Nordic Alliance for Clinical Genomics

WORKSHOP REPORT

NACG 9th workshop, 23. – 27. November 2020

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

Date of issue	Rev.	Prepared by
25.01.2021	0	Guro Meldre Pedersen (guro.meldre.pedersen@dnvgl.com) with input from workshop contributors.

Symbols

Lecture / presentation

Interactive workshop

Abbreviations

FIMM	Institute for Molecular Medicine Finland
HUS	Helsinki University Hospital
IVDR	In-Vitro Diagnostics Medical Device Regulation
LoD	Level of detection
MDR	European Medical Devices
MOMA	Department of Molecular Medicine
NACG	Nordic Alliance for Clinical Genomics
OUS AMG	Oslo University Hospital – Department for Medical Genetics
PoN	panels of normal
RP	Retinitis pigmentosa
SV	Structural variant
SVDB	Structural variant database
WGS	Whole genome sequencing

Contents

Executive summary

This report summarizes the 9th workshop of the Nordic Alliance for Clinical Genomics (NACG). Due to the global pandemic situation, the workshop was organized as a virtual NACG week, with daily two-hour lunch sessions 23. – 27. November 2020.

Even if we were unable to arrange for a physical meeting, the upside of a virtual event became very clear in that this format attracted an all-time-high audience of more than 200 registered participants[1] from about 70 different organizations in 12 countries, representing healthcare providers, governmental organizations, research and industry.

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 1).

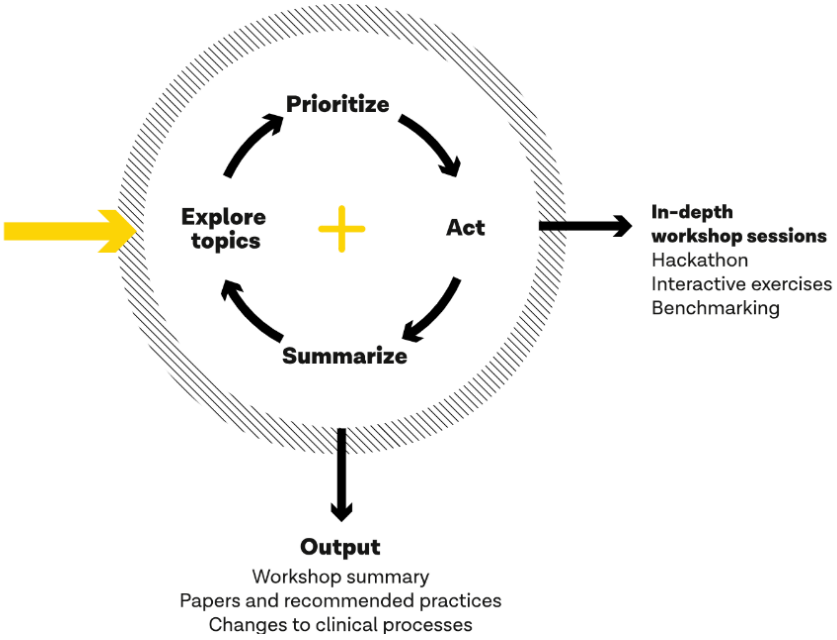


Figure 1 NACG members discuss and explore topics of interest to identify shared challenges and strategies for overcoming them. Prioritized topics are explored in in-depth interactive exercises. Findings and learnings are summarized in workshop summary reports and collaborative papers and contribute to lifting performance standards.

[1] Actual workshop attendance: Opening and keynote (109), Emerging technologies (113), Bioinformatic tools (68), Consent (79), IVDR (89), Cancer panel benchmarking (100), Variant interpretation and data sharing (107).

NACG week agenda

The agenda for the NACG week is outlined in Table 1 with further introduction of the workshop sessions details in Table 2. In parallel, the Nordic Permed Law network[2] organized a webinar on "Current challenges in Nordic law on personalised medicine"[3] Nov 24th.

Table 1 NACG virtual week - agenda

Time (Oslo)	Monday 23rd Nov	Tuesday 24th Nov	Wednesday 25th Nov	Thursday 26th Nov	Friday 27th Nov
12:00	**Opening & keynote** Professor Sir Mark Caulfield, Chief Scientist at Genomics England: *The Genomics in Health Implementation Forum – driving GA4GH standards into healthcare*.	**Collaborative software development** Tony Håndstad, Bioinformatician, Department of Medical Genetics, OUS	**Nordic consent framework and toolkit** Bobbie Ray-Sannerud, Programme Director Precision Medicine, DNV GL	**Preparing for IVDR** Cathrine Høgseth Nordhus, Section Manager Quality, Department of Medical Genetics, OUS	**Cancer panel benchmarking** Valtteri Wirta, Facility Director, SciLifeLab & Oleg Agafonov, Researcher, DNV GL
13:00	**Emerging technologies** Frederik Otzen Bagger, Head of Bioinformatics, Dept. Genomic Medicine Rigshospitalet.				**Variant interpretation and data sharing** Dag E. Undlien, Head of Department of Medical Genetics, OUS & Stephen McAdam, Digital Health Director, DNV GL **Closing**
14:00	END	END	END	END	END

[2] https://www.nordicpermedlaw.org/
[3] https://www.nordicpermedlaw.org/events/nordic-challenges-in-nordic-law

Table 2 Description of workshop sessions

Topic	Description	Contact person
Cancer panel benchmarking	The session will introduce somatic workflows in use in the Nordics and present a simple variant identification benchmark exercise using two reference samples with ddPCR verified variants.	Valtteri Wirta (valtteri.wirta@scilifelab.se) & Oleg Agafonov (oleg.agafonov@dnvgl.com)
Collaborative software development	In this workshop participants will present software projects where there is a need for further development, and we will try to match some of these projects with developers who can contribute with their expertise. There is also an opportunity to present ideas and requirements for novel software you wish was available. We will focus on practical NACG collaboration in software development; - How can we collaborate - Potential projects & prioritization of project(s) - Planning of contributions and next steps	Tony Håndstad (tony.handstad@medisin.uio.no)
Nordic consent framework and toolkit	The objective of this workshop is to gather stakeholders interested in the last phase of development for a harmonized Nordic clinical consent framework for genetic testing, consisting of an adult consent form and an information packet. You will hear from Nordic speakers on the topic of consent from legal, laboratory, and clinical perspectives. The workshop will then focus on the further development of the harmonized consent form and information packet for its content and format in terms of implementation across Nordics hospitals. NACG participants will receive the consent documents prior to the workshop to provide any input they may have.	Bobbie Nicole Ray-Sannerud (Bobbie.Nicole.Ray-Sannerud@dnvgl.com)
Emerging Technologies	Several new sequencing techniques, like variations of single cell sequencing and long read sequencing, are currently in use in research. We will explore the clinical potential for the most interesting techniques and their impacts on workflows (lab and bioinformatics), focusing on experiences, feasibility, and future clinical perspective. Specifically, we will cover - ctDNA (TSO500) and long read (PackBio) - single cell DNA (Tapestri, G&T) - RNA (10x, DropSeq, 10x Visium) library preparation methods	Frederik Otzen Bagger (frederik.otzen.bagger@regionh.dk)
Preparing for IVDR	All actors in the field of medical genetics will have to comply with the new European Medical Devices (MDR) and In-Vitro Diagnostics Medical Device Regulation (IVDR) by May 2021 and May 2022 respectively. In this session Nordic laboratories will share the status of their efforts to secure compliance to the new regulations. The goal of the session is to compare the different laboratories' approaches to these regulations and to identify areas where the NACG members can work together to address challenges. Topics to be addressed are formats for collaboration, use of open source code, factory developed test arguments and market surveillance.	Cathrine Høgseth Nordhus (cahnor@ous-hf.no)
Variant interpretation and data sharing	NACG has a continuous focus on variant interpretation including an earlier exercise to benchmark between labs according to ACMG criteria. In this session we will explore in more depth as to how ACMG criteria are used including running a new benchmarking exercise.	McAdam, Stephen (stephen.mcadam@dnvgl.com) & Dag Erik Undlien (d.e.undlien@medisin.uio.no)

NACG opening & keynote

Welcome and opening remarks

	**Speaker**	Dag E. Undlien, OUS AMG & NACG steering committee chair
	Objective	Share information on status and development of NACG
Key information	Dag welcomed to the 9th NACG workshop and introduced the organisation as well as the ambitions for the week. The broad audience and all-time-high attendance was celebrated, as the event brought together participants from more than 20 hospitals, 15 companies, academic research, patient organisations and governmental organisations, confirming NACG's position as an important platform for collaboration in the Nordics where professionals come together to collaborate and share experiences to progress clinical genomics.	

Keynote

	**Speaker**	Prof Sir Mark Caulfield, Chief Scientist for Genomics England. William Harvey Research Institute, Queen Mary University of London
	Title	The Genomics in Health Implementation Forum – driving GA4GH standards into healthcare
Key information:	Sir Mark introduced the Global Alliance for Genomics and Health (GA4GH[4]) ecosystem and their mission to accelerate progress in genomic research and human health by cultivating a common framework of standards and harmonized approaches for effective and responsible genomic and health-related data sharing. GA4GH Work Streams develop standards and tools that are founded on the Framework for Responsible Sharing of Genomic and Health-Related Data. Their work is designed to enable international genomic data sharing based on the specific needs of clinical and research driver projects from around the globe focussing on rare diseases, cancer, basic biology and complex traits. NACG is member of the Genomics in Health Implementation Forum (GHIF[5]), a subcommunity of GA4GH that is 1) focused on advancing a genomics strategy across a single country or a consortium of countries, (2) working towards enabling translation of genomics into clinical care, and (3) actively working to adopt GA4GH standards to contribute to global data sharing. Sir Mark discussed the improved diagnostic yield for patients with rare inherited diseases achieved through the 100 000 Genomes Project, where one can see a diagnostic uplift from whole genomes over usual care. Key Genomics England collaborative resources include PanelApp, the Clinical Variant Ark (CVA), the Clinical Pharmacogenetics International Consortium. The Genomics England Clinical Interpretation Partnership 100,000 Genomes Project Sept 2020 release includes 3.8 billion clinical data points alongside 111,000 genomes.	

[4] https://www.ga4gh.org/
[5] https://www.ga4gh.org/community/ghif/

	The contribution of the established infrastructures to COVID-19 response was discussed, including the detection of seven genome-wide significant loci and three potential therapies. The "Genome UK: the future of healthcare" strategy setting out the vision to extend the UK's leadership in genomic healthcare and research was published Sep 2020[6], building on existing infrastructure such as the UK Biobank and the 100 000 Genomes Project delivered by NHS England and Genomics England. The National Genomic Medicine Service will drive the introduction of WGS into routine clinical services. 2020 milestones: - Genomics UK – National Genomic Strategy - National Genomic Medicine Service for 57 million population - National standards, specifications & protocols - Standardised genomic consent for NHS care and Research - Delivering an approved national testing directory covering single gene to WGS - Building a single UK National Genomic Research Library - De-identified data for academic & industry research - Submitted a new programme to deliver on Genome UK
Q&A	How does GA4GH collaborate with ISO/CEN? - The GA4GH has not gotten involved in ISO standard development. Does GA4GH and Genomics England collaborate with the 1+ MGP? - Despite Brexit GE will collaborate and has signed up for the project. Would a GA4GH legal entity pursue FDA/MHRA/EU approval for tools? - If you are setting standards it is very useful to have a route for endorsement for key bodies to drive implementation of those standards. GA4GH is working to be an accepted and recognised standard setting legal entity to allow e.g. WHO to endorse the standards. This will not change they collaborative development of standards. Are GA4GH and/or GHIF also aiming to start delivering services or infrastructure, or will the retain focus on standards development? - Will continue focus on standard development to maintain the relation with the community and not mix roles. - No ambitions to become a commercial supplier. In variants from genomes a lot of variants were listed as pathogenic or likely pathogenic. Are the criteria used to do this available somewhere? - Information about tiering is available on Genomics England website - Willing to present more specific info in next workshop NACG initially focussed on rare diseases but is now starting to look into cancer. What is the current strategy; will GE get rid of formalin? - Fresh tissue pipelines kept for tumours where WGS will be applied - Formalin fixation will be reduced over time In Oslo we are accredited to ISO 15189, but we have not yet looked at ISO 13485. We would be interested in learning more about your experience on the latter. Would it be possible to get contact details for someone we could approach on this topic? - Will connect person who posted Q with Quality team

[6] https://www.gov.uk/government/publications/genome-uk-the-future-of-healthcare

NACG Emerging technologies

Frederik welcomed and introduced the Emerging technologies workshop as outlined in Table 3.

Table 3 Emerging technologies - overview of session

Topic	Presenters
Introduction	Frederik Otzen Bagger (Rigshospitalet, Copenhagen)
Long read DNA sequencing; Oxford Nanopore	Anna Lindstrand (Karolinska Institutet, Karolinska University Hospital)
Single cell DNA Seq; Mission Bio Tapestri and CellenOne instrument for single cell dispensing	Pirkko Mattila (FIMM)
Single cell RNA seq; Plate-based techniques (SMART-seq/G&T)	Victoria Probst (Genomic Medicine, Rigshospitalet)
Single cell RNAseq; DropSeq	Michael Knudsen (MOMA, Aarhus University Hospital)
Circulating tumour DNA sequencing (using TSO500)	Lise Barlebo Ahlborn (Genomic Medicine, Rigshospitalet)
Summary	Frederik Otzen Bagger (Rigshospitalet, Copenhagen)

Long read DNA sequencing; Oxford Nanopore

Speaker Anna Lindstrand (Karolinska Institutet, Karolinska University Hospital)

Title Long read DNA sequencing; Oxford Nanopore

Key information

- Uses 10x, oxford nanopore and Saphyr optical maps to map a highly complex germline chromosomal rearrangement.
- **Oxford nanopore**: DNA molecules are pulled through a pore and blocks ion flow; each base alters the current in a different way.
- Some junctions only found by nanopore (repeat regions), others only found by short read.
- Case: Hybrid sequencing resolves two germline ultra-complex chromosomal rearrangements consisting of 137 breakpoint junctions in a single carrier.

