  ○ Agreement and collaboration on the development side	

Finland	• Lacking national collaborations
	  ○ Do not share expertise, data or variants with other university hospitals
	  ○ Invite people from the other hospitals in this meeting?
	• Routine diagnostics methods work really well, no issue. When transition from older methods, we lack resources and experts on these areas
	  ○ Need help with developing processes further
	• National guidelines for NGS methods do not exist at all. Would be nice to have something to follow
	• Lack clinical trials based on NGS methods
	• Need to attract more clinical studies to Finland

Iceland	• Cancer: 3 testing facilities in hospital? Molecular and pathology unit merge (potentially)?
	• Confusing who's doing what
	• Word of caution about not doing extensive testing. (been free as to who orders and who performs the test)
	  ○ General practicioner who receives the answer do not understand information about variants of uncertain significance (VUS) and genetic variation. (Anm: information in clinical reports).
	  ▪ Difficult when there is no alterative diagnose.
	  ▪ Cut out false positives and variants with low penetrance. Becoming more conservative with more experience and information, limiting the list of genes as well.

Norway	• Mixing geneticists and pathologists is interesting. Formalin is a big issue. Good to discuss thee things. • Collaborations needs, meetings like this ○ Work quite isolated on a daily basis, common sites or places on internet where information can be exchanged • Guidelines: a lot of variation in the molecular and diagnostics part. Want some more aspects included on molecular diagnostics: what to report and not. Genetics is getting Laboratorieveilederen soon. • Supporting the clinical trials; trials are missed. Due to lack of infrastructure and fragmentation of labs • No one asks for help even if someone else has the competence you need to rely on • Time and having resources to test and implement new methods? Lack of time to evaluate new panels. Effect--> Norway is behind in the establishment of routine NGS in the clinic

Future Topics	Topics suggested during the course of the day were added to an online poll, and participants voted on these as topics for NACG to pursue. Participants then signed up to the top topics they were interested in. Poll Results: 21 How to standardize/harmonize bioinformatics? 17 How to support/harmonize interpretation within the country? 16 Work on nordic standards for reporting, sample handling, consent, data sharing, or other st 15 How to standardize broad panels? Or how to decide on min/max panel contents? 15 How can we exchange validation samples? Share data? 15 How to choose relevant clinical resources for annotation/interpretation? 14Developing true variant data sets and control samples 13 How to share Infrastructure, data, and legal resources? 8 Identifying the nordic contacts 8 How to collaborate between clinicians, pathology, and other diagnostic units? 6 How to get more diagnostics in the clinical guidelines? 6 Clinical Guidelines: How to get diagnostics in? How to coordinate treatment and diagnostics 6 How to best support clinical trials with NGS? 5 Harmonize sample handling, upstream routines (ie. FFPE) 5 How to promote equal standard of care within country? 4 Reimbursement for cancer tests? What about funds for validating new panels? 3 Guidelines/position on 'undiagnosis'
Conclusions	Numerous discussions surrounding the challenges of cancer sequencing in each country were held. A preliminary mapping of Nordic actors in cancer diagnostics was developed, and participants identified future topics to address.

Figure 11 Active participation by NGS attendees.

MDR and IVDR – how to address the upcoming regulations?

Seed topic 2: MDR and IVDR

- MDR and IVDR - how to address the upcoming regulations

Speaker:	- Alexey Shiryaev, DNV GL Presafe AS - Nick Baker, DNV GL Presafe AS
Objective:	Provide an overview of the European regulations on medical devices (MDR) and In Vitro Diagnostic Medical Devices (IVDR), discuss applicability and requirements for transition.

