Nordic Alliance for Clinical Genomics

WORKSHOP REPORT

NACG 6th Clinical Workshop
Copenhagen, 20.-21. November 2018

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.

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 personalised 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

Learn more about the Nordic Alliance for Clinical Genomics at https://nordicclinicalgenomics.org/ or contact us at post@nordicclinicalgenomics.org.

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Symbols

Lecture / presentation

Interactive workshop

Abbreviations

CVA	Clinical Variant Ark
GDPR	General Data Protection Regulation (EU) 2016/679
GMC	Genomic Medicine Centers
GMS	Genomic Medicine Sweden / Genomic Medicine Service (England)
HPO	Human Phenotype Ontology
LoF	Loss of Function
NACG	Nordic Alliance for Clinical Genomics
NGC	The Danish National Genome Centre
NGS	Next-generation sequencing
NHS	National Health Service (England)
OUS AMG	Oslo University Hospital, Department of Medical Genetics
SV	Structural variants
TVX	Trusted Variant eXchange
VP	Variant prioritization
VUS	Variants of uncertain significance
WGS	Whole genome sequencing

CONTENTS

EXECUTIVE SUMMARY

This report summarizes the 6th workshop of the Nordic Alliance for Clinical Genomics (NACG). The workshop took place at Rigshospitalet in Copenhagen, 20.-21. November 2018, and gathered 66 participants from 18 organizations and departments in 6 different countries (Table 1, Figure 1).

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

Table 1 Summary of workshop participation

Country	Organization	Number of participants
Denmark	Aarhus University Hospital - Department of Molecular Medicine (MOMA)	5
Denmark	Copenhagen Institute for Future Studies	1
Denmark	Danish National Genome Center	2
Denmark	Nordic Precision Medicine Initiative (NPMI), Faculty of Medicine, University of Copenhagen	1
Denmark	Rigshospitalet - Center for Genomic Medicine - Department of Clinical Genetics	16
Finland	University of Helsinki - FIMM	2
Finland	Helsinki University Hospital - Laboratory of Genetics	7
Iceland	Landspitali - The National University Hospital of Iceland - Department of Genetics and Molecular Medicine	2
Norway	DNV GL - GTR Precision Medicine - DS DHI	7
Norway	Microsoft	1
Norway	Oslo University Hospital - Department of Clinical Genetics	13
Norway	St. Olavs Hospital, Trondheim	2
Norway	University of Bergen	1
Sweden	Karolinska Institutet - SciLifeLab	4
Sweden	Karolinska University Hospital	1
UK	Genomics England	1

Figure 1 Participants at the 6th NACG clinical workshop

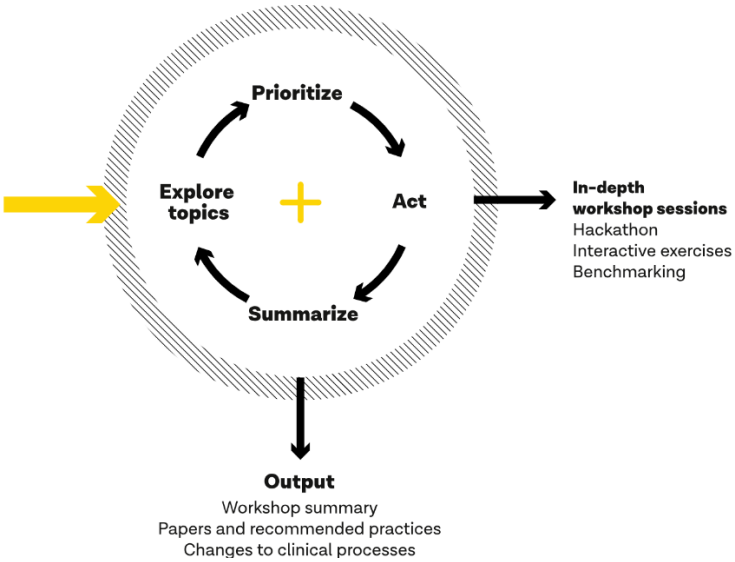


Figure 2 NACG members discuss and explore topics of interest to identify shared challenges and strategies for overcoming them. Prioritized topics are explored in in-depth interactive exercises. Findings and learnings are summarized in workshop summary reports and collaborative papers and contribute to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

WORKSHOP OUTLINE

The workshop was organized as illustrated in Figure 3 (detailed agenda available in Appendix 1). Setting the stage, the participants provided updates to the group on progress of NACG and relevant national activities in the Nordic countries, as well as from Genomics England. Main topics discussed during the workshop group to three of the NACG working group themes;

- Benchmarking, harmonisation and standardisation - Enhancing quality of data and processes
- Bioinformatic tools development
- Data sharing - Vehicles for sharing

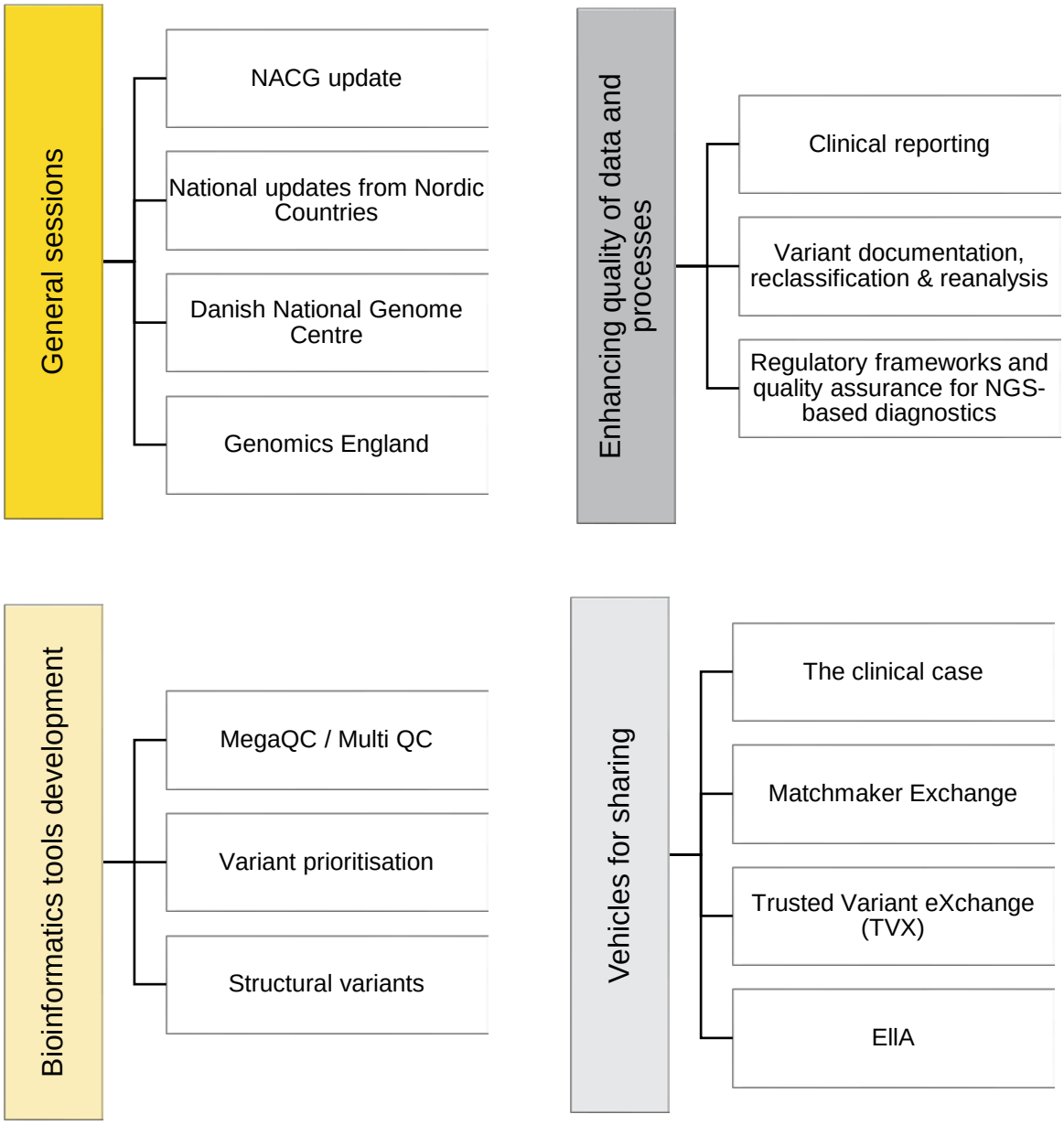
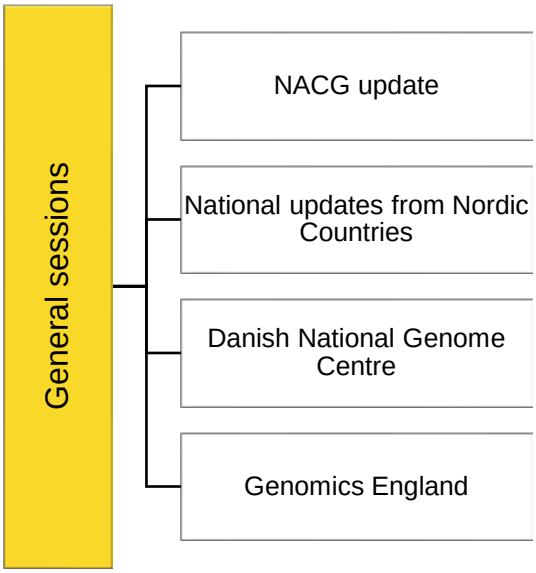


Figure 3 Workshop outline

GENERAL SESSIONS



NACG update

	Session lead:	Dag E. Undlien
	Objective:	Share information on status and development of NACG.
Key information:	- Review of development, mission, and aims of NACG - Description of partial funding from NordForsk since 2016 - Displayed recent publication of the NACG paper on Clinical reporting of NGS data: a systematic Nordic collaborative, peer-reviewed benchmarking. - Introduction of steering committee members and working group leads. - Encouragement to apply for membership, resources and information available via https://nordicclinicalgenomics.org/ - Ongoing activities to secure external funding to drive collaboration - Update to the project proposal “NorGEM” for NordForsk’s NordicPerMed call. The proposal was rejected due to formalities related to the Finnish funding agency. Further information provided by Finnish partner on the requirement for three Finnish companies providing 10% of the funding: Two of the partner companies were non-profit and had been accepted in the past; however, this time were not considered “company” or “small growing company.”	
Conclusions:	Content in the NorGEM application has potential to be re-used for future applications.	