Table 4 Technology price and feasibility overview, slide kindly shared by Anna Lindstrand

Technology	Price	Feasibility	Pros and cons
Short read WGS	$	1	+ Well functioning, identifies majority of breakpoints - Short reads, cannot bridge repetitive regions
Linked read WGS	$($)	3	- Not really useful in the clinic, very noisy and right now we need to do regular short read first. Could be different if the company was working on improving the method and analysis pipelines.
Optical mapping	$$	2	+ The longest molecules (>250kb) + Different methodology, not sequencing - Cells are needed to prep DNA - Will likely become less feasible over time, poor resolution & complex machine
Oxford nanopore	$$$	4	+ One junction only detected with nanopore - Not really useful (average 25 kbp, longest 100-150 kbp (in our libraries). Special prep necessary to get longer molecules
"Hybrid" seq	$$$$$	5	+ Very long contigues - Complex and pricy. Not ready for clinic.

Q&A	What is the resolution for a junction, is it down to single nucleotide? Or why are there so many between 4 chromosomes? - The breakpoints were pinpointed down to single nucleotide or to within a single read pair and verified by PCR. - There seems to have been two different underlying mechanisms in the two de novo rearrangements. The t(7;11) rearrangement was determined to most likely have been formed through a replicative error mechanism. As for the formation of the formation of t(X;21;19;4) our data suggest that the CCR most likely was formed through a progressive multistep process most likely chromoplexy (more details in PMID 33315133) By linked-read WGS do you mean mate-pair libraries? What size? - 10x linked read libraries and then short read WGS. We have used mate-pair libraries, but they never work great in our hands.

Single cell DNA Seq; Mission Bio Tapestri and CellenOne instrument for single cell dispensing

Speaker	Pirkko Mattila (FIMM)
Title	Single cell DNA Seq; Mission Bio Tapestri and CellenOne instrument for single cell dispensing

Key information

10xgenomics RNA-seq is a based on the principle of microfluidics, where each cell resides in one droplet, where it is lysed. Barcodes are then added to each droplet, and the library can be prepared of all the cells.

- ~30% mRNA captured per cell, 8 parallel samples and 100-10.000 cells/lane
- Case: single cell sequencing of AML patient – revealed changing cellular constitution of bone marrow
- ~ 2.000 € sample prep + 700 € seq (10k cells and 20k reads/cell), using chip for 8 samples
- Robust lab and basic bioinformatics.

10X Genomics Visium Spatial Gene Expression platform uses a slide with spots of barcodes. Spot size 55um which is between 1-10 cells

- Case: Molecular profiling of pre-pubertal ovaries to map cell types and find markers for follicle subpopulations in child ovarian cortex
- New technology, but looks promising
- 1 slide for 4 solid tissue samples ~ 5.800 € + 3.000 € seq in total

CellenONE is a single cell dispenser can do fluorescent Image Based Single Cell Isolation (4 channels) into any plate size. 100€/hour

Mission Bio Tapestri single-cell DNA seq. Microfluidics based, like 10x. 1 sample per run ~ 100k cells.

- Offers a number of targeted gene panels
- 2200€ + sequencing

Q&A	Is there a minimum number of cells as input for CellenOne? - No minimum number, but slow if you have very diluted solution. Minimum number of cells as input for Mission Bio Tapestri?

	- Needs more cells are there are two steps in the capturing process. The amount loaded should be about 100 000 cells per samples; 5-10% output.

Single cell RNA seq; Plate-based techniques (SMART-seq/G&T)

	**Speaker**	Victoria Probst (Genomic Medicine, Rigshospitalet)
	Title	Single cell RNA seq; Plate-based techniques (SMART-seq/G&T)
Key information	- Parallel genome & transcriptome sequencing (G&T-seq) is plate based, meaning that each cell is dispensed into a single well in a multi-plate using a FACS machine. - Compared to fluidics-based it gives fewer cells, but more genes. - Magnetic bead linked with oligo-d(T) used to extract DNA. - RNA and DNA can then be sequenced separately. - Case: subtyping of breast cancer reveals several tumour subtypes in a single patient.	
Q&A	How do MDA, MALBAC and PicoPLEX amplifications compare for single cell DNA analyses in your experience? - Do not have personal experience with any of these technologies but have been informed by colleagues that PicoPLEX would be the better option. Encourage to check reference literature for experiences.	

Single cell RNAseq; DropSeq

	**Speaker**	Michael Knudsen (MOMA, Aarhus University Hospital)
	Title	Single cell RNAseq; DropSeq
Key information	- Drop-Seq is a bead-based method a cell is suspended in a single droplet. Barcoding and resuspension several times yields unique barcode and UMI combinations. - Proof-of-concept could separate mouse from human cells. - Some barcodes “should not have been there”. Filtering 600k -> 470k reads. - Will not continue with Drop-Seq but move to better working 10x.	
Q&A	None	

Circulating tumour DNA sequencing (using TSO500)

	**Speaker**	Lise Barlebo Ahlborn (Genomic Medicine, Rigshospitalet)
	Title	Circulating tumour DNA sequencing (using TSO500)
Key information	- Profiling circulating tumour DNA (ctDNA). Useful tool when no tumour tissue is available - During COVID-19 we can often not get biopsies as we normally get, and then we have been able to perform tumour profiling on plasma ctDNA. - Possible to find tumour mutation in 14/20 patients	

	- We do this in routine diagnostics with for advanced solid cancers with no/limited standard treatment and no option for tumour biopsy. - We use TSO500 Illumina cancer gene panel - 500€ / sample
Q&A	What minimal Level of Detection (LoD) is required for clinical relevance? - Standard cut-off AF ≥5% but hotspot or druggable mutations can be reported down to 1%. Minimum median coverage > 600x on these panels. Is the ctDNA sample type part of your clinical guidelines under any circumstances? - Most ctDNA analyses performed at Genomic Medicine are research project, internal and external collaborations. However, for patients enrolled at the Phase 1 Unit (Oncology Department, Rigshospitalet) with a solid cancer unavailable for tissue biopsy we perform genomic profiling based on ctDNA analyses using the TSO500 gene panel. If we identify a treatment target e.g. BRAF V600E in the ctDNA, the oncologist considers this information for possible treatment. Do you accept external samples from abroad for clinical analysis of ctDNA panel TSO500? - Yes, we have collaborations established

Bioinformatic tools development

Tony welcomed to the session and introduced the NACG virtual week. While previous bioinformatics tool development sessions have included hackathons, setting up Matchmakers in the cloud, variant prioritisation, structural variants and more, *this* session will try to initiate more collaboration for the development of some open source bioinformatic tools as outlined in Table 5.

Goals for session:

- Showcase some relevant tools being developed in our community
- Discuss ideas for improvements
- Recruit new contributors to develop these projects further
- Create an understanding for how open-source software is developed

Table 5 Bioinformatic tools development - overview of session

Topic	Presenters
Introduction	Tony Håndstad
MultiQC and MegaQC	Phil Ewels, SciLifeLab & Tor Solli-Nowlan, OUS AMG
SVDB	Jesper Eisfeldt, Karolinska & Sjur Urdsson Gjerald, OUS AMG
Gene panel builder and overview	Morten C Eike, Francesco Bettella, Erik Severinsen (all OUS AMG)
Summary	Tony Håndstad

MultiQC and MegaQC

Speaker	Phil Ewels, SciLifeLab & Tor Solli-Nowlan, OUS AMG
Title	MultiQC / MegaQC
Key information – MultiQC	Phil introduced MultiQC which allows visualisation of results from common bioinformatics tools and multiple samples in one report with standardized output. MultiQC is still evolving with new modules and is being developed by an increasing number of contributors, with Phil curating the contributions. The **Multiqc.info** homepage provides all documentation needed to set up and run MultiQC and information on how to develop new modules. The code is available at **github.com/ewels/MultiQC**. Phil discussed the upside of increasing contributions, but also how he as the only product owner is becoming the bottleneck to the further development of the tool. Proposes more sustainable model where he may manage plug-ins separate from the main MultiQC-tool, avoid the slow turnaround for new releases, and keep developers responsible for their different modules.
Key information – MegaQC	MegaQC (**github.com/ewels/MegaQC)** was developed to provide an overview of multiple MultiQC runs. The overarching tool takes json files from MultiQC and puts data in a database, with the opportunity to interrogate data and visualize trends and patterns in a web-based user interface. Tor referred to the NACG hackathon in Stockholm 2018 as a starting point for his engagement with MegaQC. He provided a demo of how MegaQC is used at OUS AMG, using trend data to monitor potential quality issues. He also explained how MultiQC must be configured to allow upload of data to MegaQC from MultiQC.

Q&A	Do you have automated testing/unit testing/test configs etc. in place? Or is it you or some others testing manually? - There is some automated testing but it's not as granular as unit testing. Basically, there is a repo full of example tool outputs for every module. The CI then runs MultiQC against all of these to make sure that it doesn't break. - There are also tests for a few other cases, like that running with no samples doesn't generate a report, some code style tests (config keys etc) and other stuff. - But not yet any testing of actual parsing. This would be great to work on for a v2.0. MultiQC: Brilliant idea to split the code and responsibility. Maybe also create an organization for the modules? - Yes! In fact, I made one a while ago but never got to moving over to it properly. But this would be part of the plan. https://github.com/MultiQC Are samples always viewed by date in MegaQC, or can users choose a different axis? For example, lot number for flow cells, or which exome was used? - For trend analysis: only by time. However, you can use different filters, including flow cell type. - You can also use "compare data" to compare any two values. Is your local version of MegaQC integrated with your lab LIMS (Clarity, or whatever you have?) - No, but would be very useful. - MultiQC plug-in for working with Clarity to pull Clarity data into MultiQC report: https://github.com/MultiQC/MultiQC_Clarity How many contributors are there today for these projects? - Small team including people from SciLifeLab, OUS, Germany, Australia. Working on contingency planning. - Competence needed depends on area of contribution; python, full stack, documentation Does MultiQC have a dry run option, which does not upload to MegaQC? - Not yet Any tips for developers that develop tools for many to use? - Accessible website that allow people to easily assess if this is the tool they would like to use; grab their attention - Documentation

SVDB – Structural variant database

	**Speaker**	Jesper Eisfeldt, Karolinska UH & Sjur Urdsson Gjerald, OUS AMG
	Title	SVDB
Key information	**Background** - Need to build and query frequency database – collect and compare - Merge SV vcf files, for example for trio analysis - SVDB is build using Python and supports most SV callers and SV types	

- Goal: make svdb the best tool around!

A core problem is to assess the similarity of SVs identified; are they the same with different positions or are they different types? What are the frequencies of variants? You can compute overlap, distance, or build a graph of the genome. SVDB computes the overlap (Jaccard distance) and breakpoint distance. There are many tools available for SV similarity analysis; Bedtools, Survivor, Graphtyper (DeCode) as well as “a ton” of custom home builds. It is almost a philosophical question what the best is.

SVDB modules

Build: Load variants into SQLite DB; contains only one single table – room for improvement

Export: Export SQLite DB into a vcf. Designed to represent frequencies.

Query

- Vcf files can be annotated
- SQlite (slow, but exact, cannot be customized)
- Vcf (select fields from INFO (e.g. gnomad) or cluster based on format field)
- BEDPE (quick & dirty analysis, e.g. with truth)

Merge

- Merge a few vcf files (technologies, callers, tumour/normal, families)
- Slow (but exact – all vs all search)
- Different from svdb export (represent variants, not frequencies)

Use cases

- Use of local frequency database: svdb can be used to filter out recurring variants and artefacts and is useful even with a small database.
- QC: you can use svdb to compare batches and libraries.
- Compare technologies (paper in press): svdb query based on BEDPE truth set (Sanger)

How can you contribute?

- Everyone can contribute, available here: https://github.com/J35P312/svdb
- Open source; MIT license
- Issues: bugs (solved quickly) & features (will be developed slowly)
- Pull request: everyone is welcome!

You can also install svdb with Conda, using Python 3 or 2.7. No unit test available, will have to test yourself.

Discussion issues

Svdb could easily be developed further, e.g. adding further columns to the database.

Zygosity and SV calling is not taken into account for now; will include it in the future, contributions are welcome to enable calculation for population and allele frequencies.

Sex and variant calling: we have population and allele frequencies, mixing M and F samples will skew frequencies. Need to fix svdb to support this. Does not require much work, it is mostly about adding columns to the svdb.

Other areas of development

- Refactor; cleaning of code and unit test
- Merge: optimize the code
- Support other file formats

	- Annotation - Documentation - Large insertions A quick raise of hands indicated multiple svdb users in the audience, and a svdb hackathon was proposed for a future NACG workshop.
Q&A	Are frequencies calculated on the fly or once and for all during build? If they are calculated on the fly, it would be nice with a feature to add new variants to the database instead of creating from scratch. - Not computed during build. Need to export to calculate frequencies, or they are calculated on the fly during querying. Would you be willing to drop support for Python 2 in favour of Python 3? - It already supports Python 3; Python 2 support will be dropped. For merging, do you check for repeat regions or other masked section of the genome? That could help with some possibilities why break points are spread out. - Not right now, only checks vcf files. - Would be nice feature to add; contributions are welcome. What is most important to get done first? - Refractoring to get the code cleaned up so that it is easier for others to contribute

Gene panel builder

	Speaker	Morten C Eike, Francesco Bettella, Erik Severinsen (All OUS AMG)
	Title	Gene panel builder
Key information	For the gene panel session, Morten. C. Eike introduced the rationale and challenges in creating gene panels. This included how to choose genes and decide on inheritance model and default transcripts for each gene, with possible sources to use. Francesco Bettella continued with a walkthrough of the gene panel builder project he's been working on, with examples of how data is created. The project is planned to be released as open source for Christmas. Morten ended the session with status and plans for a separate project that Erik Severinsen has been working on to create a HTML-based solution providing search and a detailed overview of current and past versions of gene panels used in-house. People interested in contributing to the further development of the gene panel builder were encouraged to reach out to the presenters or to Tony.	
Q&A	Are there Norwegian clinical guidelines for which genes to test? - not sure, this is the responsibility of our lab doctors, but at least the decision to use PanelApp as the main source for choosing genes appears to be fairly uncontroversial.	

Nordic consent framework and toolkit

Bobbie welcomed and introduced the NACG for new participants as well as the overall structure for the session on Nordic consent framework and toolkit as outlined in Table 6.