Key information

- Alexey introduced the CE mark and necessity for transition to new regulations.
- New regulations published in 2017: Date of application in May 2020 for the MDR, and May 20220 for the IVDR .
- Key changes: Reinforcement of criteria for designation and surveillance of notified bodies. Stricter controls for high risk devices. Rules more controlled/structured on clinical evidence. Strengthened post-market surveillance for manufacturers. Introduction of an 'Implant Card'. Improved EU coordination. Improved transparency – EUDAMED (can track developments, complaints etc), unique device identification (UDI) system, nomenclature (European Medical Device Nomenclature).
- Identification within the supply chain of economic operators who have supplied or been supplied a device, as well as any health institution / professional that have been supplied a device. Effect on health institutions & healthcare professionals.
- EU commission website offers guidance documents online for MDR and IVDR. Opportunity to contribute to draft documents.
- Health institutions: required to store and keep e-data on UDI of devices if class III (implants; devices that go into the patients). In addition, member states shall encourage, and many require, health institutes and professionals to keep data on lower class devices)

	- Nick discussed the implications and new inclusion criteria of the new regulations: previously only affected 10-15% of IVD, impact will be that 85-90% of IVD's will require notified body assessment. - New risk-rule based classification system (Chapter V, annex VIII). Affects all manufacturers of IVDs. Type of assessment depends on risk classification the IVD falls in (A-low, B C D-high) A self-declare, B C D assessment by body required. - Companion diagnostics (currently self-declare) are now class C as are tests for congenital disorders, cancer markers for screening, diagnosing or classifying tumours and human genetic testing. Conformity assessment is based on a quality management system and assessment of the technical documentation on a sampling basis - Annex IX of the IVD Regulation. Assessment of companion diagnostics also require Notified Bodies to consult with the drug authorities (CA or EMA - Lab developed or in-house tests (LDTs) – if health institute then need to conform to Annex 1 only. No assessment by a notified body but still liable for auditing to a laboratory QMS e.g. . EN ISO 15189 or national equivalent. If devices manufactured and used within the same health institution are transferred to other other legal entities then it it is considered to be placed on the market and must meet all the requirements of the IVDR. - LDTs: Must be able to justify that your targets patient group specifics need cannot be met by an equivalent certified test on the market (specificity and superiority, *cost of your test being cheaper is not sufficient justification*) - Class D devices require technical documentation. Continuous monitoring of ongoing performance of test/QMS compliance available on request. The health institution must also experience gained from the clinical use of the devices. - Tests require evience of scientific validity/peer review, analytical performance, bias, clinical performance
Questions and discussion	*IVDR compared to LDT, what is the difference? LDT's only have to meet the General and Safety Performance requirements (Annex I) of the IVDR and are not assessed by the Notified Body. Health institutiona are encouraged to use the UDI system for traceabilty purposes.* *The commercial interest is low in rare diseases for LDTs of high specificity:* Industry has applied pressure that LDTs must meet conformity requirements, health institutes have been avoiding this and so have unfair competitive advantage. However Health Institutions will need to justify use of LDT's. *What are the implications of receiving or transferring results from/to other hospitals from a LDT?* There is a clause in the regulation that the device must be CE marked, due to service transfer, but this needs further clarification. *What are the implications in shared bioinformatic pipelines?* The IVDR includes software. If you base medical decision on software output, then it is included and must be assessed. If the data is transferred out of the institution then it must be CE marked. In the case of code transfer you need to assess implications, but this depends on how the competent authority chooses to enforce the IVDR. (Cathrine

	OUS: given feedback to the Norwegian competent authority: it is complicated to understand regulations and compliance on software and how they will be enforced. As yet, no response from feedback given a month ago. Rapidly developing field, challenging to find commercial solutions that can keep pace with these developments. *What is your advice going forward?* Classify your device and go through guidelines to see what is applicable to you. For LDT check your range and look for an alternative so you know scope of your accreditation requirements. *If I disagree with the notified body assessment is it possible to find a different one?* Notified Bodies will not assess LDT's If a manufacturer argues that your LDT status does not apply then the Competent Authority will decide upon the status of the test. *How should we deal with the fact that certain kits are disease-specific, but many reagents are used more broadly?* General purpose reagents can be used for a wide range of applications. Manufacturers need to be careful about what the intended use of their reagents and kits are as to whether they fall under regulations. *Are there any mechanisms for competent authorities to harmonize how to regulate LDTs or will this occur in isolation?* Provisions for competent authorities and identified bodies to collaborate and harmonies regulation procedures have been made but this may not be prioritized. A related document is expected.
Conclusions	EU has provided a factsheet on MDR and IVDR for consultation. Assess your device and consult the guidelines and regulations to ensure that you are complying. LDTs need only to conform to Annex I, but a competing commercial alternative must not be available (if there is one then IVDR/ MDR applies).