National updates from the Nordics

The objective of this session was to share key updates from the Nordic countries.

	**Country:**	Finland
	Session lead:	Janna Saarela, FIMM
Key information:	-	Changes in the regulatory environment related to genome sequencing aiming to improve diagnostics and research.
	-	Recently, more push towards the Genome Act for the Genome Center Finland and being discussed at the parliament level. Aim to have genome data use for clinical diagnostics and research.
	-	The Biobank Act was established Sept 2013, renewal process in progress but a bit behind due to Genome Act.
	-	There is a current reorganization of healthcare in Finland from regions to government and process is delaying the above activities.
	-	HUS and FIMM have established a joint clinical genome sequencing unit in 2018. This is up and running and has received a second NovaSeq6000.
Discussion:	-	Focus of Genome Center Finland is on rare disease and cancer.
	-	Legislation on secondary use of data is delayed due to restructuring of Finnish healthcare and prioritization of Genome Center Finland.
	-	FinnGen update: sample collection and genotyping at full speed, estimated completion scheduled as a 4-year project.

	**Country:**	Iceland
	Session lead:	Jón J. Jónsson, Medical Director, Dept. of Genetics and Molecular Medicine, Landspitali
Key information:	-	A recently initiated process for incidental findings in genetic research was presented.
	-	A committee appointed by the Minister of Health recommended to establish query access through Heilsuvera, the public portal for patients accessing health information. It was recommended that a new module be inserted after DeCode set up their webpage arfgerd.is where people can sign up to access information about the *BRCA2: 999del5* pathogenic variation, 0,7% carrier frequency in Iceland. If no sample is available, participants are instructed to donate a sample in order to have their specific *BRCA2* status checked.
	-	Since the launch, approx. 40,000 have signed up to query their genotype, approx. 300 confirmed carriers of the BRCA2:999del5 mutation, 30-40 previously known carriers, 262 contacted the genetic counselling unit including 100 relatives, 201 have finished genetic counselling, and 33 have received counselling and test request but have not come for confirmatory testing.

	Country:	Norway
	Session lead:	Dag E. Undlien, OUS AMG
Key information:	-	National strategy for Personalized Medicine (2017-2021) headed by Directorate of Health and Care. Two areas funded; the establishment of a national variant database (19 M NOK) and national network of competence centres (6 M NOK).
	-	Recently, politicians (health minister) stating they are 'inpatient' and want to see more activities in Personalized Medicine. Good political will as evidence by new funding in last 3 budgets; however, efforts are fragmented, there are no organizational changes to establish a National genome centre. The current plan is to do this as part of ordinary healthcare system which is different from other Nordic countries.
	-	Seems to be a current underestimation of what is needed
	-	Norway just published an action plan for research and innovation for precision medicine; however, the plan includes no additional funding.
Discussion	-	Frequency vs classified variants: strategy points out we need non- anonymous databases but to start, more conservative towards a frequency database. The discussions here have slowed the process.
	-	Question to what data: discussion to take diagnostic data, research data or biobank data, there are different takes depending on who you talk to.
	-	What is needed to improve collaboration? Funding is important, but there is a need for an organization to set up a structure where decisions can be made.

	Country:	Sweden
	Session lead:	Valtteri Wirta, SciLifeLab
Key information:	-	Genomic Medicine Sweden (GMS) program is a clinical program to bring in NGS techniques in a national coordinated way via 7 regions with Genomics Medicine Centres under formation. Focus is on rare diseases, cancer (solid tumours and haematological malignancies) and microbiology. Highlighted that the GMS is a national resource for research and innovation including industry collaborations.
	-	Review of timeline towards GMS development, from a bottom up initiative from SciLifeLab diagnostics development platform, to recently achieved funding for implementation: 4 M EUR from Vinnova and matching 4 M EUR from the healthcare regions and universities.
	-	Recently agreed on the national and regional infrastructure for the next two years (implementation phase); the national infrastructure will include national reference groups and informatics capacities.
	-	The GMS value proposition: integrated part of the Swedish healthcare with a national scope, all healthcare regions included. Analysis will be carried out in house and secure control of assay design and target selection. National variant and genome databases can link to EHR and quality registries.
	-	Desire to link GMS to existing initiatives such as NACG, GA4GH and national genomics initiatives.
	-	Arranging Genomic Medicine Sweden Symposium: *Implementing Precision Medicine in Healthcare*. May 28, 2019, Karolinska Istitutet.

	**Country:**	Denmark, Danish National Genome Centre
	Session lead:	Cathrine Jespersgaard and Martin Thomsen, Denmark National Genome Centre

Key information:	- An overview of the development for the National strategy for Personalized Medicine and the establishment of National Genome Centre (NGC). - Principals of the strategy pertains to confidentiality, patient rights, data processing, data sharing, and allocation of research funds. Strategy focus: WGS as a new tool for the medical doctor for diagnostic and treatment purposes, provided as an integrated offer for the patient, disseminated national wide. Goals for other -omics to be included at a later stage. - The NGC is established under the Ministry of Health as the main driver for the implementation of the strategy. Currently a small unit consisting of 15-20 staff financed by the state. The bill to establish the NGC was passed May 2018. Reviewed the main elements surrounding written consent, data protection, specific clause to use of data, and a voluntary donation of genetic test data. - Currently developing the elements of the national technological infrastructure for the NGC as it pertains to the cooperation of the regional healthcare system and research and development. - National boards for the strategy guide the setup of the NGC and include: Ethical, Patient & citizen committees, research and infrastructure committee, and international advisory board who guide working groups on the technological infrastructure and clinical aspect of the infrastructure. A review of the purpose and progress of these national boards were provided.
Discussion	- Questions to the storage of data: No current conclusions, in process to decide how and where but current understanding is that the location will be central and secured. - Question on genomic database: Currently working on a Genomic Variant Database for classified variants, will initially obtain raw data, search variants, but what is needed is still in discussion in the working groups, especially around the justification of storage per GDPR requirements. - How would research access data from genome database: first need to establish the clinical pipelines and legal requirements in an approved ethics committee. - Question on Nordic collaboration: confirmed a current interest in collaboration and acknowledged benefit of collaboration.
Conclusions:	Further questions from workshop members regarding the Danish National Genome Centre encouraged, can be directed to Cathrine at cje@sum.dk.

Genomics England

	**Session lead:**	Antonio Rueda, Head of Interpretation Platform, Genomics England
	Objective:	Present Genomics England and the 100,000 genomes project

Key information:

Genomics England is a company set up and owned by the UK Department of Health to run the 100,000 Genomes Project, which aims to sequence 100,000 genomes from NHS patients with a rare disease and their families, and patients with cancer.

The 100,000 Genomes Project update

- Currently 112,547 samples collected. In total, 92,297 genomes sequenced, and the results for 38,957 genomes are sent to NHS Genomic Medicine Centres (GMCs).
- The 13 NHS GMCs cover over 90 hospitals in England. Northern Ireland, Scotland and Wales have recently joined.
- Services and infrastructure had to be put in place for clinicians for validation of clinical data collected.
- Samples go to a biorepository.
- Use of Illumina as tech provider results in standardized data.

Genomics England bioinformatics services ecosystem includes:

1. **Workflow and Orchestration**
- Clinical Data Intake considered the most important
- Three workflows related to including seq data, QC and interpretation.
- Orchestrator: initiates analysis pipeline once data is received, ending with variant annotation and preparing for variant interpretation as next step.
2. **The Genomic Databases I. OpenCGA**
- A file management system that allows extraction of files, samples, individuals, families etc
- Based on Hadoop, can store up to 1 M WG.
3. **Variant Annotation**
- Use Cellbase (more features than VEP)
- Allele and genotype population frequencies for GRCh37 and 38 assemblies.
- Other annotation: phased variants, MNVs, transcripts in HGVS format
4. **Interpretation Platform**
- *API*: interface to other modules in the platform, orchestrate interpretation process, tracks of the status of each case
5. **Interpretation services**
- create interpretation results based on computation or human analysis (Exomiser)
6. **PanelApp**
- A Genomics England success, https://panelapp.genomicsengland.co.uk/
7. **Decision Support system**
- User interfaces, i.e., Opal, sapientia, and recently Illumina (in the past year).
8. **The Genomic Databases II. CVA**
- Database that stores results of interpretation of all variants from all cases, integrated across multiple cases, supporting the curation of reported variants by adding reference annotation from clinical databases.
- Interpretation process has included collaboration with high trust (a critical success factor).
- Interpretation is dynamic, the system needs to be responsive to possible new re-interpretations.
- Two design principles:
    - Results are stored at the variant level, to allow an immediate integration across the results of the whole program.
    - All variants will be stored, including false positives
- Clinicians decisions are also stored in CVA, including what clinician's opinion on the decision, and basis to improve algorithm).
- A common model for interpretation
- *Variant tiering* includes

	o Filter and classify variants o Well-defined rules, stable across the project o Applicable to any family configuration, STRs, CNVs, small SVs o Implemented using VCF/cellbase or OpenCGA o Based on GA4GH variant model o User pedigrees as defined at Genomics England (based on Phenotips format) o Uses PanelApp as source of gene panels - *Tiers definitions* o Tier 1: Likely pathogenic WTITHIN known disease gene panel(s). E.g. likely LoF and de novo missense variants. o Tier 2: Possibly pathogenic WITHIN known disease gene panel(s). o Tier 3: Plausible candidate OUTSIDE known disease gene panel(s). o Untiered: Everything else **Plans for Genomic Medicine Service (GMS)** - Initiation January 2019 - All hospitals will submit data using a common interface - Pathways depending on the type of genomic test taken, leading to a National Genomic Data Store.
Discussion / questions / clarifications	- Data is de-identified prior to arrival. - Rare diseases with likelihood of one case are still considered de-identified. - Everything is now searchable, with limits on the variant interpretation database. Rest API is used. - Updating annotation: Interpretation for case requires “freezing of everything,” an annotation update requires the clinician to ask for it with good reasons. CVA stores annotation. - Strategy for re-analysis of data is not currently in place, but establishing pipeline with user demands. Strategy must include a good schedule (annually?) and uptake of information with clinicians. - No strategy in place for handling of conflicting interpretations in CVA. - Results of variant classifications is currently not public information but classifications may have been submitted to ClinVar by clinicians as Genomics England does not own the data. - For resolution of conflicting classifications or updated information, how is the CVA updated? A case is “never closed” – includes exit questionnaire with possibility to admit clinician was wrong and included in the system