Table 6 Nordic consent framework and toolkit - overview of sessions

Section	Topic	Presenters
Part I: Secondary findings	Introduction	Bobbie Ray-Sannerud, DNV GL
	Nordic Permed Law & legal guidelines on returning secondary findings	Katharina Ó Cathaoir, University of Copenhagen and Nordic Permed Law
	Case examples from the clinic, lab, and legal perspectives	- Kaisa Kettunen, HUS Diagnostics Center - Elsebet Østergaard, Department of Clinical Genetics, Copenhagen University Hospital (Rigshospitalet) - Hrefna Dögg Gunnarsdóttir, Faculty of Law, University of Copenhagen
Part II: Nordic consent documents	Introduction to Nordic consent framework and toolkit, facilitated interactive discussion and next steps	Sharmini Alagaratnam, DNV GL

Part I: Secondary findings in genetic testing

Bobbie introduced the motivation for this session; challenges that have emerged in standardizing text for the Nordic consent framework for managing secondary findings, due to the variation of practices across the Nordic countries. The session began by defining secondary findings as test results that provide information about genetic changes (variants) unrelated to the primary purpose for the testing. The Nordic consent project encountered variation in the management of consent and secondary findings across the Nordic countries through topics such as ethical quandaries, right to know, identifying categories for consent, and inclusion of family members.

Nordic Permed Law and the legal basis for secondary findings

Speaker Katharina Ó Cathaoir, University of Copenhagen and Nordic Permed Law (katharina.o.cathaoir@jur.ku.dk)

Title Introduction to Nordic Permed Law and the legal basis for returning secondary findings

Nordic Permed Law

Katharina introduced the Nordic Permed Law network, spinning out of the Norwegian BigMed project focusing on nourishing an expanding ecosystem in precision medicine. Realizing that there are a number of legal issues that will need to be resolved to progress precision medicine and clinical genomics and recognizing that there are commonalities among Nordic legal system but also differences, a joint Nordic effort was formalized in May 2020. More information available at www.nordicpermedlaw.org.

Legal guidelines on secondary findings

Focusing on Denmark, Katharina discussed legal guidelines on secondary findings. Under law, patients have right to receive & refuse information, but health professionals can inform without consent if necessary, to prevent harm or if they feel ethically obligated to protect health (*værdispringsregel*).

The Danish National Genome Center has developed a consent form for healthcare where patients can define if they want to be informed of:

- No secondary findings
- Secondary findings that can be prevented/ treated

	- All secondary findings of importance for health There are other regulations guiding the handling of secondary findings in research projects. Research subjects should decide whether they wish to be informed of secondary findings and should not be informed if they exercise their right not to know. There are regulations guiding what a research responsible should inform on. The information must be presented by a person bound by confidentiality. Conclusions: - Secondary findings require a legal balancing act between rights and interest. - Patient information regarding secondary findings is rights-based, whereas research subjects have rights to refuse secondary findings only. - Clearer guidelines could benefit clinicians and patients, e.g. by defining significant secondary findings.
Comments, questions, and discussion	Is the Danish clinicians' right to disclose secondary findings based only on harm to the patient? What about harm to relatives? Or public health risks? - They are all different grounds, one related to the patient himself but could also be public health. - Yes, relatives can be informed under law under some circumstances, but these circumstances are not clearly defined. If the patients ask for ALL secondary findings, can the project or lab subsequently decide not to analyse those findings (e.g., for resource reasons?) There seems to be a tendency to look at these check boxes as a permission and not as creating an obligation to report. - Under Danish law the lab is not obligated to search for secondary findings; only professional duty is to diagnose the patient based on the phenotype that is the basis for doing the genetic sequencing. - If the patient has chosen "not to know", they should not receive this info. Based on family history (e.g. BRCA-related), patients may in some cases make an informed decision not to know their disposition. Not that many mutations have accurate information on the effect. How reliable does information need to be to be valid to inform the patient? - Good question: there is a concern with the professionals about which information to provide and which not. Information must be significant to health. - Need for further clarification on what is significant and not. For uncertain findings there are legal and ethical reasons not to inform. Why not provide the option, treatable /preventable instead of actionable? The content of the term "actionable" is too soft and not necessarily clinically useful. - Actionable works fine; covers both treatment and surveillance One big issue is the timing; in an acute phase the information is superfluous, should be offered at a different time.
Comments	Comment: If there are other people from Sweden following this workshop you can reach out to me at charlotta.ingvoldstad-malmgren@sll.se, to discuss how we can create a "Swedish working group" on this subject. I am involved in this area through Genomics medicine Sweden The Danish Society for Medical Genetics is working on a guideline for reporting secondary findings. Will only report class 4 and 5 findings. Reporting of carrier status should be defined through a defined list, but this is complicated and should be addressed in MDT discussions and would also have to evolve over time.

Following Katharina's introduction, a poll was held to gauge opinions on informing patients about secondary findings, see Figure 2.

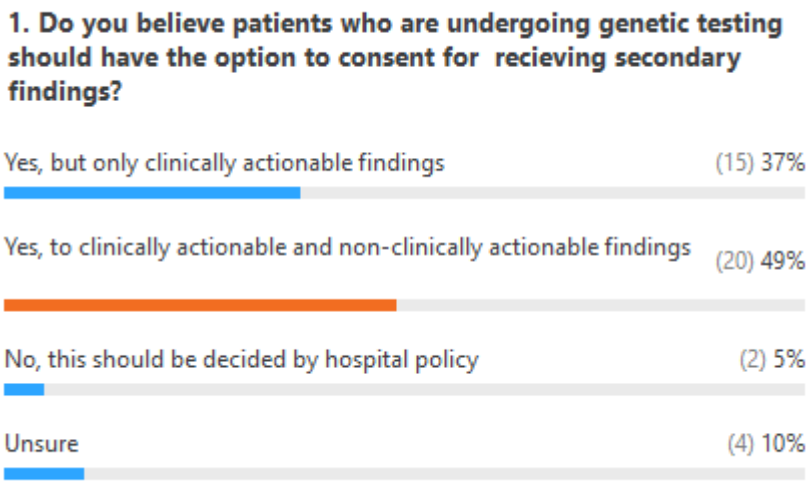


Figure 2 Opinions on informing patients about secondary findings

Challenging cases – secondary findings

Three challenging cases (Table 7 to Table 9) were presented to illustrate and discuss challenges regarding reporting of secondary findings.

Table 7 Case I: A challenging case from the lab perspective

Case I: A challenging case from the lab perspective			
Presenter: Kaisa Kettunen, Clinical laboratory geneticist, HUS Diagnostics Centre			
Clinical summary	Exome trio analysis - 1-year old boy - Global developmental delay, inability to sit, inability to stand, inability to walk, delayed speech development (only spare sounds), hypotonia, opisthotonos (hyperextension & spasticity) - Growth normal, no structural abnormalities, no dysmorphic features - No consanguinity	**Consent**	Consent for reporting incidental findings for the index (Centogene), no separate consent for the parents Consent for secondary findings? - Index: YES - Parents: NO HUSLAB Incidental findings = ACMG59
Findings	Heterozygous NM_001005463.2(EBF3):c.530C>T p.(Pro177Leu) - De novo - EBF3: Hypotonia, ataxia, and delayed development syndrome, 617330 (3), Autosomal dominant - Pathogenic (ClinVar, HGMD)		
Additional findings	Heterozygous NM_000083.2(CLCN1):c.2680C>T p.(Arg894*) - Inherited from the father - CLCN1: Myotonia congenita, dominant, 160800 (3), Autosomal dominant; Myotonia levior, recessive (3); Myotonia congenita, recessive, 255700 (3), Autosomal recessive - ClinVar: Conflicting interpretations of pathogenicity LP(1); P(9); VUS(1) - ClinVar pathogenic submissions > AR disorder - Pathogenic in AD Myotonia congenita? - High frequency or carriers > incomplete penetrance? - Could there be an additional effect on the phenotype? Later onset of symptoms? Milder phenotype? - CLCN1-mutation carriers may be at increased risk for adverse anaesthesia-related events Hemizygous NM_000495.4(COL4A5):c.1871G>A p.(Gly624Asp) - Inherited from the mother (het) - Alport syndrome 1, X-linked, 301050 (3), X-linked dominant		

	- GnomAD: Observed in 16/182998 (0.009%) alleles, including 4 hemizygous. - ClinVar: Pathogenic/Likely pathogenic > het & hemizygous - Not on the ACMG59 list Could be beneficial for the family if the carrier's kidney function would be followed up.
Summary	Which variants should be reported for the index patient? - Primary findings: - EBF3 c.530C>T p.(Pro177Leu) - Secondary findings: - CLCN1 c.2680C>T p.(Arg894*) - > Not known if pathogenic also in AD form - COL4A5 c.1871G>A p.(Gly624Asp) - > Late onset, follow-up of kidney function Should the secondary findings be reported for the index? - Not directly connected with the phenotype & outside the ACMG59 list Should the secondary findings be reported for the parents? - No consent received
Q&A	Should carrier status for an autosomal recessive disease be communicated? I think so. - We are communicating if linked to phenotype investigated. Do not communicate carrier status for other phenotypes. Have these cases changed your view / routines for reporting secondary finding? - This case has broadened the presenter's personal view; this family should know. - So far, no changes to the consent form implemented; focus on ACMG59 list of genes. - Would be good to have some more flexibility

Table 8 CASE II: Secondary finding in a gene associated with retinitis pigmentosa

Case II: Secondary finding in a gene associated with retinitis pigmentosa			
Speaker: Elsebet Østergaard, Department of Clinical Genetics, Copenhagen University Hospital Rigshospitalet			
Case presentation	- Girl born by Caesarean section week 35. - Pregnancy: severe IUGR and oligohydramnios - Birth weight 1,600 g (- 40% SGA), Apgar scores 10/1 and 10/5 - Lactic acidosis shortly after birth - On day 3, silent, pale and hypotonic, episodes with apnea - Intubated on day 5 due to epilepsy	**Evaluation & consent**	- Mitochondrial disorder suspected from clinical findings - Parents offered exome sequencing (singleton), analysis of 5,000 – 6,000 disease genes Parents opted for reporting of findings related to the child's condition only.
Diagnostic findings	Two variants in *NDUFA12*, encoding a structural protein in complex I of the respiratory chain		

Secondary finding	Heterozygous *RP1* variant c.2360T>A, p.Leu787*, classified as pathogenic. There was no family history of retinitis pigmentosa or other eye disorders.
	
	RP1
	
	- Pathogenic variants are associated with both autosomal recessive and dominant RP
	- Dominant RP1-related retinitis pigmentosa:
	  o Associated with adult-onset visual loss
	  o Incomplete penetrance
	  o Gene therapy is under development
	- No retinitis pigmentosa genes are included in the ACMG list of reportable secondary findings.		

Discussion and conclusion	Should we report the *RP1* variant in the index patient? Cons - Parents had solely opted for information on variants related to the indication - The variant is associated with an adult-onset disease - Incomplete penetrance Pros - Parents in a very difficult emergency situation when they had the counselling		

	- Therapy may be developed In conclusion, the secondary finding was not reported to the parents.
Q&A	Is there any law regulating the right to receive information about the secondary findings by paediatric patients when they become adults if parents originally chose not to receive them? - In this case, the patient passed away. If we report secondary findings, it is available in the child's file.
Comments	In DK if the secondary findings are not recorded in the child's patient journal, there would be no right to this info. If they are, the child can access the info but of course they would have to know to search

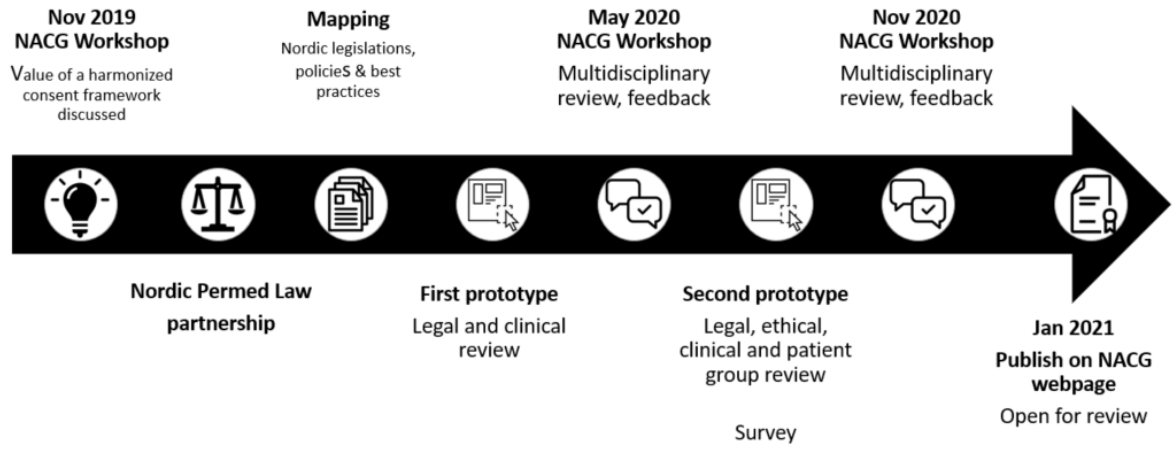
Table 9 CASE III: Secondary findings – legal and ethical issues

Case III: Secondary findings - Legal and ethical issues	
Speaker: Hrefna Dögg Gunnarsdóttir, Faculty of Law, University of Copenhagen	
Secondary findings – Case study	Existing data held in Icelandic health data banks, collected with a research purpose. There is an ongoing discussion about using this data to inform individuals if they are likely to carry mutated BRCA1 and/or BRCA2 gene. Actions - The Icelandic Directorate of Health decision 2011 - The Minister of Health working group on notifications to participants in scientific studies in the health sector 2014 - The Minister of Health working group on the use of genetic data for precision medicine 2016-2018. Outcome - At the governmental level: Status quo - Private initiative: DeCode's www.arfgerd.is, where individuals can take contact and request information.
Legal and ethical issues	Autonomy - Art. 10 of the European Convention of Human Rights and Biomedicine 1997 - UNESCO Declaration on the Human Genome - Declaration on the Rights of the Patient (1981, 1995) - The WHO "Guidelines on Ethical Issues in Medical Genetics and the Provision of Genetic Services" (1997) Data and samples

	- Charter of Fundamental Rights Art. 7 and 8. - European Convention of Human Rights Art. 8 - The General Data Protection Regulation Other international, regional, and domestic law on autonomy, data, samples, and other appropriate issues such as: - Right of patients and participants in scientific studies - Right to information - Medical records, Insurance, Social welfare law etc.
Conclusions	Autonomy - (Presumed) right not to know - "Burden of knowing" - (Activated) right not to know - Disregarded in other scenarios e.g. in the face of natural hazard - Solidarity Data and samples - Collection of new, informed, explicit consent - Collection of new samples - Use of already collected, wide and dynamic consent - Use of already collected samples Other - Evolution of the patient/participant relationship with medical doctor/scientific studies - The legal implications of the information becoming part of medical records - Providing the appropriate follow up support
Q&A	Is it known how the public views open access to potential genomic variants based on anonymised blood relative data in healthcare records? Hrefna has replied that she is not aware of any studies regarding the views of the public in this regard.
Comments	If you are interested to learn more about return of Decode´s BRCA2 results in Iceland please see the paper Stefansdottir V, Thorolfsdottir E, Hognason HB, Patch C, Van El C, Hentze S, Cordier C, Mendes A, Jonsson, JJ. Web-based return of BRCA2 research results: One-year genetic counselling experience in Iceland. Euro J Hum Genet 2020 doi: 10.1038/s41431-020-0665-1. Online ahead of print.