Conclusions and next steps

In line with the organization's Constitution, the NACG will continue to work to include more stakeholders to clinical genomics in the Nordic countries in the meetings and encourage them to seek membership in line with governing documents available at the organization's website. The NACG working groups and their focuses should be continuously re-evaluated to ensure that relevant topics from the group are prioritized and resulting in learnings and outcomes that are useful to clinical work processes for the membership.

Next NACG meeting

The next NACG meeting is scheduled to take place 11th – 12th May 2020 in Reykjavik, Iceland. Once venue is confirmed, the workshop will be announced per email to the NACG membership and through the NACG website https://nordicclinicalgenomics.org/.

Appendix 1: Agenda overview

Overview

	Mon 18. Nov	Tue 19. Nov	Wed 20. Nov	Thu 21. Nov
Morning	The legal framework for pers. med.	The legal framework for pers. med.	NACG symposium	NACG workshops
Afternoon	The legal framework for pers. med.	NACG symposium	NACG workshops	NACG workshops
Evening		Reception & Dinner		

Workshops

	Wednesday 20. Nov		Thursday 21. Nov	
Morning			9:00 Consent (Room: Big Blue 1)	9:00 Structural variants (Room: Big Blue 2)
Lunch	12:00		12:00	
After-noon	13:00 NGS for cancer diagnostics (Room: Big Blue 1)	13:00 Structural variants (Room: Big Blue 2)	13:00 MDR and IVDR - how to address the upcoming regulations? 14:00 Next steps 15:00 End	

Appendix 2: Symposium agenda

Tuesday 19th November 2019

11:30	Registration and lunch	
12:30	Welcome and opening remarks	Dag E. Undlien, OUS, NACG chair Kenneth Vareide, CEO Digital Solutions, DNV GL Paul Chaffey, State Secretary to the Norwegian Minister of Digitalisation
13:15	Keynote National initiatives: Denmark	Bettina Lundgren, Director of the Danish National Genome Centre
14:00	National initiatives: Finland	Aarno Palotie, research director of the Human Genomics program at FIMM, Finland
14:30	Break	
15:00	National initiatives: Sweden	Anna Lindstrand, Genomic Medicine Sweden / Karolinska Institute
15:30	The European 1+ Million Genomes Initiative from a Norwegian perspective	Grethe Synnøve Foss, project manager for the Norwegian Strategy for Personalised Medicine at the Directorate for Health and Care
16:00	Nordic Per Med Law initiative on the regulatory framework for personalised medicine	Gjertrud Bøhn Mageli, OUS
16:15	Variant Exchange experiences – practical cross-border sharing	Stephen McAdam, Digital Health Development Director, DNV GL
16:35	Break	
17:00	Next generation sequencing of Common and Rare diseases in Iceland	Patrick Sulem, Head of Clinical sequencing, deCODE genetics Iceland
17:30	A partnership framework to support Population Genomics @ scale	Paul Jones, Head of Population Genomics, EMEA, Illumina
18:00	Reception	At Veritas Centre
18:30	NACG symposium dinner	At Veritas Centre