NACG joint publications

	Session lead:	Bobbie Ray-Sannerud, DNV GL
	Objective:	Discussion on preferred NACG publication format
Key information	A review of the publication process for the NACG paper was provided. In response to conflicting opinions on publication format for the first NACG paper, time was reserved for a discussion on preferred NACG publication format to be considered by the NACG Steering Committee. NACG WS participants were asked to discuss their preferred format and to log their response anonymously onto a digital tool for sharing through the auditorium projector (Figure 4). Suggestions ranged from sharing through newsletters or NACG website to positioning of NACG and knowledge sharing through white papers and peer reviewed journals, the latter providing a different level of recognition and	

	bringing the contribution to a wider audience and into the international discussion. Some suggested development of Nordic recommendations / guidelines, which was recognised as non-trivial work. It was emphasized that the format should be chosen based on optimum reach for the specific target audience per topic and take message and goal for communicating into consideration. It was discussed that the work required to produce the different formats vary, and that the effort must be balanced. Any communication within the group should be kept at low threshold. Workshop reports summarize discussions for the group and are shared via email and website. Recognizing the expertise present, it was suggested that the NACG participants should take responsibility for spreading knowledge, for example by building and using common slide-deck to teach other relevant people.	
Conclusions	Communication format should be determined on a case-by-case basis, taking resources available, communication message and goal, as well as target audience into consideration.	
Actions / responsible	Review findings with Master student developing proposal for NACG strategy.	Guro Meldre Pedersen

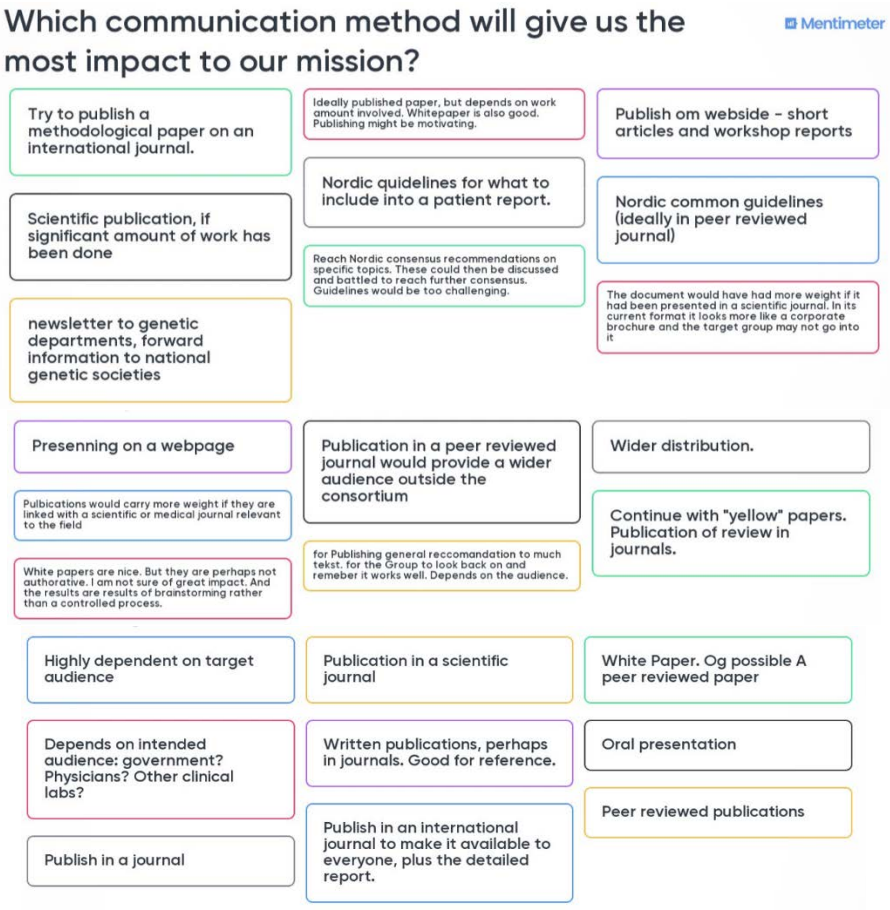
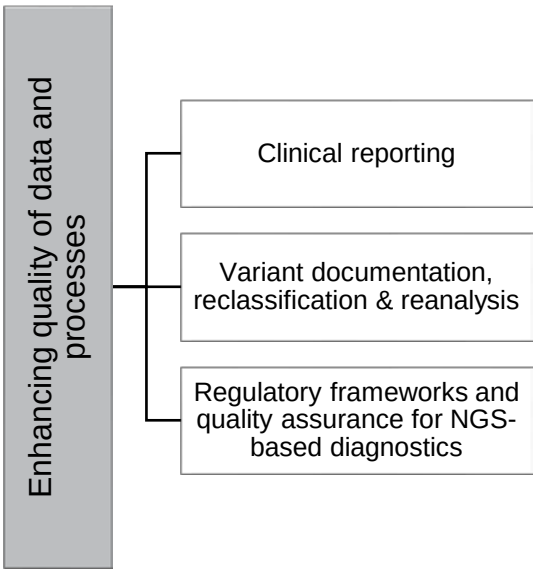


Figure 4 NACG workshop participants comments to communication format discussion

ENHANCING QUALITY OF DATA AND PROCESSES

Working group lead: Sharmini Alagaratnam & Courtney Nadeau, DNV GL.



Clinical reporting of NGS data: a systematic Nordic collaborative, peer-reviewed benchmarking

	Session lead:	Oleg Agafonov and Sharmini Alagaratnam, DNV GL
	Objective:	Based on the examination of clinical genomics reporting in WS5, a working group established to investigate the topic further. This session will report on the findings published in the first NACG position paper and discuss possible next steps.

Key information:

This session reviewed the process for developing the NACG "yellow" paper "Clinical reporting of NGS data: as systematic Nordic collaborative, peer-reviewed benchmarking", available at https://nordicclinicalgenomics.org/. The activities included in the paper were a) review of recommendations, b) identification of elements of the clinical reports, c) benchmarking of Nordic clinical reports, and d) in-depth interviews with producers (NGS laboratories) and users (clinicians) of clinical reports on NGS data.

Review of recommendations

- Over 25 recommendations including over 400 recommendation items were reviewed, as well as national guidelines in Norway, Denmark, and Sweden.
- From the 16 recommendations that addressed clinical reporting specifically, 14 topics were identified. Four topics were recognized as challenging; variants of uncertain significance (VUS), secondary findings, reanalysis and data delivery to the patient.

	Identification of elements of the clinical reports - To share best practices between NACG members, an exercise was conducted to identify and discuss the contents of clinical reports at the 5th NACG clinical workshop. 4-5 reports were reviewed, and elements of the report were categorized into nice to have, essential, should be eliminated, and challenging. - Results concluded that a benchmarking exercise would provide learning value. DNV GL led this task with selected NACG partners. **Peer-reviewed benchmarking of Nordic clinical reports** - Three fictitious clinical cases were distributed to participating labs, which then produced reports using their current production systems. These reports were systematically evaluated by other labs, and DNV GL. - The work concluded that although reports are generally clearly written, users are not always able to find specific information in the reports. Sometimes users also find information that was not included in the reports. **Interviews on clinical reporting of challenging topics** - Interviews with producers and users of clinical reports on NGS data were conducted to understand current approaches to challenging topics identified. - *VUS*: most stated that it is beneficial to include information on VUS in the report - *Secondary findings*: most do not have policy for secondary findings. - *Reanalysis*: most labs do not perform systematic reanalysis of data but believe this is beneficial and should be organized. - *Data delivery to patient:* most patients do not request their data, nevertheless there should be a procedure to handle such requests.
Conclusions	The paper shows that clinical reporting of NGS data as a critical hand-off between units represents a risk to patient safety if improperly executed and suggests specific improvements for this process.
Actions	Sharm provided an overview of a recent initiation of a design-driven innovation project (DIP) to redesign the communication interface. The goal of the project is to create an effective and accurate knowledge transfer pathway that will support and qualify clinician in their task to interpret test results for taking appropriate clinical actions for management of patient's condition. Workshop participants were invited to participate in the workshop on clinical reporting outlined below to provide input to this project.

Clinical Reporting Workshop

	Session lead:	Sharmini Alagaratnam (DNV GL), Sigrun Vik (Eggs) 15 participants from NACG
	Objective	This workshop aimed to get producers of NGS clinical reports to identify the range of the report users (receivers), and to discuss and explore ways of improving today's process
	Workshop outline	1) Identification of users of clinical NGS reports 2) Identification of user needs and challenges
1) Task A: Identification of users of clinical NGS reports	Tool used for task A is included in Figure 5. 1. In pairs, participants were asked to identify typical users of clinical NGS reports. 2. In pairs, participants were asked to identify challenging users of clinical NGS reports.	