Part II: Pan-Nordic consent framework & toolkit

	Session lead	Sharmini Alagaratnam, DNV GL
	Objectives	- Introduce the Pan-Nordic consent framework & toolkit project and process - Gain understanding of what is done in practice - Share and compare opinions on the different sections to ensure the documents developed respond sufficiently to needs
Motivation for initiative		- As the leading precision medicine initiative in the Nordics, NACG is well-positioned to initiate and co-ordinate discussions around consent practices across the Nordic countries in genetic testing. - Development of a harmonized consent framework as a vehicle to harmonize and identify categories for discussion in consent in genetic testing and data sharing across the Nordic countries. - Develop partnerships across disciplines and borders in consent in clinical genetic testing.
Contributors to the project		From across the Nordic countries; contributors from Nordic Permed Law, healthcare institutions, industry, and patient groups



Draft products

NACG Pan-Nordic clinical consent framework for genetic testing includes

1. Adult information packet
2. Adult consent form
3. Guidance to the process of delivering consent

The Information packet is a 3-page document including the following sections:

- What is genetic testing and its purpose
- Benefits, risks, and limitations of genetic testing
- Voluntary nature of the genetic test
- Implications of genetic diagnosis including uncertain and secondary findings, and for relatives
- Right to know and not to know
- Delivery of results
- Reanalysis and recontact
- Data sharing and privacy

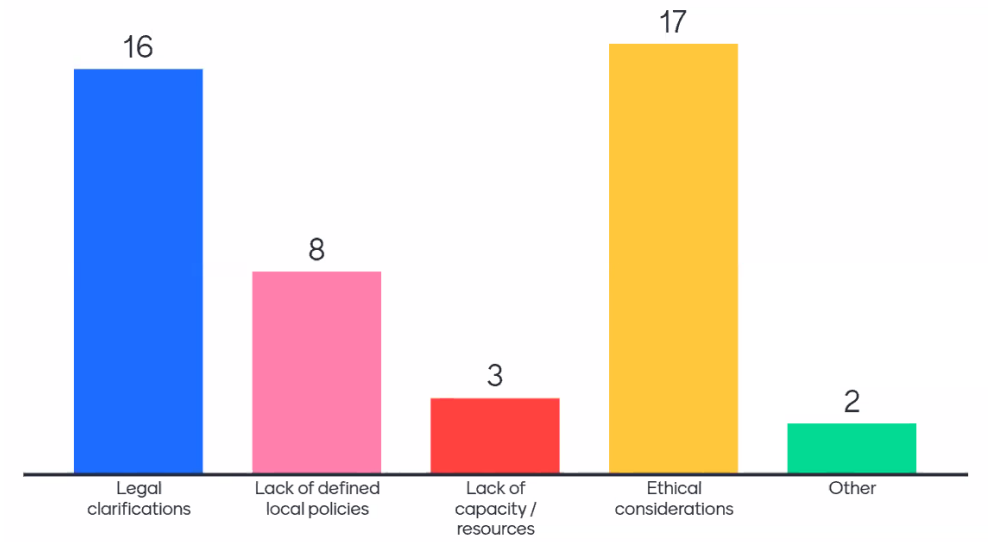
- Withdrawal and modification of consent

The adult consent form is a 2-page document including:

- consent to test
- about the test
- potential outcomes
- data sharing
- research
- signature

Interactive session	To gain understanding of what is done in practice and share and compare opinions on the different sections, participants were invited to respond to poll questions and follow up discussions on selected topics.

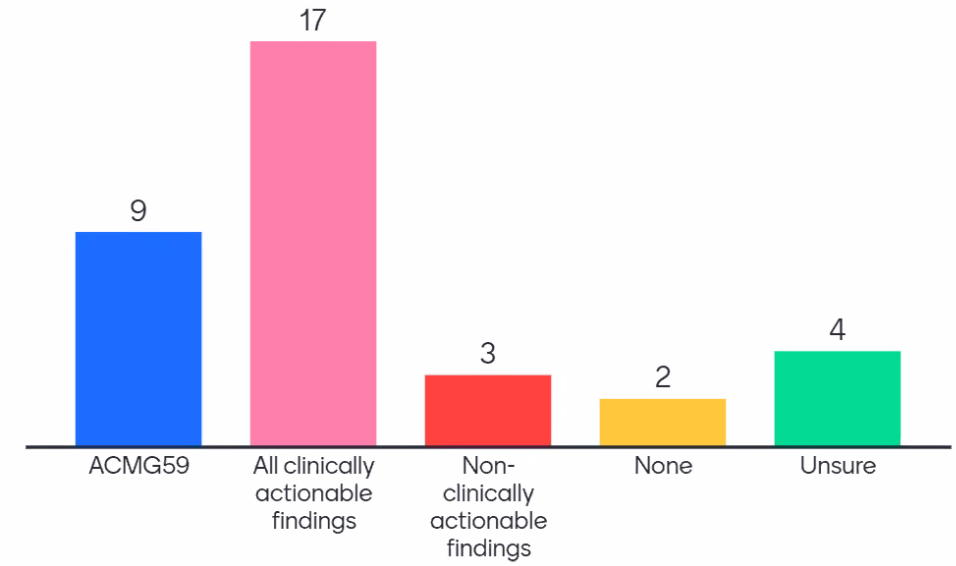
What are the main challenges in developing consent processes?



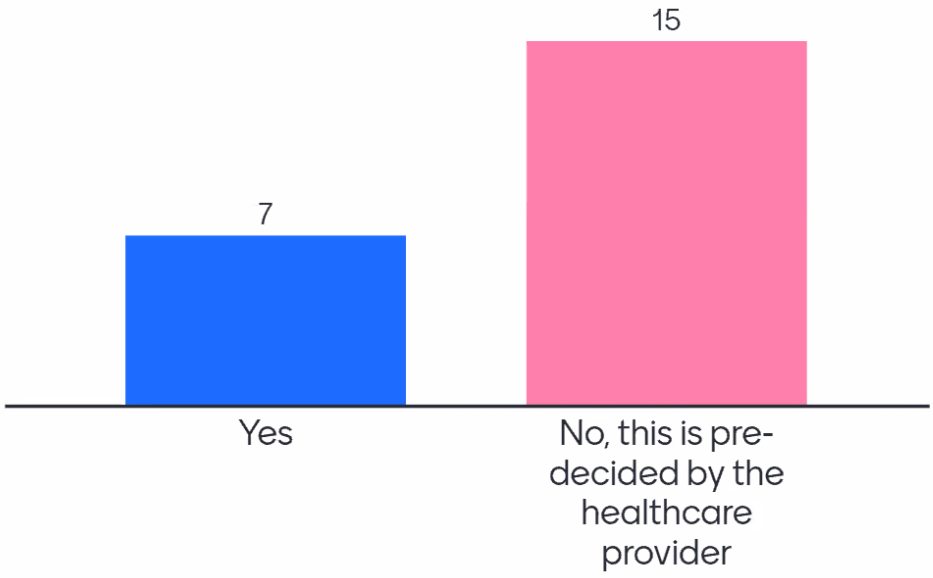
Discussion & comments

- The main challenge is how to assure actual, real, informed, consent.
- “Other” category: ensuring informed consent (prob tied to both ethical/legal considerations of what "informed" is)
- If we don’t know what the “standard of care” is in clinical genomics for secondary findings, reanalysis, and data sharing, it’s hard to select the right consent language to describe what the lab is doing
- Relates to resources in the process itself, training, understanding, informing, clear message, validity over the course of time.

In practice, to your knowledge, what kinds of secondary findings get returned to patients?



Following up on the previous question; do patients have the option to choose what they would like returned?



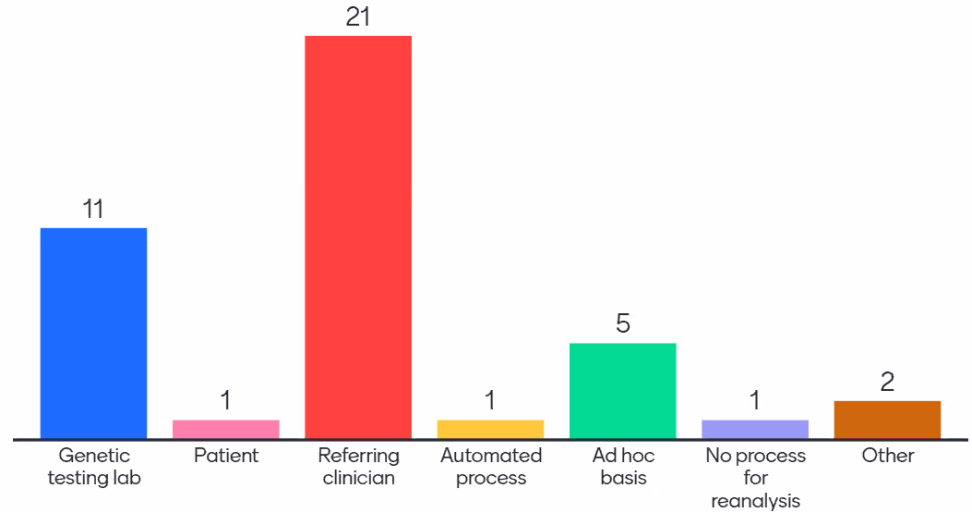
Discussion & comments

- Which country says patients can decide?
- Is there any relationship between whether labs report ACMG59 vs all actionable findings and whether the lab provides results to genetic counsellors versus straight to physicians?
    - Finland: report primarily ACMG59 list findings. Genetic counselling is often done by clinical geneticists and requisitioning physicians in Finland.
- Those who do report all actionable findings, do you actively analyse those genes from your exome / genome data? How do you define "all actionable genes"? Or do you report if you happen to find something?
    - Only if they happen to arise. We rarely find reportable, and we don't look specifically - but we sometimes come by variants that will then be discussed with relevant specialists before reporting.

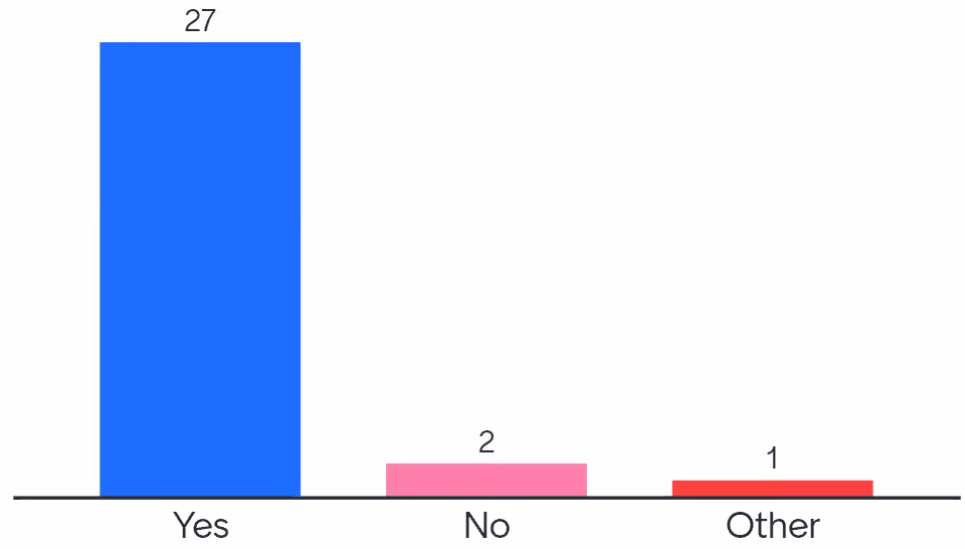
- At Rigshospitalet, Copenhagen, we would also report variants in other genes, e.g. for porphyria. It is hard to distinguish clinically actionable and not; this also changes over time
- Always inform about clinically irrelevant findings and secondary findings
- Do not go through the whole exome to check for secondary findings; focus on the phenotype in questions.
- Doesn't the bar for being clinically relevant change based on how results are used in the healthcare system? For example, ACMG59 might be appropriate if a lab delivers results often to physicians without a lot of genetic expertise, but something like the RP example could be more appropriate if results are going to specialists?

- Discussion on secondary findings
  - Timing of providing information about secondary findings should be discussed; most people would like to have information, but not during acute phase.
  - On the right not to know: "I do not want to know this at this point of time; maybe later."

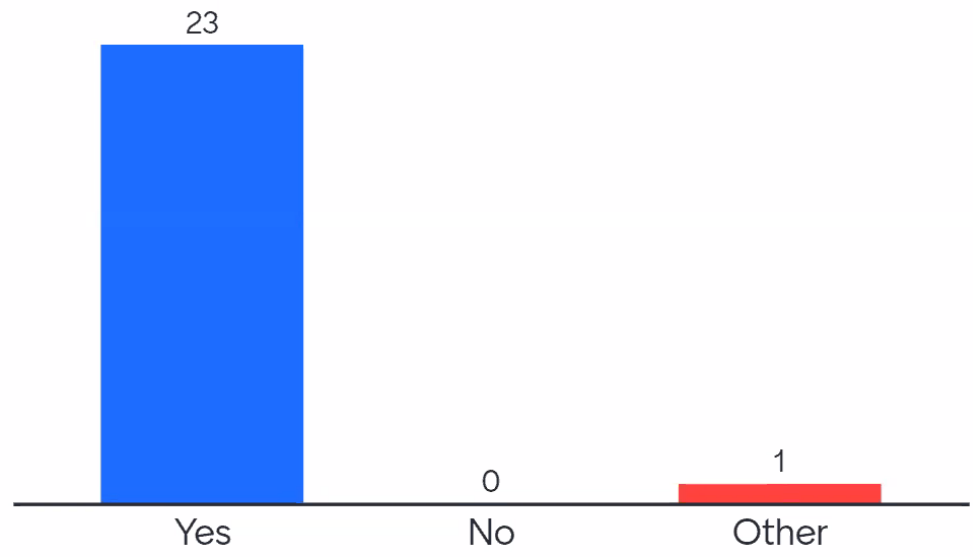
In practice, to your knowledge, who determines if and when reanalysis occurs?