Wednesday 20th November 2019

8:00	NACG Steering committee meeting	
8:30	Morning coffee	
9:00	Genomic medicine in cancer & clinical trials	Valtteri Wirta, Facility Director, Clinical Genomics, SciLifeLab Kristoffer Rohrberg, head of phase I unit, Rigshospitalet, Copenhagen Caroline Heckman, Institute for Molecular Medicine Finland (FIMM)
10:30	Genomic medicine in cancer & clinical trials – precision drugs	James Hadfield, Director and Principal Diagnostic Scientist, Precision Medicine Laboratories at AstraZeneca Duarte Marchand, Country Manager for Takeda.
11:10	Panel discussion with speakers from morning sessions	
11:50	Symposium closing remarks	Dag E. Undlien, OUS, NACG chair
12:00	Lunch	
13:00	NACG workshops start	

Appendix 3: NACG Workshops

	Wednesday 20. Nov		Thursday 21. Nov	
Morning			Room: Big Blue 1 **9:00 Consent** - Comparison of consent practices - Challenges with consent in the use of NGS in clinical diagnostics	Room: Big Blue 2 **9:00 Structural variants** - SV annotation and interpretation - Visualization of SV: tools and best practices
Lunch	12:00		12:00	
After-noon	Room: Big Blue 1 **13:00 NGS for cancer diagnostics**	Room: Big Blue 2 **13:00 Structural variants** - Nordic benchmarking of SV calling pipelines - Integration of long and short reads sequencing for clinical genetics diagnostics. - Status updates from NACG labs.	**13:00 MDR and IVDR - how to address the upcoming regulations?** **14:00 Next steps** **15:00 End**	

Workshop	Description	Facilitated by
Consent for NGS	This 3-hour workshop aims to compare different approaches to consent in clinical genomics, as well as to identify and discuss common challenges and unresolved issues related specifically to the use of NGS in clinical diagnostics.	Sharmini Alagaratnam, DNV GL and Kaisa Kettunen, FIMM
Structural variants and Bioinformatic tools development (combined workstreams)	In this session, Nordic laboratories will share their experiences in using SVs for clinical diagnostics. We will first examine SV calling methodology and compare benchmarking results from different laboratories. Then we will go into more detail on downstream processing, including tools and strategies for clustering/merging results of multiple callers, annotation, and frequency counting. Finally, we will discuss how to best visualize SVs and interpret them	Oleg Agafonov, DNV GL, Mads Bak, Rigshospitalet, Tony Håndstad, OUS AMG and Rasmus Lykke Marvig, Rigshospitalet
NGS for cancer diagnostics	This session will examine topics related to the patient pathways, guidelines, and technical pipelines for somatic sequencing in the Nordics. Preliminary data from the BigMed project, which has mapped molecular diagnostics supporting cancer treatment at several Nordic hospitals, will be presented. The goal of this workshop is to share an overview of routine somatic sequencing in the different countries and to identify important topics to address through the NACG forum.	Vibeke Binz Vallevik and Courtney Nadeau, DNV GL
MDR and IVDR - how to address the upcoming regulations?	All actors involved with medical devices, from their manufacture to their use, will have to comply with the new regulations by May 2020 (May 2022 for in vitro diagnostic medical devices). This session will provide an introduction to the European regulations on Medical Devices (MDR) and In Vitro Diagnostics Medical Devices (IVDR), followed by a discussion on applicability to hospital (lab) developed tests (LDTs) and preparations for the transition.	Alexey Shiryaev and Nick Baker, DNV GL Presafe AS

Appendix 4: List of participants[1]