		3. In groups, participants were asked to identify and name users at the extremities of the following axes: generalist vs. specialist, distant vs. close relationship to the NGS diagnostic lab, rare vs. frequent requisitioning of NGS tests, low vs. high genomic literacy, and young vs. old. **Results**: • **Task A1.** These were identified to include: clinical geneticists, patients, patient's families, referring physicians, specialists (in local hospitals), other clinicians, other labs, other healthcare providers, genetics novices, genetics experts, lay groups and researchers. • **Task A2.** Users with a variety of backgrounds, from none to significant genetics knowledge, and who lack a common language, users who lack understanding of what NGS test does/what has been ordered, physicians who provide insufficient clinical info, clinicians who overinterpret findings, clinicians who overestimate their genetics knowledge, Dr. Google. • **Task A3.** A number of individuals spanning the scales named were identified.
2)	Task B: Identification of user needs and challenges	Tool for task B is included in Figure 6 below. 1. In groups, participants were asked to identify what specific needs and challenges their users have 2. In groups, participants were to conceive of an ideal-world alternative to today's current form of report **Results** **Task B1.** Needs and challenges faced by the requisitioners were described as follows: • Clear, easy to find diagnosis, conclusion and other essential information • Understanding nomenclature/interpretation behind classes/results and taking correct action • Implementing (recommendations for) correct treatment and/or follow up/further testing • Understanding consequences for family members • Understanding possibilities and limitations of NGS test • Understanding negative/uncertain results, VUS, if/when to reanalyze • Conveying the result to patients **Task B2.** 'The Dream': alternatives to today's report • More effective reporting • Interactive report with several information layers • Interactive report with links to resources and terminology • Systems which ensure visibility of results in patient journal over time • Visualization of results – what was done/not done, methods • Hotline for questions (from clinicians and patients) • Secure video conference to get questions answered directly • (International) multidisciplinary meetings • Personal communication • Possibilities for consenting patients for recontact, reanalysis and research/trials Other useful factors: • A good referral: automatic/easy to fill in, with HPO terms • Practical training in NGS

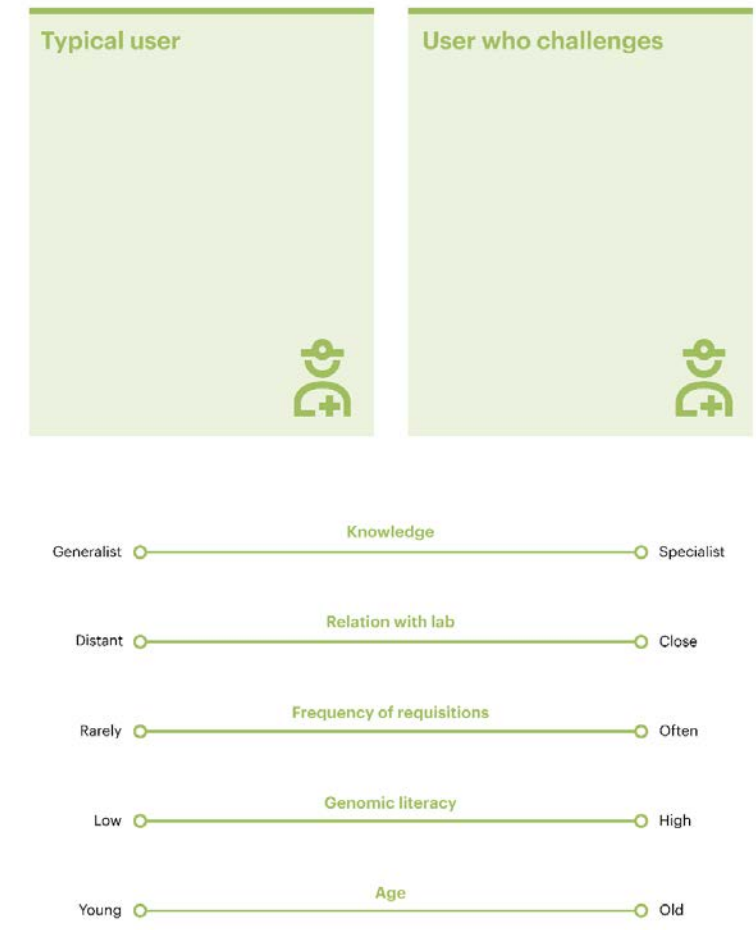


Figure 5 Identification of users (requisitioning doctors)

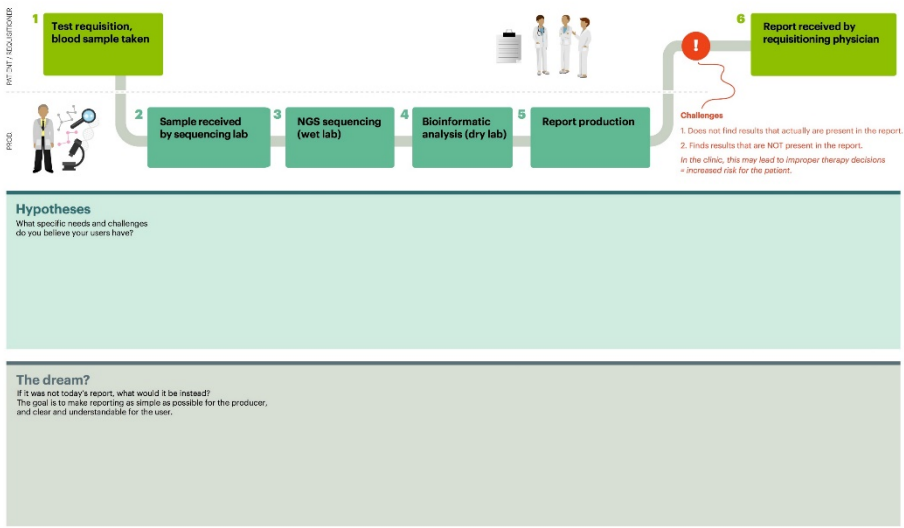


Figure 6 Identification of user needs and challenges

Variant documentation, reclassification & reanalysis

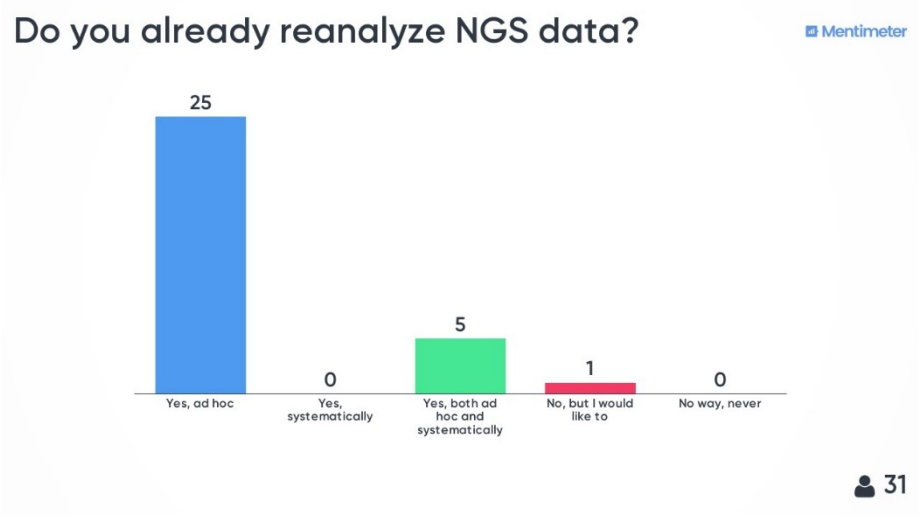
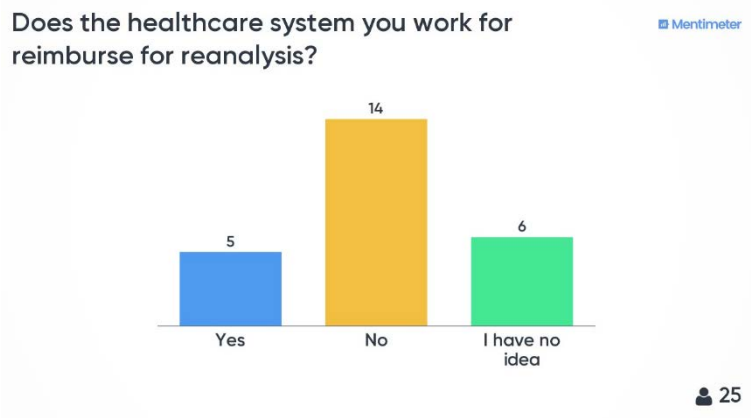
Session lead:	Morten Eike, OUS AMG; Kaisa Kettunen, FIMM and Sharmini Alagaratnam, DNV GL
Objective:	A recurring theme of concern is managing reclassification and reanalysis of genetic variants/ data. This session mapped and compared automation and standardization strategies for variant documentation and reanalysis under consideration/ in production at partner labs and review existing literature.
Workshop outline	1) Introduction to theme 2) Real-world examples 3) Literature review 4) Survey on Nordic reanalysis practices 5) Identification of challenges around reanalysis 6) Detailing of challenges and suggestions for approaches/ solutions.

1) Introduction to the theme from existing guidelines (Kaisa Kettunen, FIMM)

- Studies prove that reanalysis of unresolved cases increases the diagnostic rate. Reanalysis of data is not required on a regular basis. However, labs are responsible for reanalyzing available data if a variant is reclassified.
- Labs should provide clear policies on the reanalysis of data and are encouraged to explore innovative approaches to give patients and providers more efficient access to updated information.
- Recommendations are that labs suggest periodic inquiry by healthcare providers to determine if knowledge has changed on variants reported as VUS or likely pathogenic. Evolving knowledge calls for flexibility.
- A general duty to recontact patients is not sustainable with current model where the scope is essentially unlimited.

2) Examples of real-world reanalysis situations at OUS (Morten Eike, OUS AMG)

- Cancer genetics: needed to identify and reanalyse variants with changed ACMG-criteria:
    - BS1: frequency higher than expected for the disease, results in a change from class 3 to a class 2.
    - PM2: Absent from controls, supportive to moderate and went from class 3 to a class 4.
    - PVS1: null variant and contains new guidelines regarding interpretation. Class 5 now reclassified as a Class 3 which is clinically relevant
- Favourite variants lab is interested in tracking
- CDKN2A c353C>T and 392G>C was treated as pathogenic, but class 3 as family history was only evidence
- MLH1 c.1153C>T: Class 5 --> 3: Requisitioning physician wants periodic check to see if it changes to benign/pathogenic
- Example of having to follow certain variants to try to reach a conclusion

3)	**Literature review on reanalysis (Sharmini Alagaratnam, DNV GL)**	Sharm presented a review of nine articles systematically examining increase in diagnostic yield with reanalysis (Figure 7). Main learnings included: - Performing reanalysis annually can increase diagnostic yield by 10-15%. - Systematic reanalysis requires automation and up-to-date variant databases. - improved bioinformatics tools also result in increase of diagnostic yield. A comment was made that the gain from reanalyzing is different in different patient populations.
4)	**Survey on reanalysis**	A survey was conducted with workshop participants asking the questions: 1) do you already reanalyse NGS data? 2) Does the healthcare system you work for reimburse for reanalysis? Survey results were displayed directly to the participants and commented where relevant.  Comment: Finland: roughly 500 patients (and growing) within their reanalysis bank. 