In your opinion, should the healthcare institution inform patients about reanalysis procedures?



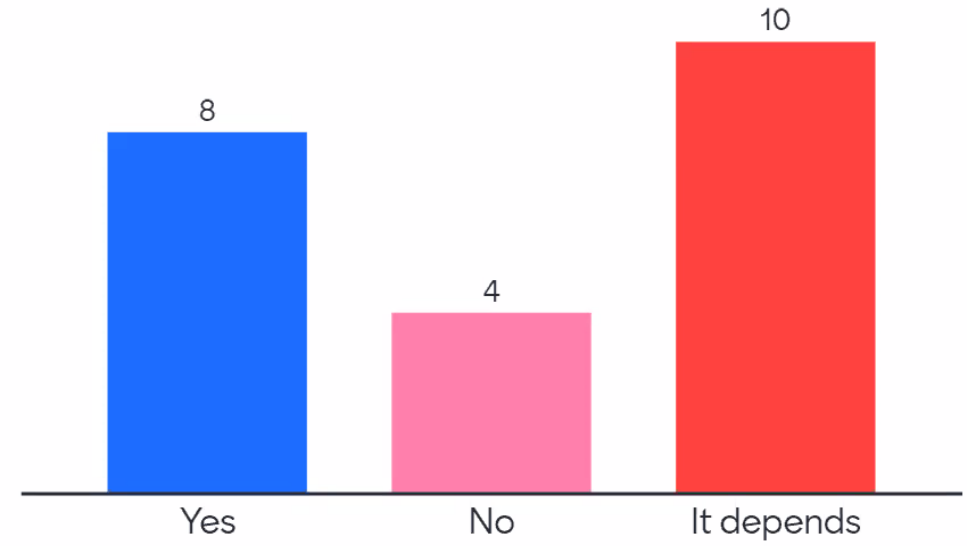
In your opinion, should the patient have the option (or not) to consent for reanalysis?



Discussion & comments

- The areas we know the least of are the ones we spend the most time on in the consent, maybe rather focus on the main issues at hand?
- Should proceed with caution not to complicate the core issues.
- Reasons for not informing: there is limited systematic reanalysis in the first place (so it's an empty promise). Mentioning reinterpretation is confusing (undermines the patients faith in the original result).
- Reanalysis should maybe be informed only if there is a significant new finding.
- Some paternalism is needed in health care, patient cannot understand all implications and issues at stake.

In your opinion, is it appropriate that patient consent should determine if their personal data is shared for diagnostic purposes?



Discussion / comments

- It depends; if we are doing family studies, we never share
- Difficult cases are discussed with colleagues, and cases are shared to help diagnose similar patients

	- We need to be able to develop evidence-based medicine and use patient data, but inform them about it and make safeguards - at least in welfare states where universal access to health care. I mean sharing to improve diagnostics via databases etc. - In Finland, these issues are being discussed; revising biobank act and setting up genome centre.
How can the process of obtaining consent be improved?	- More clear direction for grey areas - Digital format; allow the patient overview of their consent preferences - When possible, updates to consent via patient dataportal. - Working together to develop consent forms that take into account the patients health competency - More time, recources and genetic counsellors - Electronic consent forms available online at patient's convenience and including deeper explanations of topics - General public knbowledge about genetic analysis - The broader "massive" education of variable health care providers - The need for consent may differ whether it is for sharing information with relatives vs. sharing different types of genetic data in bioinformatic tools and databases to help develop genetic knowledge world wide. Different approaches are needed. - Digital dynamic consent
Next steps and future perspectives	- Consent framework was open for comment for a week following the workshop - v1.0 to be published Jan 2021 at the NACG website https://nordicclinicalgenomics.org/projects/nacg-pan-nordic-consent-project - Living documents; will be continuously improved - Opportunity to expand with research focus, potential synergies with GA4GH - Encourages the audience to connect & contribute

Preparing for IVDR

	Speaker	Cathrine Høgseth Nordhus, Section Manager for Quality at the Department of Medical Genetics at OUS
	Title	Preparing for IVDR[7]
	Objective	To establish a network of professionals within NACG to collaborate on the interpretation of the IVDR and to share the burden of securing compliance with the new regulation

Introduction

Cathrine introduced herself and her experience with Quality Management from different industries, as well as the affiliations of meeting participants; healthcare institutions, industry, biobanks, governmental organisations, NGOs, and research. A preliminary survey indicated that very few of the participants felt well prepared for the IVDR entering into force. A quick poll was carried out to map participant expectations:

Background – IVDR at NACG workshops

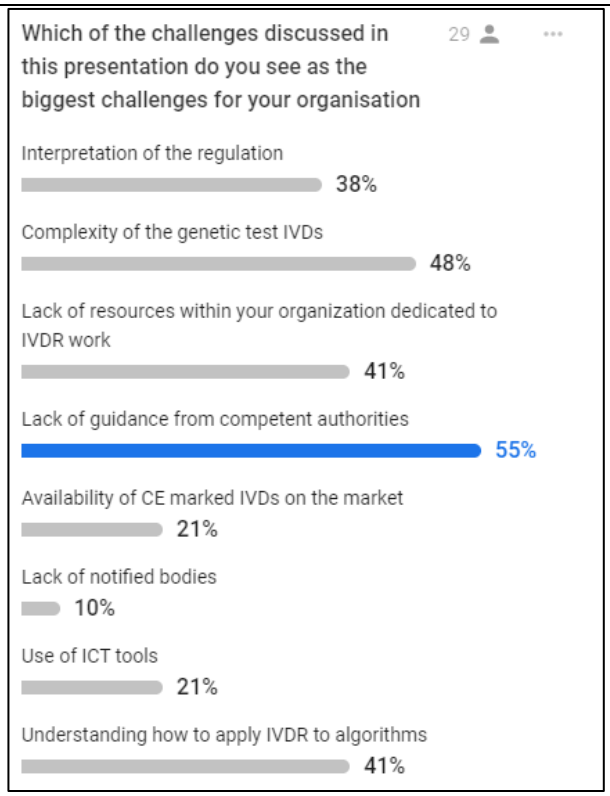
IVDR has been a topic at two Previous NACG workshops as described in the workshop reports[8]:

- In November 2018, Courtney Nadeau (DNV GL) presented an introduction to the IVDR requirements.
- In November 2019, Alexey Shiryaev and Nick Baker (both DNV GL) gave an overview of the regulation and discussed the applicability and requirements for transition.

Relevant papers are also available through the BigMed project[9].

[7] For this session, slides and other resources are made available at https://nordicclinicalgenomics.org/projects/preparing-for-ivdr.
[8] https://nordicclinicalgenomics.org/resources#report
[9] https://bigmed.no/assets/Reports/clinical_decision_support_software.pdf and https://bigmed.no/assets/Reports/clinical-sequencin-g_regulatory-frameworks-and-quality-assurance-for-ngs-based-diagnostics.pdf

IVDR requirements – Highlights	In May 2017, the European published the Medical Devices Directive (MDR) and the In Vitro Diagnostics Regulation (IVDR). The MDR replaces the Medical Devices Directive (MDD) and the Active Implantable Medical Devices Directive (AIMD). The IVDR replaces the In-Vitro Diagnostics Directive (IVDD). - A directive is a legislative act that sets out a goal that all EU countries must achieve, however it is up to the individual countries to decide how. A directive lists objectives to be achieved. - A regulation is a biding legislative act and must be applied in its entirety across the EU. A regulation is a rule. The planned transition period for the MDR was supposed to end May 2020 but has been extended due to the ongoing Covid-19 situation. No information on extension for the IVDR transition period has been provided yet. EUDAMED is the database in which CE marked devices will be registered. There has also been delays in the development of this, and the planned release date is now coinciding with the end of the transition period for IVDR. Cathrine discussed the rationale for establishing the new regulations and impact of the IVDR on different stakeholders and mapped the differences between the old IVDD and the new IVDD. Classification of genetic tests under the IVDR is simple: **All genetic test IVDs are class C devices:** - All class C IVDs will require the involvement of Notified Bodies for their placement on the market. - Most genetic tests in use in Norway today typically fit into what is called the Health Institution Exemption/ In House Exemption
IVDR status for Oslo University Hospital (Norway)	There are five medical genetics departments in Norway. An overview of genetic tests offered is available at www.genetikkportalen.no.The number of people involved with addressing IVDR within the medical genetics discipline is small and resources are limited. Assuming the situation is the same in the other Nordic countries, NACG could be a great platform for collaboration on this topic. In 2019 Health South East (one of the four health regions) started a project to address the requirements in the new IVDR, led by Espen Kibsgård (Dep. of Microbiology, OUS). The genetics group was set up in early 2020, led by Mohsen Shahidi (Dep. of Pathology, OUS). Work has been initiated along three main activities: communication with the competent authority, mapping, and classification of IVDs and development of procedures for IVDR compliance.
IVDR challenges for the genetics field	Cathrine discussed key risks and challenges such as; - General concerns - Complexity of genetic tests - Availability of commercial CE marked kits/reagents and equipment - Health Institution Exemption - ICT Tools - Algorithms and IVDR A poll was conducted to map the most pressing areas of concern for the participants.



A second poll was held to map other risks and challenges, resulting in the following list:

- Increased costs of diagnostics
- Reimbursement?
- it will be economically challenging to introduce CE marked assays
- Pricing and flexibility of new CE-tests
- If CE-marked test is available, can we still develop an in-house test?
- We don't fully understand the impact IVDR will have for us
- Maintenance is important to keep in mind when setting up the system; should not be too comprehensive.
- This field develops rapidly, how will we keep up?
- Does in house exemption apply if you provide services to external partners / other legal entities?
- in genetics, variant interpretation (on the agenda tomorrow) is very important. Will /should that be part of IVDR - and how to do that?
- Should a bioinformatics pipeline be considered medical equipment under IVDR? If not, could it be considered an accessory? The "in-house" provision allows the development and use without CE certification, however the requirements in Annex I still need fulfilling.
- Establishing national laws to allow use of In-house exemption for institutions without ISO 15189.

In-House Exemption/ Health Institution Exemption	The IVDR allows health institutions under certain conditions to manufacture, modify and use laboratory developed tests. A minimum requirement is that all inhouse tests must meet the safety and performance requirements described in Annex 1 of the IVDR. The other relevant conditions are: - Internal use only - One legal entity - Appropriate quality management systems (ISO13485) - Laboratory must be compliant with ISO15189 - Patient group's specific needs cannot be met by commercial alternative

- Health institution must provide information upon request on the use of LDTs to its competent authority
- Health institution must make declaration (stating safety and performance requirements compliance) publicly available
- Specific to Class D IVDs (but can be required by national competent authority for lower risk class IVDs)
- Specific to Class D IVDs (but can be required by national competent authority for lower risk class IVDs)
- The health institution must review experience gained from clinical use of the devices and take necessary corrective action.

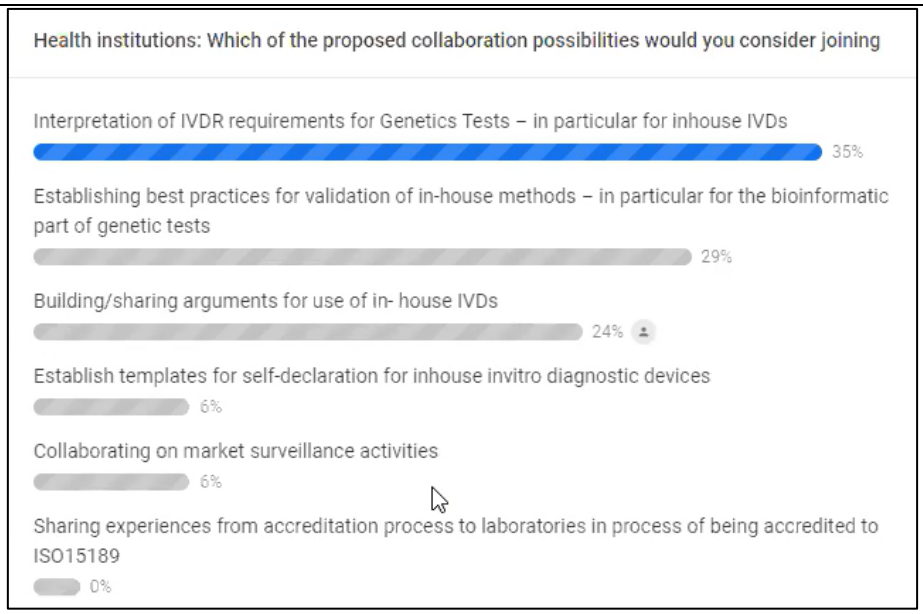
Cathrine went through some of the conditions for In-House Exemption/ Health Institution Exemption and discussed implications for genetic testing and status in Norway[10].

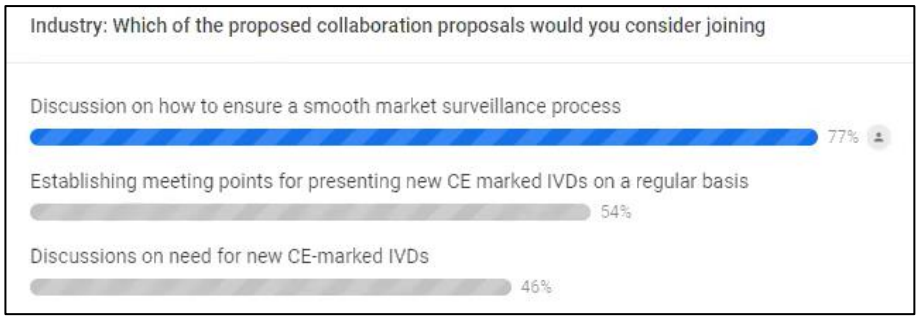
For documenting IVDs under the in-house exemption, two new requirements must be met:

- A declaration must be made publicly available for all In House IVDs
    - Part A defines the legal entity within which the IVD can be used and declares the inhouse exemption, relevant safety and performance requirements and manufacture under an appropriate QMS.
    - Part B states the scope of the declaration
    - Per Part B Scope, Part C outlines intended purpose, that the patient group need cannot be met by commercially available and CE marked IVD and shows IVD classification with rationale
- The Health Institution must justify and document that the patient need cannot be met with a commercial CE marked IVD – this would typically be done through a market surveillance process.
    - Procedures and templates are available through the Norwegian project
    - Market surveys will have to be carried out on a regular basis to cover market developments
    - Collaboration between health institutions and between industry and health institutions will help to reduce the burden of ensuring compliance.