Country	Organisation	Department	First name	Last name
Denmark	Aarhus University Hospital	Department of Molecular Medicine (MOMA)	Maria	Bach Laursen
Denmark	Aarhus University Hospital	Department of Molecular Medicine (MOMA)	Piotr	Starnawski
Denmark	CIFS	Health	Bogi	Eliasen
Denmark	Danish National Genome Center		Cathrine	Jespersgaard
Denmark	Danish National Genome Center		Kasper	Thorsen
Denmark	Danish National Genome Center		Peter	Johansen
Denmark	Rigshospitalet	Center for Genomic Medicine	Birgitte	Bertelsen
Denmark	Rigshospitalet	Center for Genomic Medicine	Ane Yde	Schmidt
Denmark	Rigshospitalet	Center for Genomic Medicine	Frederik Otzen	Bagger
Denmark	Rigshospitalet	Center for Genomic Medicine	Majbritt	Busk Madsen
Denmark	Rigshospitalet	Center for Genomic Medicine	Rasmus	Marvig
Denmark	Rigshospitalet	Department of Clinical Genetics	Morten	Dunø
Denmark	Rigshospitalet	Center for Genomic Medicine	Christina Westmose	Yde
Denmark	Rigshospitalet	Center for Genomic Medicine	Line	Borgwardt
Denmark	University of Copenhagen and NSHG-PM	Dean's Office	Hakon	Heimer
Denmark	Vejle Hospital	Department of Clinical Genetics	Mads	Jørgensen
Finland	HUSLAB	Laboratory of Genetics	Kaisa	Kettunen
Finland	HUSLAB	Laboratory of Genetics	Emma	Andersson
Finland	University of Helsinki	FIMM	Henrikki	Almusa
Finland	University of Helsinki	FIMM	Janna	Saarela
Finland	University of Helsinki	FIMM	Aarno	Palotie
Finland	University of Helsinki	FIMM	Katja	Kivinen
Iceland	Landspitali - Univ. of Iceland	Genetics and Molecular Medicine	Jon J.	Jonsson

[1] Listing only participants who have consented to this.

Norway	BigMed		Alia	Zaka
Norway	LMI	Research and Innovation	Monica	Larsen
Norway	Oslo University Hospital	Department of Medical Genetics	Svein Tore	Seljebotn
Norway	Oslo University Hospital	Department of Medical Genetics	Tom Egil	Sørlie
Norway	Oslo University Hospital	Department of Medical Genetics	Tor	Solli-Nowlan
Norway	Oslo University Hospital	Department of Medical Genetics	Lise	Larsen
Norway	Oslo University Hospital	Department of Medical Genetics	Anita	Kaupang
Norway	Oslo University Hospital	Department of Medical Genetics	Beate	Skinningsrud
Norway	Oslo University Hospital	Department of Medical Genetics	Knut Erik	Berge
Norway	Oslo University Hospital	Department of Medical Genetics	Eidi	Nafstad
Norway	Oslo University Hospital	Department of Medical Genetics	Lars	Retterstøl
Norway	Oslo University Hospital	Department of Medical Genetics	Øyvind	Evju
Norway	Oslo University Hospital	Department of Medical Genetics	Xuyang	Yuan
Norway	Oslo University Hospital	Department of Medical Genetics	Morten C.	Eike
Norway	Oslo University Hospital	Department of Medical Genetics	Robert	Lyle
Norway	Oslo University Hospital	Department of Medical Genetics	Tony	Håndstad
Norway	Oslo University Hospital	Department of Medical Genetics	Ying	Sheng
Norway	Oslo University Hospital	Department of Medical Genetics	Annika	Panagopoulos
Norway	Oslo University Hospital	Department of Medical Genetics	Olaug	Rødningen
Norway	Oslo University Hospital	Department of Medical Genetics	Sjur	Gjerald
Norway	Oslo University Hospital	Department of Medical Genetics	Dag	Undlien
Norway	Oslo University Hospital	Department of Medical Genetics	Doriana	Misceo
Norway	Oslo University Hospital	Department of Medical Genetics	Vessela	Kristensen
Norway	Oslo University Hospital	Department of Medical Genetics	Sarah	Ariansen
Norway	Oslo University Hospital	Department of Medical Genetics	Cathrine	Nordhus
Norway	Oslo University Hospital	Department of Pathology	Signe	Spetalen
Norway	Oslo University Hospital	Department of Pathology	Mohsen	Shadidi
Norway	Oslo University Hospital	Department of Tumor Biology	Vigdis	Nygaard
Norway	Oslo University Hospital	Genomics Core Facility	Leonardo A.	Meza-Zepeda
Norway	Oslo University Hospital	Genomics Core Facility	Susanne	Lorenz