5)	**Identification of challenges around reanalysis**	Workshop participants conducted a brainstorming to identify challenges around reanalysis. The items identified are displayed as a word cloud below. The following top five areas were voted as the most challenging: resources, communication, technical, ethical/consent, and triggers. 
6)	**Detailing of challenges and suggestions for approaches/ solutions.**	Workshop participants were divided into seven groups to detail the challenges and suggest approaches or solutions to overcome the challenges. The outcomes of these discussions are summarized in Table 2 and Table 3 below. Towards the end of this session, participants were additionally challenged to conceive of a potential Nordic collaborative project that would help address their topic (Table 4).
Conclusion		This topic raised many questions and challenges and was deemed to be of potential interest for a NACG focus area, either in a project or workshop format.

	Wright et al., 2018	Wenger et al., 2016	Nambot et al. 2018	Costain et al. 2018	Hiatt et al., 2018	Ewans et al. 2018	Eldomery et al., 2017	Al-Nabhani et al, 2018	SoRelle et al., 2018
	1133	40	156	64	494	54	74	50	185
	13%	10%	15%	10.9%	16%	11%	36%	12%	11%
	3 y	2 y	1 y	2 y	1 y	1 y	2-3 y	2-3 y	1-5 y

Figure 7 Literature review examining increased diagnostic yield upon reanalysis. The rows summarize number of patients in study, increased diagnostic yield and timespan of study and relevant articles.

Table 2 Challenges as described by and mapped to areas by the workshop participants.

Challenging area	Detailing of challenges
Ethics / Consent	- Do the patient & clinician still want the answer? - Do not have consent solutions in place or dynamic consent to facilitate opt-out possibility - Legal: how long should / can we store data - Lack of consent. - Is the patient's consent up to date? Does the patient still want to know? 1) related to phenotype and 2) secondary findings
Triggers	- When to reanalyze which cases, what are the selection criteria? - Un-solved cases? Whole database? - Thresholds to reanalysis? - Who asked us to reanalyze - At what levels should we reanalyze? E.g., sample, BAM, VCF, others - Trigger human reviews of automated process and when to re-contact?
Documentation	- Lack of sufficient documentation of variant classifications
Re-phenotyping	- Relevant family history and clinical data for re-phenotyping - Incomplete diagnosis - When phenotype does not explain genotype, re-phonotype when reanalyzing
Communication of new findings	- Communicate what changed to clinicians
Technical	- Workflows are non-automated, need of automation - Automate first line: who goes in the re-analysis pool? - Analyze original data or run new analysis? - Re-analysis or re-annotation? - Flexible data structures - Lack of good databases - Keep track of previous results, versioning - Computation resources (power and cost), if starting from raw data - Systematic approach
Resources	- Re-analysis is a time-consuming manual job (lack of automation), what is reasonable use of resources? - Resources: Bioinformatics competence; persons and time - Workload is chronically increasing - Time for assessing interpretation of new variants if large number - Lack of evidenced criteria in pervious classified variants - Prioritizing patients - Re-analysis or new sample? - Diminishing returns, when does it yield enough - Lack of sharing of classifications - Need for better databases - Reimbursement - Keeping data available (storage), costs (CPU, storage), and capacity.
Etc.	- Prioritization - Young vs old patients - Pros are new rare disease variants and changes that effect diagnosis, cons are cost and not knowing what they can act on.

Table 3 Challenge deep-dives by specific groups and suggested approaches or solutions

Group	Detailed challenge	Suggested approaches or solutions
Resources	- Manpower: Personnel resources - Issues related to IT infrastructure - Budget: where to spend and prioritize. - Time: what can we do with the manpower we have - Time: new technology produces more data - Informatic challenge: link change in database (e.g., Clinvar) to classified variants.	- To mitigate manpower: automation, decision support, data version control, hiring & training people to deal with this. - Budget: define criteria in doing the analysis (scheduled vs ad hoc) as this will influences resources. - Personnel resources: re-educate and train persons in healthcare - Data-sharing of phenotypes: a classification with evidence criteria - Time: new technology
Technical	- Computational power: e.g., re-run does not work how it is supposed to. - Versioning of files, report etc. - IT communication with clinician when they want to re-run - At what level do re-analysis? Need a system that is flexible - For what time frame is data stored? - What is the threshold for human review? Who is eligible? - Several groups use in house databases, but variant interpretation changes. - Automation	- Improved bioinformatics and decision support tools - Saving, analysis, versioning in database. - New referral, ticket system, check if there is still consent. - Need criteria to prompt re-analysis - How to understand - When in doubt get a new sample, if possible. - Routine to check API (every month we check what we reuse) - A system to check for patient consent (before reanalysis) - Automation: Desire to have software and database to keep track of previous data
Triggers	**Triggers associated with labs in reanalysis in terms of external vs internal.** **External:** - Clinician request new - analysis new phenotype data - Patient request new re-analysis - ACMG guideline on reanalysis **Internal:** - Reclassification of the variant: in-house vs Nordic vs worldwide - Virtual gene panels, new genes trigger reanalysis - Search VUS in databases (e.g., matchmaker exchange) - Changes made to the variant calling pipeline, may want to make a reanalysis of the sample - Technical problems - Unsolved cases - Early phase panel or early phase exomes, at what point do you want to go to the reanalysis of DNA (improved chemistry/hardware)	Stated that the approaches to all other challenges will support challenges related to triggers.

Consent / ethics	- Difference between reanalyzing data and reclassifying variants - Difference between complete and incomplete diagnostics - Patients problems change over time and reanalysis and consent needs to reflect this. - Follow-up: New-assay, new knowledge, new HPO - Unclear laws: statute of limitations? Durations? - Clinical implications - Patient death and relatives: how to not send out new diagnostics to someone who has passed. - Patient expectations: one-time testing vs continuous care	Stakeholder collaboration and engagement was ranked: 1. Patient and relatives 2. Society 3. Physician 4. Government 5. Stakeholders What does the patient want? - Best standard of care - Want to be a part of decision around analysis and be informed **Patient one-time vs continuous:** - How to stay in contact - Consulting mode, patient/physician relationship
Communication	**Communication in terms of 1) clinician and patient and 2) clinician and lab** **Communication with patient:** - This should be final and evidence-based, do not communicate something that is being investigated. **Communication with lab:** - Relationship with clinician is very important to discuss with him/her when reanalysis is important. - What if there is a classification change 3-5? Communicate this, but not 1-2. - Did the patient consent to reanalysis and how does the patient communicate that they change their mind? - Questions regarding new phenotypes: which physician do you contact and how should this information be communicated? - Variant prioritization	- Policy should be written in clinical report on reanalysis - New findings should be communicated through meetings or databases. - Collaborative action: letting other know via software solutions - Have an automated system where lab is updated if a new gene is reported in the literature – but there can be problems in terms of resources on how to react to this. How often should it occur? Depends on resources. - Lab receives a notification if a patient dies, therefore can choose to terminate reanalysis. - A system to prioritize variants

Table 4 Project ideas to address challenges in reanalysis

Proposed project to address challenge	Presenter
Look at different scenarios to look at the cost, time, and resources. Example: Will you do re-analysis on all the genes?	Jim Thorson, OUS
Where do you gain new insights: 1) variant annotation, 2) return pipeline, and 3) redo lab analysis	Morten Dunø, Rigshospitalet
We need a trusted database for variant interpretation that is shared (other than ClinVar). It is done but how do we start using it?	Chiari Rasi, SciLifeLab
Joint Nordic database where all partners can re-classify variants within their analysis.	Janna Saarela, FIMM
Need a software that scans the web and notifies of new or updated resources	Chiari Rasi, Scilifelab
Benchmarking of re-analysis	Janna Saarela, FIMM
Detail phenotype-based cohort analysis of unsolved cases	Janna Saarela, FIMM
Consent for continuous care instead of one-time diagnostics	Jón Jónsson, Landspitali

Can NACG come up with standards for communication of reanalysis?	Piotr Starnawski, Aarhus
Develop a questionnaire sent out to different labs and departments including clinicians	Maria Rossing, Rigshospitalet
Behind numbers – automatic solutions (e.g. with ClinVar) – how much work does that actual require?	Dag Undlien, OUS
Host workshops on specific to informatic challenges, include the issues of sharing data. What are the risks and how do we move forward?	Maria Rossing, Rigshospitalet

Regulatory frameworks and quality assurance for NGS-based diagnostics

	**Session lead:**	Courtney Nadeau, DNV GL
	Objective:	In-house developed tests are regulated by the 2017/746 EU In Vitro Diagnostic Medical Device Regulation (IVDR). This session introduces the IVDR and highlights aspects relevant to health institutions that develop and make available diagnostics based on research-use-only technologies as lab-developed tests.

Key information:

Courtney introduced the IVDR which replaces previous IVD directive 98/79/EC and takes primacy over national law. The following was discussed:

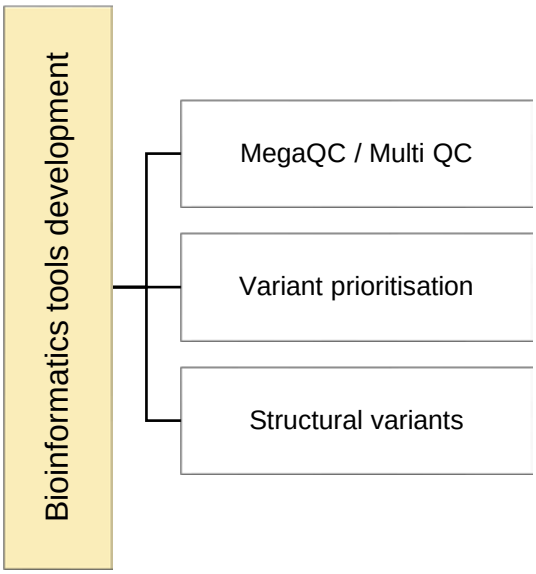
- Overview of new aspects in IVDR provided.
- NGS assays are considered IVDs
- Overview of full scope for CE compliance
- Introduction of second regulatory pathway for lab-developed tests
- Overview of article 5: rules for LDTs
    - Cannot transfer to another legal entity, Art 5(5a)
    - Used only under appropriate quality management systems
    - Lab is compliant with ISO 15189 or applicable national provisions
    - Justification that target patient group's specific needs cannot be met with an equivalent IVD. Discussion of somatic panels, what happens when new test is approved.
    - Provide information on request to competent authority
    - Public declaration available
    - Meets the safety and performance requirement in Annex I
    - System for exceptions and corrective action
- Overview of Annex I: Quality and performance
    - Risk management (3-8)
    - Analytical Performance (9.1a)
    - Clinical Performance (9.1b)
- Overview of scope for LDTs
- Bioinformatics tools can be medical devices, discussion of software classification

Conclusions

- IVDR is coming, directly impacts clinical labs
- Covers NGS assays and bioinformatics software
- Best option is to start compliance work early

BIOINFORMATICS TOOLS DEVELOPMENT

Working group lead: Kjell Petersen, University of Bergen and Tony Håndstad, Oslo University Hospital AMG



MegaQC / MultiQC

Session lead: Tor Solli-Nowlan, OUS AMG

Objective: To provide an introduction and overview of MultiQC & MegaQC, and update since April 2018 NACG hackathon.