Areas for collaboration	Cathrine suggested a list of areas where members of NACG could collaborate to ensure a smooth transition to IVDR, both between health institutions and between health institutions and industry. The audience's preferences were polled as shown below.

[10] See https://nordicclinicalgenomics.org/projects/preparing-for-ivdr for details.





Additional potential areas of collaboration were identified:

- Should health institutions be more aggressive when it comes to patents when we are forced to buy from commercial parts?
- Definition of gene panel content
- Unmet needs that can be provided by external partner?

Discussion / questions / comments	Is there a risk that documentation will diverge when we will have similar parallel information, for accreditation and for IVDR? - Should be aligned with already existing documentation in the QMS; utilizing what is already made. It would be interesting to hear from the other countries as well as from other departments What are, in your experience, the resource and time requirements of completing relevant documentation? - This will depend on the services that you offer. For our laboratory we see a workload for several years ahead.
Resources	Internal resources - Presentations given by Espen Kibsgård and Rolf Anton Klaasen at Norwegian information meeting in October IVDR: - https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32017R0746

Various resources on the internet:

- https://www.phgfoundation.org/briefing/what-is-the-ivdr
- https://www.phgfoundation.org/documents/algorithms-ivdr-gdpr-workshop-report.pdf
- https://www.phgfoundation.org/documents/algorithms-as-medical-devices.pdf
- https://d2evkimvhatqav.cloudfront.net/documents/md_wp_ivdr.pdf
- https://www.nice.org.uk/about/what-we-do/our-programmes/evidence-standards-framework-for-digital-health-technologies
- https://blog.limbus-medtec.com/the-ivdr-affects-how-genetic-testing-laboratories-can-operate-all-over-europe-c39749e8ef07

Nando – Database with list of Notified Bodies:

- https://ec.europa.eu/growth/tools-databases/nando/index.cfm

From meeting participants

- EUDAMED actor registration module should be going live next week: https://ec.europa.eu/health/md_eudamed/actors_registration_en
- You might want to check out the MDCG publications, they put out interpretations on a ton of topics on a fairly regular basis. https://ec.europa.eu/health/md_sector/new_regulations/guidance_en
- Check out MDCG 2019-11 "Guidance on Qualification and Classification of Software in Regulation (EU) 2017/745 – MDR and Regulation (EU) 2017/746 – IVDR"

New resources can be added to https://nordicclinicalgenomics.org/projects/preparing-for-ivdr, please inform us at post@nordicclinicalgenomics.org.

Cancer panel benchmarking

Valtteri welcomed to the session and introduced NACG and the early steps into the field of somatic cancer genomics.

	**Speaker**	Valtteri Wirta (SciLifeLab) and Oleg Agafonov (DNV GL)
	Title	Cancer panel benchmarking
	Objective	- Introduction to somatic testing workflows in use or in development across the Nordics - Simple variant identification benchmark exercise using two reference samples with ddPCR verified variants - Establish a network of Nordic labs involved in somatic testing to facilitate future collaborations

Cancer panel benchmarking was performed with two reference samples:	**Sample A: OncoSpan FFPE, Catalog ID:HD832, Horizon Discovery** - Cell line-derived, >380 variants across 152 key cancer genes - 238 variants with a COSMIC ID and 28 INDELs (>22 deletions and 6 insertions, ranging from 1-16 base pairs) - 1-100% AF, with 50 variants present at ≤ 20% AF for LoD - 25 ddPCR-validated variants **Sample B: Structural Multiplex Reference Standard FFPE, Catalog ID:HD789, Horizon Discovery** - CNA, translocations, and large insertions/deletions. - Genomic context of variants within regions of specific GC-content (high vs. low). - 9 ddPCR-validated variants with allelic frequencies ranging from 3.5% to 9.7% and CNVs at 4.5x and 8.5x amplification
Sample preparation	- 10 FFPE slices / sample extracted - Eluates pooled to even out differences - Quantification using Qubit - Aliquot sent out to each participating lab, blinded for everyone
Instructions to labs	- Convert 50 ng into library; use the provided concentration - Use SOP established at each lab - Sequence to sufficient depth to enable detection of variants down to 1% AF, or provide your limit of detection

Table 10 Overview of data generation and bioinformatic workflow at participating labs.

Lab	Wet lab / data generation	Bioinformatic workflow
FIMM	Panel sequencing using custom 989 cancer gene panel Twist EF library prep and enrichment chemistry. IDT xGen Dual Index UMI adapters Overnight 8-plex capture Sequencing PE100 on NovaSeq v1.5 Downsampling to 60 M reads on 6.2 Mb target (ca 1000x technical coverage)	Custom workflow: downsampling (seqtk), UMI processing (fgbio), alignment (bwamem). Variant calling - SNV/INDEL using Mutect2 - CNA visualised using custom RPKM normalised coverage Filtering: Keep DP ≥100, AD ≥4
Aarhus - MOMA	Panel sequencing using comprehensive exome from Twist + MOMA spike-in (MSK) Twist EF library prep and enrichment chemistry. IDT xGen Dual Index UMI adapters Input 50 ng Sequencing PE150 on NovaSeq Aim >200x mean coverage	Custom workflow: trimming (cutadapt), alignment (bwamem). Variant calling - SNV/INDEL using Mutect2 - CNA using using CNVkit - SV using Delly Filtering: Keep variants that are not in noisy sites (PON based), are in MSK-IMPACT v2 panel (+10 bp padding), AF>0.02, AD>=5 CNA: Keep copy number = 0 or >=6 SV: MSK target regions, PON filter, AD>=10
Rigs-hospitalet	Panel sequencing using Illumina TSO500 Input 100 ng Sequencing PE150 on NovaSeq S1	GATK workflow (primary diagnostic workflow): trimming (bbduk), alignment (bwamem). Variant calling: SNV/INDEL using **Mutect2** Filtering: keep confident somatic calls using FilterMutectCalls, remove gnomAD >5% Illumina workflow: TruSightOnc500 v2.1 - TMB, CNV, MSI
Helsinki - HUS	Exome sequencing using Twist Human Core exome + spike-in Twist EF library prep and enrichment chemistry. Sequencing on NovaSeq	Custom workflow: trimming (trimmomatic), alignment (bwa mem) Variant calling: SNV/INDEL using **Mutect2** Filtering Liberal: Remove AF>=45%, AF <=5%, DP<=15, AD<=5, PON Filtering Strict: liberal + remove gnomAD >1.5%
SciLifeLab	Panel sequencing using custom 370 gene panel designed for solid tumours Kapa library preparation and Twist enrichment chemistry. IDT xGen Duplex Seq adapters Sequencing PE150 on NovaSeq S4, aiming at 40 M r-p Aim >1000x median coverage	Custom workflow BALSAMIC Trimming (fastp), alignment (bwamem). Variant calling - SNV/INDEL using **VarDict** - CNA using **CNVkit** - SV using **Manta** Filtering: Keep variants that have DP>100, AD>5, AF>0.01, MQ>=55, gnomAD AF_popmax <0.001
OUS	For this exercise OUS did not perform sequencing and used sequencing data provided by SciLifeLab	GATK workflow: (primary diagnostic), alignment to hg19 (bwa mem) Variant calling - SNV/INDEL using **Mutect2** - CNV using **CoNVaDing** (not applied in this benchmark) Filtering: AF <0.05, gnomAD and in-house database >xx% Illumina workflow: DRAGEN pipeline

Table 11 Summary of assays used

Lab	Technology	Library prep	Sequencing	Bioinformatics
FIMM technology center (Helsinki)	Panel, custom 986 genes	Twist	NovaSeq PE100, SP	SNV, indel, CNV
MOMA (Aarhus)	Exome, comprehensive + add-on spike set	Twist	NovaSeq PE150	SNV, indel, CNV, Delly
Rigshospitalet (Copenhagen)	TSO500 (Illumina)	Illumina	NovaSeq PE150, S1	SNV, indel
HUS (Helsinki)	Exome, comprehensive + add-on spike set	Twist	NovaSeq	SNV, indel
SciLifeLab (Stockholm)	Panel, custom 370 genes	Kapa&Twist	NovaSeq PE150, S4	SNV, indel, CNV
OUS (Oslo)	(data from SciLifeLab)			SNV, indel

QC results and number of detected variants are presented in Table 12 and Table 13. Results are pseudonymised, as agreed prior to the exercise.

Table 12 QC results

	Exome				Panels					
	W	W	G	G	C	C	A	A	R	R
	HD 832	HD 789	HD 832	HD 789	HD 832	HD 789	HD 832	HD 789	HD 832	HD 789
Number of reads and read-pairs (down-sampled)	260	239	60	81	30	30	95	112	60	65
Insert size, median	196	197				171	162	154	234	223
% duplicates			8%	9%	21%	11%	59%	61%	28%	28%
Median target coverage	200	200	125	165	200	200	2091	2325	1791	1867
% target bases covered at 100x or more	96%	96%	92%	97%	98%	99%	99%	100%	100%	100%
% target bases covered at 250x or more			20%	45%	88%	93%	99%	99%	100%	100%
% target bases covered at 500x or more			1%	3%	14%	36%	97%	97%	100%	100%
Fold 80 base penalty	1,8	1,7	1,5	1,5	1,5	1,8	1,2	1,3	1,3	1,3
% bases off target			20%	19%	36%	34%			19%	20%

Number of detected variants for received VCF files are presented in Table 13. Some laboratories provided several versions of the results (e.g. with different filtering strategies) details are not disclosed to keep pseudonymization.

Table 13 Number of detected variants

		Sample A (HD832)	Sample B (HD789)
Lab	**Version**	**Number of variants (PASS only)**	**Number of variants (PASS only)**
G	liberal	855	900
G	strict	831	882
A	one	890	5699
C	pass	3850	4631
W	liberal	6060	19456
W	strict	3706	7970
E	I	8649	9710
E	II	4622	4881
R	one	2821	2521

Benchmarking results - ddPCR confirmed SNVs and short INDELs

- In this exercise we used only ddPCR confirmed variants - 26 SNVs and short INDELS from two reference standards, 2 CNVs and 2 fusions.
- Most of the variants were covered by the assays
- Due to the nature of reference samples we assessed only TP and FN
- Six ddPCR validated variants in the reference samples have established gnomAD populational AF which were used by laboratories to filter variants

Table 14 ddPCR confirmed SNVs in both HD832 and HD789

								LAB	A	E	E	R	G	G	C	W	W
								Filter	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS	PASS
								Genome	37	37	37	37	38	38	38	38	38
								Details	one	I	II	one	liberal	strict	one	liberal	strict
CHR	**POS 37**	**POS 38**	**REF**	**ALT**	**AF 37**	**gnomAD AF**	**Gene**	**Sample**	**AF**	**AF**	**AF**	**AF**	**AF**	**AF**	**AF**	**AF**	**AF**
1	115256530	114713909	G	T	0.125		NRAS	HD832	0.1177	0.117		0.122	0.144	0.144	0.1		
2	29416025	29193159	C	CATTG	0.045	0.2651	ALK	HD832	NA	NA	NA	NA	NA	NA			
3	41266101	41224610	C	A	0.3		CTNNB1	HD832	0.3074	0.326		0.3055	0.223	0.223		0.149	0.149
3	41266133	41224642	CCTT	C	0.05		CTNNB1	HD832	0.0949	0.123		0.0839	0.113	0.113			
3	78936091	179218303	G	A	0.045		PIK3CA	HD789					0.071	0.071	0.031		
3	178952085	179234297	A	G	0.2		PIK3CA	HD832	0.1879	0.191		0.1881	0.175	0.175	0.163		
4	55599321	54733155	A	T	0.085		KIT	HD832	0.1028	0.097		0.0996	0.055		0.055		
4	55602765	54736599	G	C	0.07	0.162	KIT	HD832		0.082							
4	153244155	152323003	TC	T	0.32		FBXW7	HD832	0.3295	0.333		0.2797	0.295	0.295	0.329	0.16	0.16
5	112175770	112840073	G	A	0.31	0.6016	APC	HD832		0.363	0.361						0.179
7	55241707	55174014	G	A	0.225		EGFR	HD832	0.2418	0.243	0.24	0.2264	0.294	0.294	0.233		
7	55242464	55174771	AGGA	A	0.044		EGFR	HD789	0.0353	0.038	0.039	0.0361	0.042	0.042	0.031		
7	55249009	55181316	G	GGCCA	0.044		EGFR	HD789									
7	55249063	55181370	G	A	0.175	0.5143	EGFR	HD832		0.127							
7	55259515	55191822	T	G	0.045		EGFR	HD832	0.0413	0.035		0.0358	0.036	0.036			
7	116339847	116699793	GT	G	0.05		MET	HD832	0.0585	0.059	0.062	0.0585	0.069	0.069	0.031		
7	116436022	116795968	G	A	0.055	0.3504	MET	HD832		0.066							
7	140453136	140753336	A	T	0.085		BRAF	HD832	0.1188	0.116	0.112	0.1152	0.14	0.14	0.092		
9	139409754	136515302	G	A	0.295		NOTCH1	HD832	0.3056	0.283	0.287	0.2766	0.332	0.332	0.255		
10	43613843	43118395	G	T	0.595	0.7846	RET	HD832		0.605	0.607						0.556
12	25398281	25245347	C	T	0.13		KRAS	HD832	0.1595	0.12		0.1161	0.14	0.14	0.139		
13	28578214	28004077	GGA	G	0.085		FLT3	HD832	0.0785	NA	NA	NA	0.083	0.083			
13	32913558	32339421	CA	C	0.215		BRCA2	HD832	0.3333	0.319	0.334	0.2923	0.317	0.317	0.343	0.118	0.118
14	105246551	104780214	C	T	0.035		AKT1	HD789	0.0399	0.037		0.0323	0.05	0.05			
17	7579472	7676154	G	C	0.94		TP53	HD832		0.91							1
19	3118942	3118944	A	T	0.044		GNA11	HD789	0.0447	0.047		0.0434	0.038	0.038	0.037		
SUM				**26**					**18**	**24**	**10**	**18**	**19**	**18**	**13**	**3**	**6**
SUM (Exluding NA)			NA	Variants outside target BED files					**17**	**22**	**8**	**16**	**18**	**17**	**13**	**3**	**6**

For the SNVs and short indels laboratories correctly detected variant allele frequency in the samples, see Figure 3.