Norway	Oslo University Hospital	Institute for Cancer Research	ALFONSO	URBANUCCI
Norway	Oslo University Hospital	Legal Department	Oda	Bakken
Norway	Oslo University Hospital	Legal Department	Gjertrud Bøhn	Mageli
Norway	Oslo University Hospital	Pathology	Gunhild	Trøen
Norway	Oslo University Hospital	Pathology	Lilach	Kleinberg
Norway	Oslo University Hospital	Pathology	Ranjan	Chrisanthar
Norway	Oslo University Hospital	Pathology	Helen	Vålerhaugen
Norway	Oslo University Hospital	Research, Innovation and Edication	Matthias	Kolberg
Norway	Oslo University Hospital	Bioinformatics Core Facility	Charitra Kumar	Mishra
Norway	Oslo University Hospital	Department of Tumor Biology	Sen	ZHAO
Norway	Oslo University Hospital	Department of Tumor Biology	Fatemeh	Kaveh
Norway	St. Olavs Hospital		Maren F.	Olsen
Norway	The Norwegian Directorate of Health	Health Law and Biotechnology	Kari	Steig
Norway	The Norwegian Directorate of Health	Health Law and Biotechnology	Grethe	Foss
Norway	Universitetet i Oslo	Department of Medical Genetics	Eirik	Frengen
Norway	University Hospital of North Norway	Clinical pathology	Thomas	Berg
Norway	University Hospital of North Norway	Institute for Clinical Medicine	Mehrdad	Rakaee
Sweden	Karolinska Institutet	Clinical Genomics	Hassan	Foroughi Asl
Sweden	Karolinska University Hospital	Clinical Genomics	Jesper	Eisfeldt
Sweden	SciLifeLab	Clinical Genomics	Anders	Jemt
Sweden	SciLifeLab	Clinical Genomics	Adam	Rosenbaum
Sweden	SciLifeLab	CMMS	Henrik	Stranneheim
Sweden	SciLifeLab	Clinical Genomics	Valtteri	Wirta
International	Agilent	Clinical Informatics	Mikaela	Gabrielli
International	Astrazeneca Nordics	Diagnostics	Per	Barfod Andersen
International	DNV GL	GTR Precision Medicine	Courtney	Nadeau
International	DNV GL	GTR Precision Medicine	Guro Meldre	Pedersen
International	DNV GL	Digital Solutions	Jahn Henry	LØVAAS
International	DNV GL	Group Legal	Marija	Jokubaviciute
International	DNV GL	Digital Solutions	Marlon	Polo de Melo

International	DNV GL	GTR Precision Medicine	Oleg	Agafonov
International	DNV GL	GTR Precision Medicine	Serena	Marshall
International	DNV GL	GTR Precision Medicine	Sharmini	Alagaratnam
International	DNV GL	Digital Solutions	Stephen	McAdam
International	DNV GL	Digital Solutions	Øyvind	Strand
International	DNV GL	GTR Precision Medicine	Vibeke	Binz Vallevik
International	DNV GL	GTR Precision Medicine	Bobbie	Ray-Sannerud
International	Illumina	Population Genomics	Paul	Jones
International	Illumina	Population Genomics	Simon	Partridge
International	Limbus Medical Technologies GmbH	Clinical Applications	Ben	Liesfeld
International	NEC OncoImmunity	NGS	Hugues	Fontenelle
International	Oxford Nanopore	Nordics	Jakob	Ørtvig
International	Roche Diagnostics	Medical Affairs	Birgitte	Lygren
International	Roche Norge AS	.	Ingvild	Hagen
International	Thermo Fisher Scientific	Clinical sequencing	Xiaolin	Wang
International	Twist Bioscience	Sales	Christofer	Flood

Nordic Alliance for Clinical Genomics