Key information:

A review of MultiQC was provided, information available at www.multiqc.info and github.com/ewels/multiqc. MultiQC:

- Searches a given directory for analysis logs and compiles a static HTML report
- Supports several tools, such as
    - Pre-alignment: FastQC, Adapter Removal
    - Alignment: Bowtie 1 & 2, Kallisto, Salmon, STAR, TopHat
    - Post-alignment: Bamtools, GATK, Hap.py, Picard, (Bam|SAM|VCF)tools

A review of MegaQC was provided, information available at www.megaqc.info - github.com/ewels/megaqc. MegaQC:

- Stores and looks at MultiQC reports over time
- Provides trend analysis, variable comparisons and dashboards
- NACG spring hackathon, resulted in a spike in activities in April (Figure 8).

Conclusions	Positive experience in developing in utilizing the NACG forum for a hackathon to improve software. Tor (tor.solli-nowlan@medisin.uio.no) offers support to NACG with Mega/ MultiQC if needed. He is also interested to know if there are other projects similar to the NACG April 2018 hackathon, or any tools used internally in labs that could be useful for others to know about. NACG WS participants are encouraged to contact Tor.

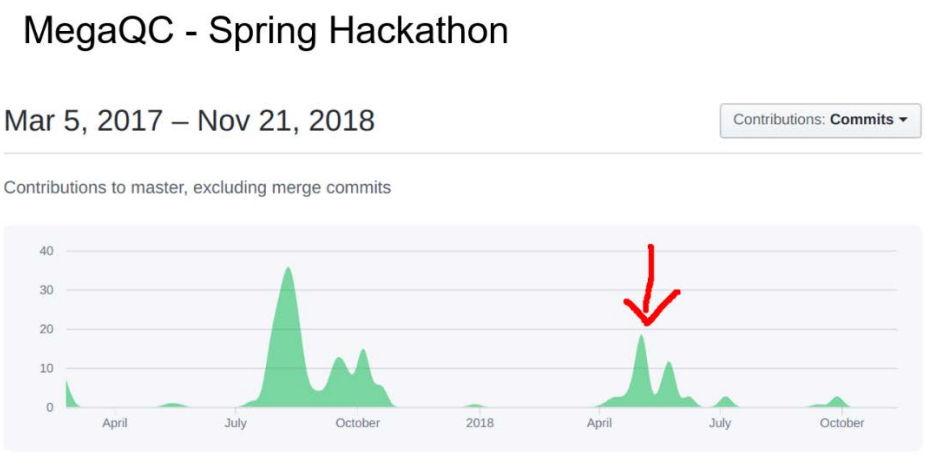


Figure 8 Contributions to MegaQC peaked during NACG April 2018 workshop

Variant prioritization

	Session lead:	Kjell Petersen, UiB and Tony Håndstad, OUS AMG
	Objective:	Provide an introduction to variant prioritization (VP) and review findings from the 5th NACG workshop
	Session outline:	1) Introduction to variant prioritization and review of findings from the 5th NACG clinical workshop 2) Variant prioritization using Scout at SciLifeLab 3) Landspitali perspective
1) Introduction to variant prioritization and review of findings from the 5th NACG workshop (Tony Håndstad, OUS AMG)	Variant prioritization is having a computer rank the variants you find according to their predicted pathogenicity. Variant prioritization is done to - Increase efficiency - Standardize analysis - Help not overlook something in the data During the 5th NACG workshop () variant prioritization was discussed[1], and a review of this discussion was provided. The discussions revealed a need for clarification of the term "variant prioritization", and what it includes.	

[1] Workshop report available at https://nordicclinicalgenomics.org/resources

- Manual interpretation
- Annotation /external data
- Automatic processing
- Filtering
- Criteria
- Ranking

Processes in variant prioritization

- Quality control, preprocessing variant, and calling
- Automatic ranking
- Manual interpretation (loading and filtering)

Generic criteria

- Variant /position specific criteria
- Region based criteria
- Unstructured knowledge related criteria

Alternative categorization

- Clinical evidence or functional evidence?
- Technical data (sample specific)
- Process of variant interpretation: evaluate population data, expected effect, clinical case reports, and functional experiments and predictive data.

Key questions identified following the previous workshop were:

- How can we trust that the automatic party of VP is sound?
- Can we run the same dataset through different labs' VP procedure and compare the results?
- Moving sensitive data to all labs' VP pipeline, or moving VP pipeline to other labs sensitive data is hard and complex, can we do something else?
- Is it possible to create a synthetic /artificial test dataset with realistic variants on a non-sensitive background?

2)	**Variant prioritization with use of Scout at SciLifeLab (Henrik Stranneheim, SciLifeLab)**	Henrik presented SciLifeLab's quality assured rapid workflow for rare inherited disease diagnostics. Analyzing 100 whole genomes per month and requires an organized way to prioritize the data, which is achieved using Scout. Scout is custom-developed, browser-based interpretation tool enabling collaborating clinicians to vet the ranked variants. Ranking of variants in Scout: - Different categories are used: genetic region, genomic consequence, known pathogenicity, severity, conservation, variant quality, and allele frequency – which produces a score that can be ranked. - The rank model is very flexible and can be given a criterion rank and score. - GnomAD is used as frequency database where criterion weights are assigned, then sum criterion scores to get your rank score. - Rank score: each variant is assigned a rank score based on the variant level annotation using weighted sum. - Scout then produces a single rank score per variant. Scout contains variant information necessary to make an export from Scout to be added to another database, an open source software to be tested shortly, called MutAcc.

3)	**Landspitali perspective, motivation to use commercial software and experiences with Fabric Genomics (Eirikur Briem, Dep. of Genetics and Molecular Medicine, Landspitali)**	Landspitali has a desire to increase NGS effort with bigger in-house panels but have challenges related to lack of infrastructure to deal with the amount of data produced. Benefit of using commercial software is that it comes with storage, provides access to bioinformaticians if needed, and variant prioritization is made easier. Fabric Genomics is an example, claims made include: - Single platform supports analysis of any NGS test, genomes, exomes, panels for pediatric genetics, rare diseases, oncology, and neurology - Clinical grade data analysis with speed and quality with fully customizable clinical reports with ready sign out in less than 2 hours for whole genome - AI technology used to drive scientific accuracy and efficiency - For advanced probabilistic ranking algorithms: VAAST and Phevor - Automated support for ACMG and CAP guidelines for classification - Fabric classified variant database: downfall is it is then limited to only those who use Fabric. - Rapid turnaround time through increased test throughput using configurable SOP-based workflows - Clinical reports are ready for sign out in less time - For ranking: VAAST and Phenor is used for WES /WGS cases A demo was provided.

Variant prioritization workshop

Session lead:	Kjell Petersen, UiB and Tony Håndstad, OUS AMG
Objective:	The objective was to discuss if it is possible to generate a sufficiently detailed artificial (non-sensitive) data set for sharing. The workshop focused on how we can generate non-sensitive realistic variants for VP test data set. Group work will have the objective of developing a strategy to generate realistic synthetic variants: - Evaluate risk of identifying underlying patients /case - Assess how realistic that it represents real biological variation - Assess how important / critical this type of variants is for the test dataset
Workshop outline	1) Introduction 2) Group discussions 3) Plenary discussion

1)	**A synthetic dataset for testing of variant prioritization, Øyvind Evju and Yngve Sejersted,OUS.**	The pros and cons of a synthetic dataset for testing of VP were discussed, with the proposed approach to create five synthetic cases with variants and associated HPO terms. Pros included: - Creation of data sets is very easy - Customizable - Realistic background - Common approach Cons discussed: - Biased: using hard cutoff on 1000g variants will immediately return the variants of interest and requires a priori pathogenic variant - VCF based, not read based Tools discussed: - VASST - MutationTaster2 - PhenIX - Genomiser
2)	**Group work**	A group work was carried out to creatively generate cases by implanting artificial variants: - Inspiration - Describe an approach to generate non-sensitive variants linked to a phenotype - Assess how realistic your data will represent biological variation - Assess the risk of re-identification patients with the given phenotype - Grade how important it is to include this type of variant/cases in the test-bed to make it useful.

Clinical cases:

1. Cardiomyopathy
2. Hereditary Cancer
3. Syndromology
4. Arrhythmia
5. Visual impairment

The participants were asked "*Can we improve the pilot just presented into a realistic test-bed for usage across multiple VP approaches in NACG?"* The response was the same before and after the group discussions; Yes =15, uncertain=9, and no =0.

3) Plenary session

The outcomes of the group work were discussed in a plenary session.

Possible

- 8 cases were possible to look at and put into the dataset.
- Groups did not have a variant that they were not able to anonymize.
- Shared approach suggested: shift variants a little bit, keep in the same domain, get a lot of homozygous variants that have the same rank.
- Acknowledged that a more difficult case is if more variants in one gene is recessive and dominant.

Volume

How many cases do we need in this dataset before it becomes useful?

- Use of different types of variants was suggested, ideally multiple replicas, but not feasible to do.

How many samples would you like to see that you consider it is worth it?

- Workshop members suggest bootstrapping as an approach. Desire to have enough samples to calculate a power analysis for confidence.

Effort

The group discussed whether NACG should continue this work.

- Is it useful?
- If we are at 20-30 cases (without bootstrapping), is that too ambitious for NACG to make more descriptive cases than what was done today?
- What is the problem we are trying to solve?
- Not your VP pipeline, rather, if we make an effort to get 20-30 cases, will it be useful across labs?

It was suggested that there is a need for confidence around the sample size, what is enough based on probability (false neg and false positive) for the correct volume. Simple cases require little effort, while complicated cases take more time and are also more important. It was suggested to map the space to build a frame to know how to properly address how many complicated cases are needed to ensure that the variant prioritization is working before moving forward.

The problem of current rank models is not the ranking algorithms, but rather having enough data to say something about the variants (frequency, etc.), i.e. we need to find better predictors.