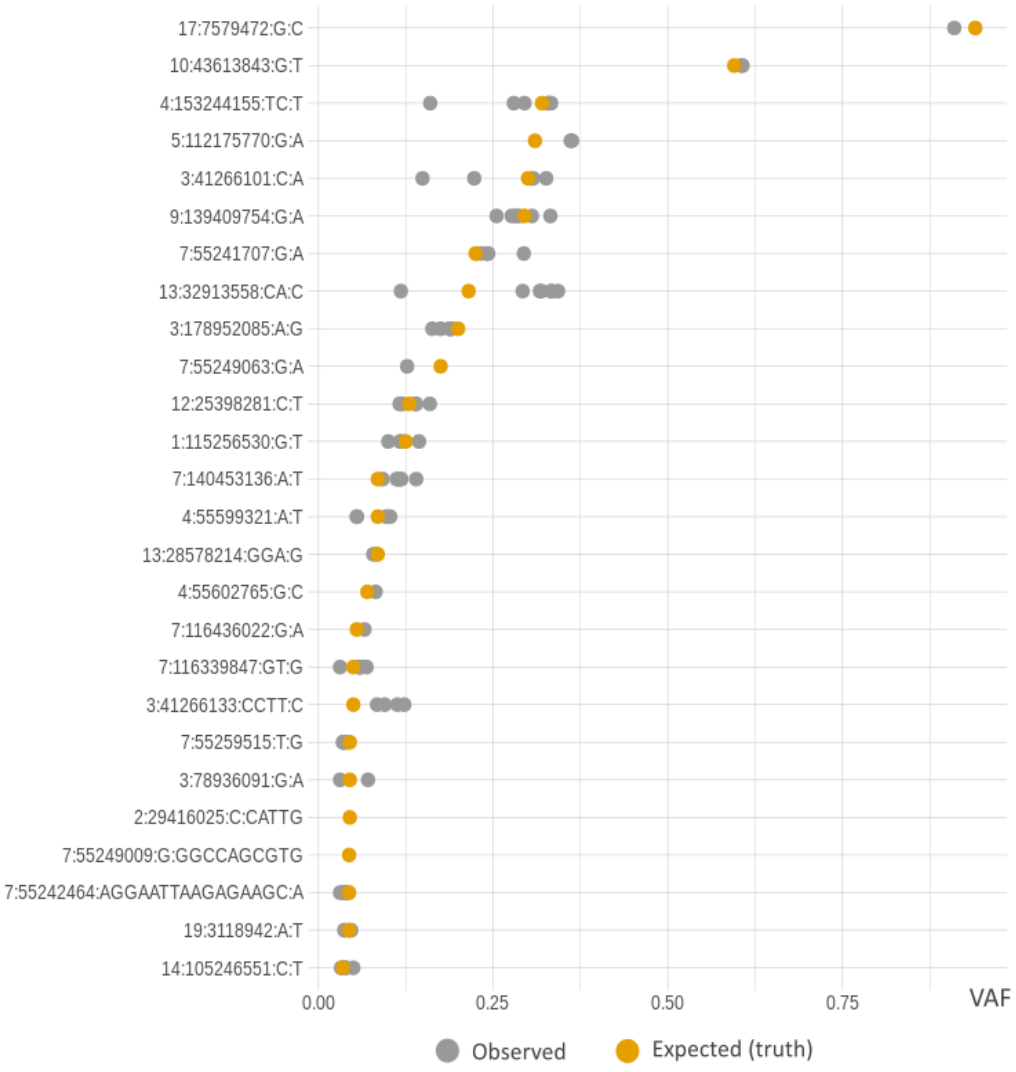


Figure 3 Expected and observed variant allele frequency.

Table 15 Detection of copy number variants

	CHR	2	7
	Expected FC	8.5 copies	4.5 copies
	Variant Type	Amp	Amp
Lab	**Gene**	MYC-N	MET
R	Analysed	Yes	Yes
	Detected FC	Undetected	2.05821
E	Analysed	No	No
	Detected FC		
A	Analysed	Yes	Yes
	Detected FC	5.746	2.037
C	Analysed	Yes	Yes
	Detected FC	6	Undetected
W	Analysed	No	No
	Detected FC		
G	Analysed	Yes	Yes
	Detected FC	12	Undetected

Table 16 Detection of fusions

CHR	**4,6**	**10**
Expected AF (%)	**9.7**	**4.6**
Variant Type	**Fusion**	**Fusion**
Gene	**ROS1**	**RET**
Lab R analysed?	Yes	Yes
Lab R detected?	No	No
Lab G analysed?	Yes	Yes
Lab G Detected?	Yes	Detected INV variant

Conclusions

- Different assay technologies in use across Nordics (panels, exomes), but Twist technology used by most labs.
- There was large variability in aimed coverage

Oleg and Valtteri then organised a poll-based discussion about current workflows and status in the labs and continued by gauging the interest for further benchmarking exercises.

Poll: What parameters does your lab use to filter variants?

Responses:

- gnomAD, gnomAD in-house database AF
- Allele frequency
- Targeted regions (with padding)
- Panel of normal
- Different quality parameters
- MAF
- Number of supporting reads
- Exonic
- Targeted regions
- Gene list
- Variants in gene list
- Variants only called with defined roi
- VAF

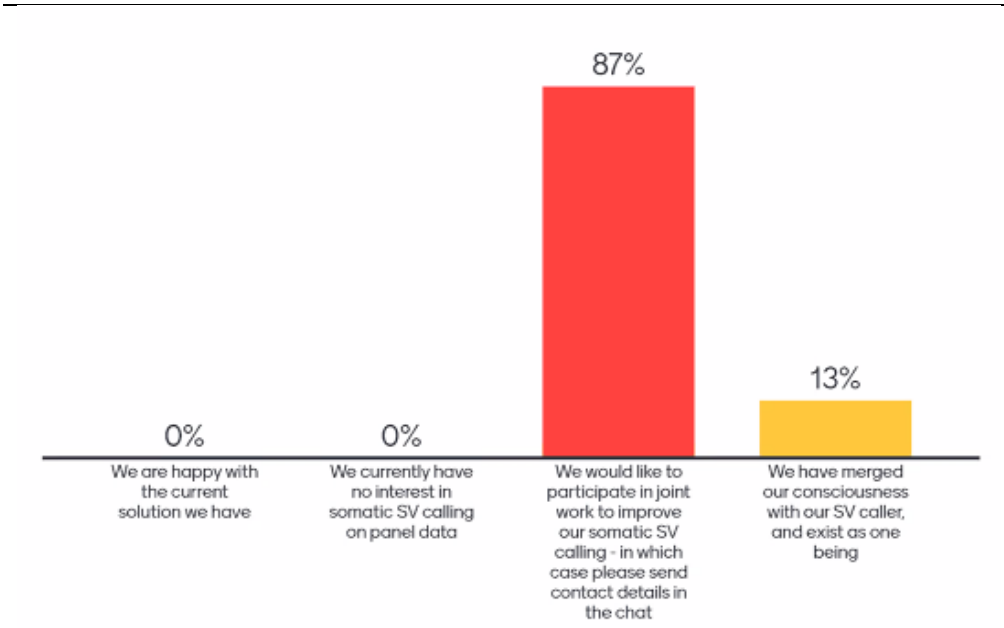
Discussion / questions / comments

- How are panels of normal (PoN) created?
    - OUS: ~48 samples are analysed using same sequencer, sample prep and pipelines, PoN created from collected variants.
    - SciLifeLab: no PoN established yet
    - Aarhus: no PoN created yet. Risk removing important information.

Poll: What is the status of your somatic SV calling?

Is there interest in establishing a group for discussion on how to improve and implement SV calling on panel data?

- Design of panel assay (where do you place the baits?)
- Selection of tools (callers) and parameter settings
- Databases for removal of false positives

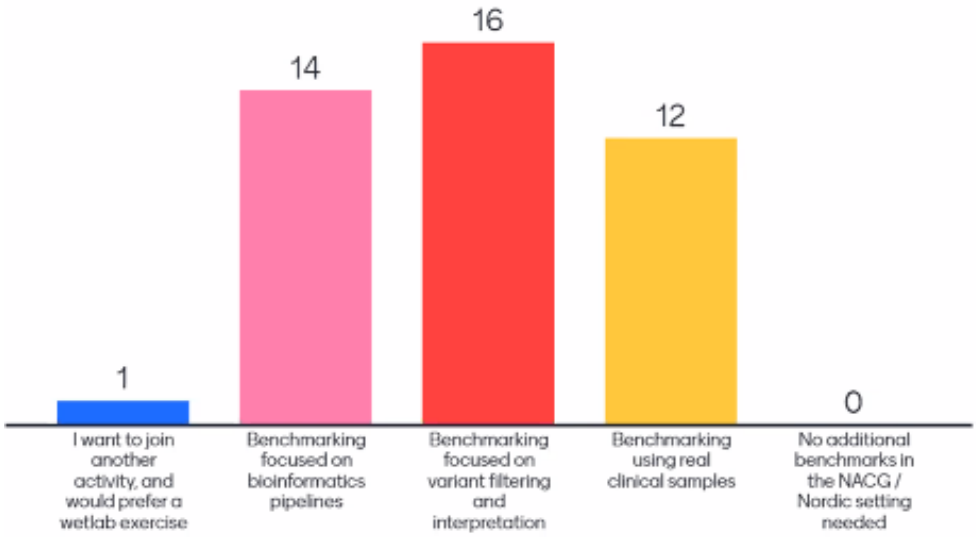


Discussion / questions / comments

Interested participants signed up for the joint work to improve the somatic SV calling. The discussion clarified that any collaborative effort would be of interest, both RNA and DNA focussed, and also both the wet assay and bioinformatics parts.

Poll: Additional benchmarks?

- How could a follow-up benchmark look like? (Real world samples, highly characterized samples with bioinformatically injected variants)
- What labs would be interested in participating?



Discussion / questions / comments

- There is an overlap between red (focus on variant filtering and interpretation) and yellow (benchmarking with real clinical samples) alternatives; relevant melanoma case is available.

- European level benchmarking is planned on somatic WGS organised by Barcelona using real patient samples. There is a limited number of samples, but benchmarking is open for participation in the bioinformatics part.

Key observations / conclusions	Different assay technologies in use across Nordics (panels, exomes), but Twist technology used by most labs. There was large variability in aimed coverage. Discussion topics - Different strategies for variant filtering - Calling of CNV and SV - Further benchmark work

Variant interpretation and data sharing

Dag introduced this session and took the opportunity to celebrate the first incidence of Nordic data sharing on the variant interpretation side. The need for data sharing has been discussed since the first NACG workshop but has been hard to achieve in practice on a Nordic level. This session focussed on early initial experiences of sharing variant classifications between a Danish and a Norwegian lab. An important objective was to identify interest in other labs of taking part in future work in this direction.

Table 17 Variant interpretation and data sharing - overview of session

Topic	Presenters
Introduction	Dag E. Undlien, OUS AMG
Emerging professional duties in genomics: to share, re-analyse, and recontact	Adrian Thorogood
Experience and results from initial sharing between OUS and Rigshospitalet	Dag Undlien, OUS AMG Majbritt Busk Madsen, Genomic Medicine, Rigshospitalet, Denmark Sarah Louise Ariansen, OUS AMG.
Nordic Benchmarking – who is interested?	Dag Undlien, OUS AMG
Resolving discordance of variant classifications. Practices and experience from other consortia and should we develop a Nordic process?	
Summary and way forward	

Emerging professional duties in clinical genomics: to share, re-analyse, recontact?

	Speaker	Adrian Thorogood, BCL/LLB, LLM, Legal and Ethics Specialist, University of Luxembourg (adrian.thorogood@uni.lu)
	Title	Emerging professional duties in clinical genomics: to share, re-analyse, recontact?
Professional duties	Adrian introduced elements of professional liability where legal duties in health include to inform, to diagnose/ treat, to follow up and confidentiality. Breaching a legal duty is one element in a broader professional malpractice context; the breach must also have caused harm. Liability is assessed against standard of care; what would a reasonable physician do in same circumstances. This is established through expert testimony. Courts are generally hesitant to recognize new duties.	
Professional Duties in Clinical Genomics	Professional duties in genomics context are less clear. Duty to Interpret is difficult as genomic info is vast and not fully understood, laboratory practices are evolving and standards for interpretation are unclear. There is an ongoing discussion regarding the duty to recontact. A patient's genome is stable over time, while genetic knowledge is advancing rapidly. This means that the meaning of a patient's results is going to change over time. What are the legal and ethical implications regarding the obligation to recontact the patient, and is there a duty to warn family members?	
Case: South Carolina	Professional duties in clinical genomics were discussed through the South Carolina lawsuit *Athena v Williams* (2018), where the plaintiff alleged that the	

lawsuit *Athena v Williams* (2018).	laboratory failed to provide an accurate genetic result given that they had specific knowledge that the variant was pathogenic (evident from publications and patent application) and did not follow its own scheme for classification. The plaintiff claimed that the lab failed to update the patient when the variant was reclassified. The patient continued to receive treatment with contra-indicated medication, resulting in death of the child. The conclusion of the lawsuit was that the plaintiff failed to prove the lab failed to meet the standard of care for interpretation (reflecting the uncertainty at the cutting-edge of genetics over the standard for variant interpretation or reinterpretation). Standard is not perfection, but appropriate judgement, and the lab exceeded ACMG Guidelines and standard of care. There was insufficient initial evidence to definitively classify the variant, additional evidence later emerged to prompt the reclassification. The plaintiff failed to prove "a causal nexus"; that the new result would have changed treatment and that a change in treatment would have prevented the outcome. Interesting comments in verdict on the duty to recontact: - Expert witness in *Athena v Williams:* there is no general duty to recontact "given the transient nature of patient relationships, the everchanging variant database information, and the large number of samples that laboratories like Athena test and report every year." - ACMG Policy Statement, Patient re-contact after revision of genomic test results: points to consider. (Dec 2018) = *Patient beware!* - Laboratories only reclassify variants on a case-by-case basis.
Opportunities	**Systematic reinterpretation** represents a shift from individual responsibility to institutional / healthcare system responsibility, with the opportunity to significantly increase diagnostic yields. Adrian discussed the opportunity of **data sharing** between labs as an ethical obligation and crucial contribution to improving genetic health care. - 4.5% of ClinVar variants submitted had conflicts that would affect patient management - In the Canadian Open Genetics Repository, BRCA1/2 - 30% discordant - Data sharing can trigger re-classification = duty to recontact? Liability risk? - Data sharing can be an important quality control tool for both interpretation processes and data. - Data sharing results in variant reinterpretation.
1+MGP	Adrian concluded by referring to the 1 million genomes project which aims to make 1 million genomes accessible in the EU by 2022 by linking access to existing and future genomic databases across the EU, providing a sufficient scale for new clinically impactful associations in research.
References	Knoppers BM, Zawati M, Thorogood A, *Relearning the 3 R's? Reinterpretation, recontact, and return of genetic variants* *Genetics in Med 2019* Thorogood A et al., "A Legal Duty of Genetic Recontact in Canada" (*Health Law in Canada*) 2019 Ray T, "Quest Diagnostics Wins in Wrongful Death Case Reveals Ongoing Challenges for Variant Classification." *Genome Web* (Nov 2020) Accessed November 17, 2020. link to the 1+ Million Genomes Project use case workshop on clinical data sharing: https://docs.google.com/document/d/11r9Wogh8Rz0HGVVU874RutRG4npQkDvZ6jmmfu7niPo/edit?usp=sharing