It was suggested to make a map to show what we are searching for (and where the holes are) to increase awareness.

	Comments & discussion points - Suggestions to use already available datasets and evaluate their performance. - Questions on how to evaluate performance of VP pipeline in one country vs another as rank models and scales can change. - Phenotypes are hard to use, so if clinicians don't use phenotyping, we are selecting them away. This means losing variants rather than gaining them. - Reference to PhiliX tool with combined phenotypical data – tested removing and inserting phenotypes. Most open source tools are bases on Phenotypes. No point in creating our own algorithms when they are already out there. - Scales: are some more robust than others? Frequency data – don't remove founder effects – need to find the right threshold. It's up to you to decide, test on your data, and deicide. It becomes a tedious process. Would like to consider a more elaborate process. - Starting with a VCF and manipulating variants/data onwards. Is it sufficient to start with VCF and not be so concerned with variant quality? Will information ranking be dependent on the cause? The workshop participants agreed that it is easier to start with VCF as you can only push through so many samples.
4) Conclusions	The groups recorded their input in provided forms collected by session leads for further consideration. One opportunity is to at the next workshop have 20-30 cases in total and have each selected NACG lab run the test dataset in their VP pipeline. This was agreed from OUS AMG and Sweden, with interest also from Iceland.

Structural variants workshop

Session lead:	Oleg Agafonov, DNV GL
Objective:	Implementation of a structural variants (SV) pipeline is a hot topic for many NACCG members. This session will be mapping challenges, discussing potential solutions, and sharing know-how.
Workshop structure:	1) Status at SciLifeLab 2) Status at OUS AMG 3) Identification of challenges 4) Prioritization of challenges 5) Discussion on potential solutions and further NACG actions

1)	**Status at SciLifeLab (Henrik Stranneheim, SciLifeLab)**	- 100 WGS analyses per month, >4000 samples since 2014, turnaround time 5-14 day, focus on custom developed informatics tools - Detection of repeat expansions by Expansion hunter, Illumina - Scout has got a feature of visualization of repeat expansions - Introduction of LoqusDB - A simple observation count database for SVs - New features for TIDDIT (a tool for identification of chromosomal rearrangements)- Mitochondrial deletion detection, Aneuploidy detection, Improved overall sensitivity and precision - New Features for Scout - Vcf2cytosure file download (CGH), allows snv/indel/SV compound analysis
2)	**Status at OUS AMG (Tony Håndstad, OUS AMG)**	- WES is a standard for rare disease diagnostics - WES CNV calling with in-house depth base caller - WES CNV calling considered a "bonus" (i.e. not part of accredited test). - Planning to use Parliament2 for WGS SV. For validation, will compare against aCGH data and use GIAB SV as a benchmark.
3)	**Identification and prioritization of challenges**	Workshop members were divided into 5 groups and asked to discuss their greatest challenges around structural variants and place them around the following process: FASTQ → VCF → report. The identified challenges are gathered in Table 5, including count of votes on participants' top priority challenges.
4)	**Discussion on potential solutions and further NACG actions**	Workshop groups were asked to consider a project that NACG could run between now and the next workshop to address each or all of the top four challenges. The outcomes of the group discussions are summarized in Table 6.
Conclusion		Oleg (oleg.agafonov@dnvgl.com) encouraged workshop participants to consider the potential actions and solutions for follow-up at the next NACG clinical workshop. Interested participants can raise issues with the Steering committee, working group leads or directly with Oleg.

Table 5 Identified challenges related to structural variants, including votes on highest priority in brackets. The top four challenges are highlighted in green.

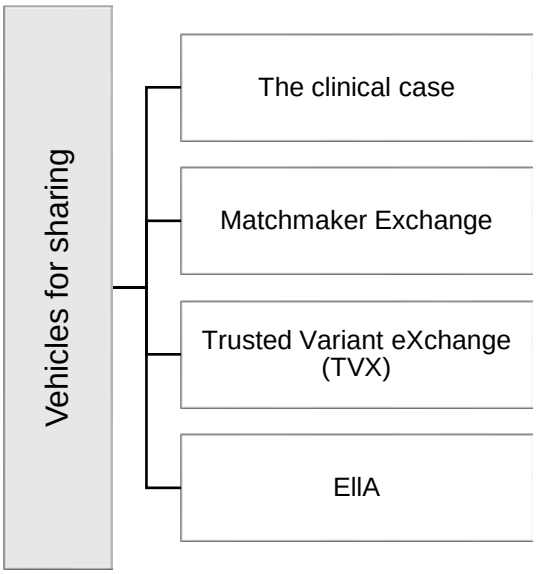
FASTQ	VCF	Report
Sequencing (3)	Lack of resources for structural variants (11)	Lack of standardization around the nomenclature for picking this up (18)
No good suitable reference genome (0)	SV that are not CNVs, how do you detect them? (7)	Lack of population frequencies (6)
No single tool for targeted analysis, technology WGS vs Exome vs panel (5)	Noise: difficult to cut off true positives, False positive, false negatives (17)	Dark matter region (8)
	No tool set- need for multiple callers (17)	Interpreting, clinical evaluation (11)
	Harder to find smaller variants (1)	Verification (0)
	Challenge to merge variants called & standard representation (7)	Public opinion (0)
	No tools for checking discordance (low concordance) for different variants and sizes of variants. (4)	Lack of annotation resources, comparing annotating (8)
	Lack of gold standards for CNVs: no truth sets. (27)	

Table 6 Output from group discussions on potential solutions and actions for the top 4 priority challenges related to structural variants.

Group	Discussion output
1	- tools: in terms of the need for multiple callers, can we get a presentation of hard facts: what works, what does not work. - False positives: table until standards are developed - Truth dataset: can we get a preview or early access to Horizon who is working on this. Talk to GA4GH. - GIAB might solve the reference issue.
2	- False positives: have an internal database for tracking false positives. Also, suggest looking into a tool called duphold That annotates CNVs and can signify if they are false positive or not.
3	- Truth sets: wait and see. Keep a look out for resources - Nomenclature: benchmark exercise (10 variants) and identify BRCA10 and name them according to the standard and see if there is an issue
4	- Trust sets: also agreed to wait - Nomenclature for SVs may already exist? - OUS is looking into Parliment2 (combines different callers) and can report on this at the next workshop.
5	- Tools: Share experiences on tools. - Tools: develop an internal database and share frequencies on positions. - Update on standard nomenclature? How to reflect different technologies – breaking points known vs tiling array.

VEHICLES FOR SHARING

Working group lead: Henrik Stranneheim / Chiara Rasi, SciLifeLab



Introduction - the clinical case and data sharing

	Session lead:	Henrik Stranneheim, SciLifeLab
	Objective:	Introduction – The clinical case
Key information:	Setting the stage for the Vehicles for sharing-session, Henrik reminded the group about the motivations for sharing: - Avoid reinventing the wheel; reuse what is already available - We may want to reinvent the wheel in some way but via an evolution perspective and contribute to developments of a common starting point Putting the sharing mechanisms on the agenda into context, Henrik presented a clinical case to show relevant tools for sharing along the pipeline (Figure 9).	

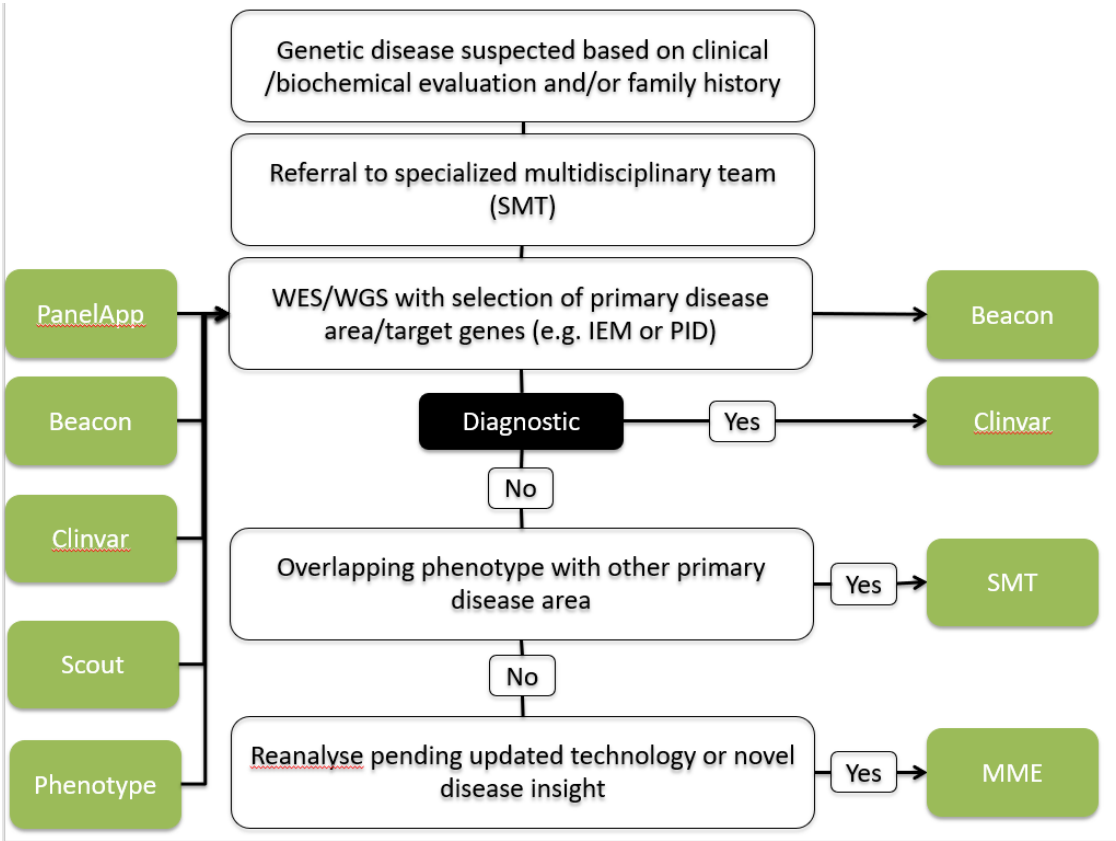


Figure 9 The clinical case and sharing mechanisms along the bioinformatic pipeline

Setting up a clinical genomics Matchmaker Exchange (MME) node

	**Session lead:**	Chiara Rasi, SciLifeLab
	Objective:	Share strategies and resources needed to set up a Matchmaker Exchange node, as well as experiences with sharing unsolved cases on the platform for rare disease gene discovery.