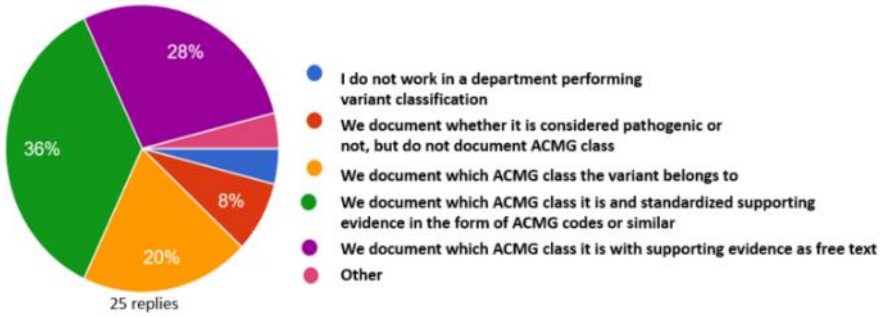
Discussion / questions / comments	Regarding the case: what are the discussions around how reliable a variant is provided the problems with GWAS etc. and what is "reasonable"? - Some of the quality issues with the test itself would be dealt with by medical device regulations. In a medical context the reliability of the test should be established before it is used as part of patient care. So, if it's an approved test for the patient's indication, then it would be reasonable to use it. - The problem is that medical device regulations don't generally address the step of interpreting the clinical relevance of the variant (which is left to professional judgement). - The n of 1 issue reflects that this context concerns a rare mutation. Often the best evidence we have is 1 or 2 other patients, but it's hard to define a "standard" here. - In this case there was a big discussion if the lab should have requested paternal testing.

Initial variant sharing between OUS and Rigshospitalet

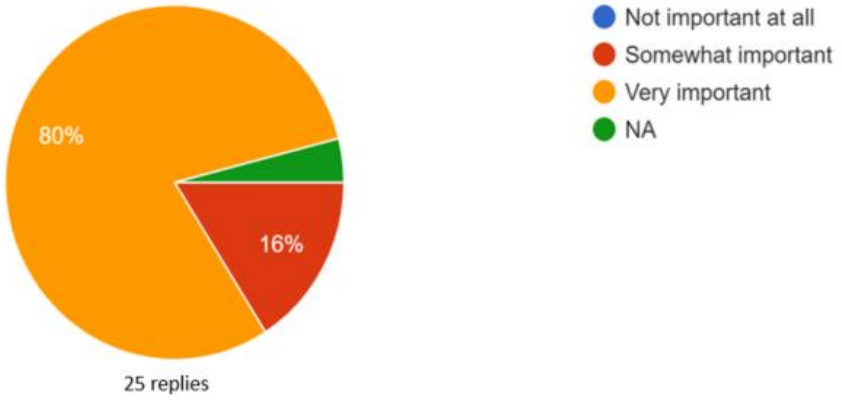
Speakers	Dag Undlien, OUS AMG Majbritt Busk Madsen, *MSc. PhD,* Genomic Medicine, Rigshospitalet, Denmark Sarah Louise Ariansen, OUS AMG.
Title	Initial variant sharing between OUS and Rigshospitalet
Objective	Review initial experiences of sharing variant classifications between a Danish and a Norwegian lab.

Introduction

A pre-workshop survey on documentation of variant classification confirmed that more labs are now documenting ACMG classes, but there is variation in how labs are documenting supporting evidence.



When asked about the importance of having supporting evidence such as ACMG codes, references, the vast majority said that this was very important.



Variant sharing	Variant sharing was piloted between Oslo University Hospital and Rigshospitalet from Oct / Nov 2020, focussing on seven breast cancer genes: BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, TP53.
	- Total variants shared: 1650
	- Unique Variants: 1535
	- Discordant variants[11]:
	  ○ 2 (two tiers: class 1+2+3 vs class 4+5)
	  ○ 43 (three tiers: class 1+2 vs class 3 vs class 4+5)
	  ○ 54 (five tiers: class 1-5 separately)
	Data sharing was done through DNV GL's Variant Exchange as part of beta testing programme, which provides a dashboard with overview of discordances.

Rigshospitalet experiences	Majbritt underlined the importance of data sharing and that it is an automated and continuous upload of variants to ensure updated information on classifications instead of snapshot uploads to e.g. ClinVar. Opportunities for notifications in case of discordant classifications from other labs is also important to allow for re-evaluation of own classifications and re-contact patient and family. In Denmark variant classifications are shared between labs, which allows for national harmonisation and equal quality of care. Data sharing on a Nordic level would contribute to quality assurance and harmonisation across the Nordic countries.
OUS AMG experiences	Sarah celebrated the opportunity to share variant classifications and concurred with Majbritt on the importance of discordance notifications provided by Variant Exchange. She also discussed the quality assurance aspect of having a database available where you can check other lab's evaluations when assessing difficult variants. The continuous update ensures that the available interpretations are up to date, but there is a need to balance information available per variant with ease of updating. To make data sharing useful and valuable for work with rare disease, it is important to have many contributors.

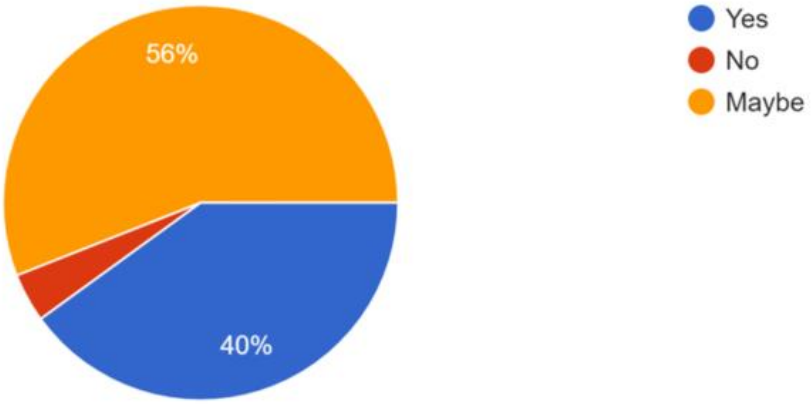
[11] Lebo, M., Zakoor, KR., Chun, K. et al. Data sharing as a national quality improvement program: reporting on BRCA1 and BRCA2 variant-interpretation comparisons through the Canadian Open Genetics Repository (COGR). Genet Med 20, 294–302 (2018). https://doi.org/10.1038/gim.2017.80

Data sharing and resolving discordances in variant classifications

	Speakers	Dag Undlien, OUS AMG Sharmini Alagaratnam, DNV GL (Sharmini.alagaratnam@dnvgl.com)
	Objective	Identify interest in other labs for taking part in future work in this direction

Variant sharing project group

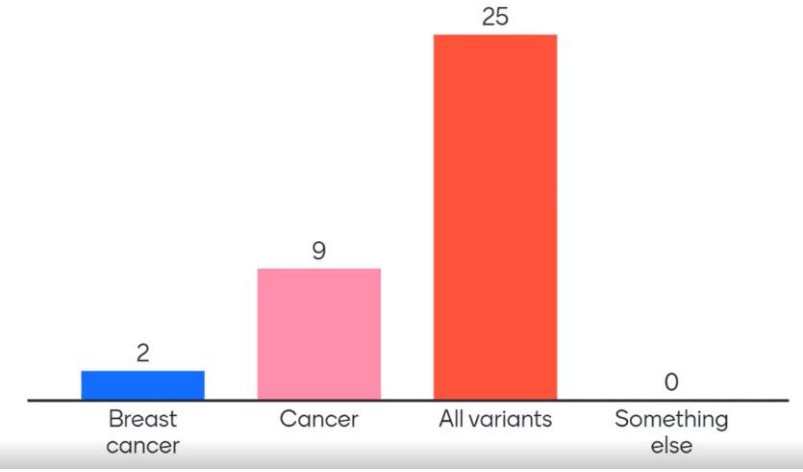
A pre-workshop survey regarding the interest to participate in an exercise to benchmark not only ACMG classification of variants, but also ACMG codes as supporting evidence indicated a significant interest.



A variant sharing project group was proposed by Dag, encouraging participants to connect to take part in this. The group could;

- Meet approximately monthly (on-line)
- Share clinical variants
- Cooperate with “resolution working group”
- Establish project plan and scope in first meetings
- Report back to next NACG workshop in spring 2021
- Indicate interest to participate in chat - confirm by responding to the email that will be distributed to registered participants next week

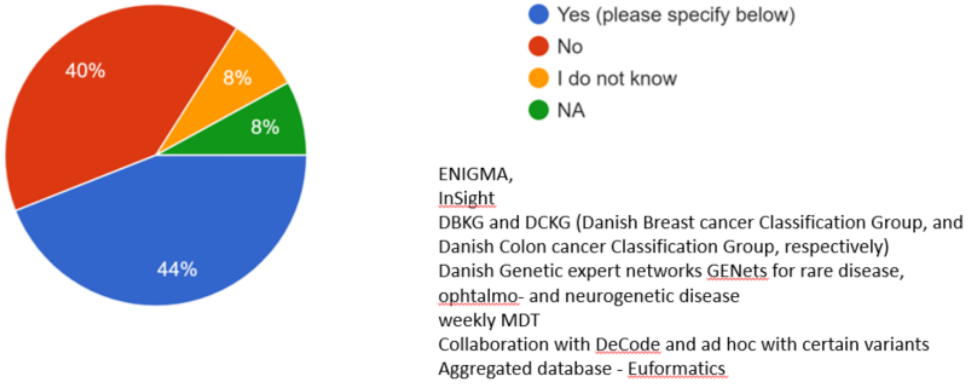
Potential initial focus was gauged through a poll, where the majority expressed an interest in data sharing on “all variants”.



Resolving discordance of variant classifications

Sharm introduced herself as one of the leaders of the NACG working group on benchmarking, harmonisation, and standardisation, where a joint NACG effort on discordance resolution would naturally belong.

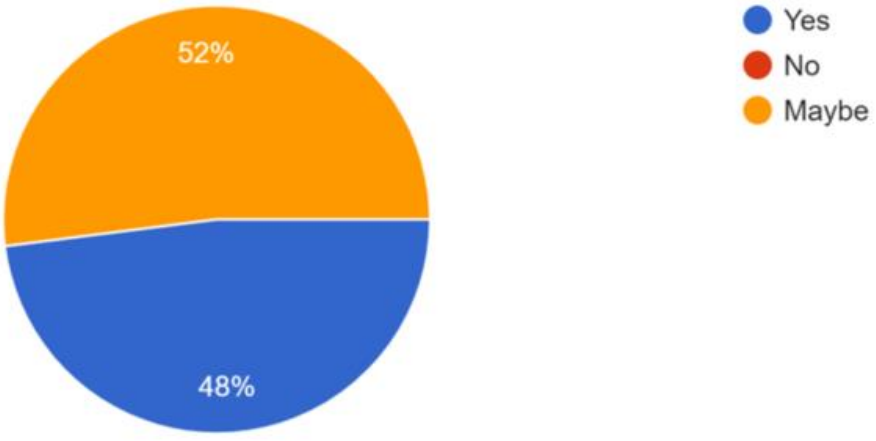
In a pre-workshop survey participants were asked if they participate in any collaborative efforts to resolve conflicts.



The relevance of discordance resolution as a quality improvement measure was discussed. The initiative would require resources to be sustainable, but benefits would include:

- Discordance flagging and potential resolution
- Validation of own classifications
- Building a truth set/knowledge base
- Time saving (reanalysis, reclassification)

Through the pre-workshop survey, significant interest in participating in a workshop on how to resolve conflicting variant classifications between labs was confirmed.



Sharm invited participants interested in proposed NACG project group on discordance resolution to connect with her.

Experiences with discordance resolution from national initiatives

There are different national approaches to resolution of discordances, such as

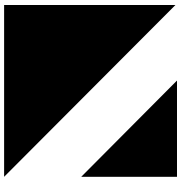
- Canada: COGR, manuscript in prep
- USA: CSAR, Almendola 2020
- Denmark
- Netherlands, VKGL, Fokkema 2019
- Australian Genomics, paper in print

	After reaching out to them, a few commonalities were identified: - Regional/national sharing of variant classifications - Reinventing the wheel: all employ unique platforms - Alerts to all/individual labs with discordances - Resolution occurs bilaterally Majbritt explained how five labs in Denmark are collaborating on classification of breast cancer genes through in person meetings once or twice a year. In prep, all would collect all newly reported variants in a spreadsheet. The variants would then be discussed. For some variants, consensus is easily reached, others require more extensive discussions and take more time to resolve. The spreadsheet is distributed to all participating labs as a reference database for further work, ensuring same conclusions for patients across the country.
Comments	To developers of variant Exchange: an illustration of the tiers-system would be good to avoid misunderstandings. Denmark reports at one lab, that is not the case for Norway yet, we have no formal infrastructure for national collaboration. We should work together nationally and report together to this initiative Comment to the usefulness of having individual ACMG criteria in a shared database: I think this will make it much easier to identify any systematic differences in interpretation procedures between labs, as opposed to rely on comparisons of class and/or free text summaries alone. But depends on the size of the database, of course Labs with many different persons or several groups doing variant interpretation have experience with variants ending up with conflicting classifications and has been forced to develop procedures for this. For example, when a variant is involved both in dominant vs recessive inheritance, should be interpreted by persons focusing on different phenotypes. Use that experience. - Being able to identify and connect the individuals who have detailed and specialist knowledge who classify variants has been flagged as a difficult challenge to overcome properly. The Nordic population is not very large. Why aren't you talking to other countries like China? Mexico? Australia? Surely, they have advanced health systems and can contribute variants and annotations.

Next NACG workshop

The next NACG workshop will be arranged June 2021. Alternative dates:

- 3. - 4. June for a physical event
- 1. - 4. June for a virtual event



Nordic Alliance for Clinical Genomics