Key information:

MME was launched for diagnostics of rare diseases.

Before MME you were looking through many different databases, different servers and countries. The idea was MME to have one location with a common language, therefore data can be dispatched to many different nodes.

Currently there are 7 main nodes of MME:

1. Phenome central
2. Gene Matcher
3. Decipher
4. Matchbox
5. IRUD
6. Patient archive
7. MyGene2

When working with MME you can share data through an existing node or create your own node. Creating your own node has the following advantages:

- No need to deposit data outside facility.
- Database maintains autonomy and primary purpose.
- You can define your own matchmaking algorithms and ranking of returned results.

However, setting up your own node is complicated and requires more time.

A review of open-source implementations was provided. Amongst these, a performance comparison between MME reference server and Matchbox (see Table 7). As semantic search is preferred, SciLifeLab will adopt the Matchbox solution (after it has been fixed). Looking to integrate MME as a Scout module. Working on an interface for authorized clinicians for submitting patients from Scout. (e.g., a code to send clinicians via email notifications).

Conclusions

Establishing your own node is recommended for security reasons.

Chiara welcomes collaboration from NACG WS members. NACG workshop members suggested collaboration to:

- spin a node up

- register to the network

- add a couple of real patient cases

Table 7 Performance comparison between MME reference server and Matchbox

	MME reference server	Matchbox
installation	Just follow instructions	Bugs, docker installation, does not work
HTTP(S) request	Easy (curl, custom)	Easy (curl, custom)
HTTP(S) response	Fast, smooth, expected result	Slow because of scoring algorithms, genotyping score does not work as it should, Json is not well formatted.
Search	Non-semantic search	Semantic search

The Trusted Variant eXchange (TVX)

Session lead: Stephen McAdam, DNV GL

Objective: The TVX enables secure sharing of variant classifications and evidence between trusted partners. Updates from pilot user testing.

Key information:

At the first NACG WS in 2016 a discussion took place around the need to share data and *what can we share easily*. It was determined that sharing classification variants can be useful. DNV GL received funding via the BigMed project[2] to develop a prototype, TVX.

- April 2018 prototype was delivered.
- Also developed a competence group around the legal aspects for sharing data

TVX was built to:

- Improve quality control and variant classification
- Secure sharing of classification criteria with partners of choice
- Provide access to shared variants
- Detect discordances in classifications
- Provide performance dashboard
- Provide functionality through GUI and API

A Demo of TVX highlighted its user interface, management of users, different types of access, identify API users, permissions management, with a statement that permissions can be reconfigured based on user needs as there is an option to be time bound or revoked. Other areas discussed in the demo were:

- Classification screen shows conflicts between classifications with their justification. Can include attachments to support argument; however, there are legal concerns here and feedback is welcomed to the value added or missed if this option is removed.
- Search: within where you have been given permission, HGVS terms, or by gene names.
- Dashboard includes a display of the submission from your organization (including number of views and rate of successful submissions), a classification overview and classifications over time.

[2] www.bigmed.no

Questions & comments:	- Question about the different between TVX and ClinVar: Limitations to ClinVar due to lack of submissions and legal issues. ClinVar requires a min of variants annually (requires more staff to be approved to submit). TVX has a desire to create a Nordic community to share variants. TVX has the benefit of creating an infrastructure to choose who you want to share with and not (option to "share with all"). - Comment from audience that free-text tends to have most evidence, but there is not a lot of value missed without it.
Next steps:	- Legal clarification about anonymity of classification data - Vulnerability and risk assessment in progress - Developing a governance model and terms and conditions - Consideration around a contractual framework for data sharing between partners - Beta testing scheduled for Q1 2019 - Exploring sustainable business models

EllA

Session lead:	Svein Tore Seljebotn, OUS AMG
Objective:	Demonstration of the OUS EllA variant interpretation tool in production mode

Key information:

Svein Tore provided a demonstration of EllA, a variant interpretation software developed at OUS with strong focus on documentation and classification. It is open-source and ACMG centric in design. Features include:

- Select genepanel or custom panel
- Imports direct to EllA
- Currently used on inheritable cancer genetics
- Categorization of analysis with findings (class 3-5 and class 1-2).
- Includes a medical review
- In terms of classification, you can choose to reevaluate.
- Option to see classification history.

In production since Feb 2018 and since has:

- Solved high-volume, small panel issue.
- Next step is large analysis
- Users have analyzed 3600 samples in the past 8 months

Ella can categorize samples direct only into only normal variants, valid class 3,4, or 5, missing or outdated classification.

Since last week, normal only HTS samples are finalized automatically by the system.

Complications met along the way:

- 25 users, different people perform different tasks
- Requires 100% coverage
- Req: Sanger verification: to shorten answering times, samples with findings or new variants are put on Sanger verification right after deliver even before interpretation.

Conclusions	Lessons learned - Improving workflows and efficiency is a lot of work and takes a lot of communication - Value when sitting close with users, developing software in-house providers a good learning experience reaching far outside of the software itself. - Having total control and access to the data, with good integration abilities, provides a lot of benefits.

CONCLUSIONS AND NEXT STEPS

In line with the organization's Constitution, the NACG will continue to work to include more stakeholders to clinical genomics in the Nordic countries in the meetings and encourage them to seek membership in line with governing documents available at the organisation's website.

The NACG working groups and their focuses should be continuously re-evaluated to ensure that relevant topics from the group are prioritized and resulting in learnings and outcomes that are useful to clinical work processes for the membership. This will be a focus at all meetings, as will sharing of experiences of clinical implementation of workshop learnings and outcomes. The membership is encouraged to continuously nominate topics of interest to the Working Group leads, the Steering Committee or to the Secretariat.

The NACG will continue to seek opportunities for joint projects.

The next workshop will take place in Helsinki 6. & 7. May 2019 followed by a symposium / workshop in Oslo 19.-21. November 2019. The events will be announced to the NACG membership per email and on https://nordicclinicalgenomics.org/.

Appendix 1: Agenda

Table 8 Agenda Tuesday 20. November 2018

Time	Title	Content	Session lead
General sessions			
10:00	Welcome	Welcome and NACG update	Dag Undlien, OUS AMG & Guro Meldre Pedersen, DNV GL
11:00	National updates	Key updates from the Nordic countries	NACG Steering Committee
11:30	Danish National Genome Centre		Cathrine Jespersgaard, Chief consultant & Martin Thomsen, Lead bioinformatician, Danish National Genome Centre
12:00	Lunch		
13:00	Genomics England		Augusto Rendon, Director of Bioinformatics, Genomics England
Working group: Enhancing data quality and processes Lead: Sharmini Alagaratnam & Courtney Nadeau, DNV GL			
14:00	Clinical reporting	Based on the examination of clinical genomics reporting in WS5, a working group established to investigate the topic further. This session will report on the findings published in the first NACG position paper and discuss possible next steps.	Oleg Agafonov and Sharmini Alagaratnam, DNV GL
14:45	Variant documentation, reclassification & reanalysis	A recurring theme of concern is managing reclassification and reanalysis of variants/data. This session will map and compare automation and standardization strategies for variant documentation and reanalysis under consideration/ in production at partner labs and review existing literature.	Morten Eike, OUS AMG and Sharmini Alagaratnam, DNV GL
17:15	Regulatory frameworks and quality assurance for NGS-based diagnostics	Clinical in-house developed genetics tests are regulated by the EU IVDR introduced in 2017. This session will introduce the regulatory framework and relevant international standards, and discuss examples of activities and systems to ensure regulation compliance	Courtney Nadeau, DNV GL
18:00	Closing day 1		
20:00	Dinner		

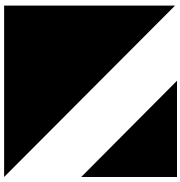
Table 9 Agenda Wednesday 21. November 2018

Time	Title	Content	Session lead
Working group: Bioinformatics tools development Lead: Kjell Petersen University of Bergen / Tony Håndstad, Oslo University Hospital AMG			
8:30	MegaQC/ MultiQC	Update on cross-border collaboration	Phil Ewels, SciLifeLab & Tor Solli-Nowlan, OUS AMG
9:00	Variant prioritization	This session will focus on how we can develop a common testing dataset and performance evaluation strategy for NACG variant prioritization pipelines, including establishing and maintaining a common vocabulary for variant prioritization.	Kjell Petersen UiB / Tony Håndstad, OUS AMG
10:00	Variant prioritization	Workshop – what will it take to trust variant prioritization output from other labs?	Kjell Petersen UiB / Tony Håndstad, OUS AMG
12:00	Lunch		
Working group: Vehicles for sharing Lead: Henrik Stranneheim / Chiara Rasi, SciLifeLab			
13:00	Vehicles for sharing	Introduction – the clinical case	Henrik Stranneheim, SciLifeLab
13:15	Matchmaker Exchange	Strategies and resources needed to set up a Matchmaker Exchange node. Experiences with sharing unsolved cases on the platform for rare disease gene discovery.	Chiara Rasi, SciLifeLab
14:00	Trusted Variant eXchange	The TVX enables secure sharing of variant classifications and evidence between trusted partners. Updates from pilot user testing.	Stephen McAdam, DNV GL
14:15	EllA	Demonstration of the EllA variant classification tool in production mode.	Svein Tore Seljebotn, OUS AMG
General session			
15:00	Closing	Workshop summary and next steps	Guro Pedersen, DNV GL
Working group: Bioinformatics tools development			
15:30	Structural variants	Implementation of a SV pipeline is a hot topic for many NACG members. This session will be mapping challenges, discussing potential solutions and sharing know-how.	Oleg Agafonov, DNV GL

Appendix 2: List of participants

Organisation	Country	First name	Last name
Aarhus University Hospital	Denmark	Ole Halfdan	Larsen
Aarhus University Hospital	Denmark	Kasper	Thorsen
Aarhus University Hospital	Denmark	Lise	Christensen
Aarhus University Hospital	Denmark	Piotr	Starnawski
Aarhus University Hospital	Denmark	Søren	Vang
Copenhagen Institute for Future Studies	Denmark	Bogi	Eliasen
Danish National Genome Center	Denmark	Cathrine	Jespersgaard
Danish National Genome Center	Denmark	Martin	Thomsen
DNV GL	Norway	Bobbie	Ray-Sannerud
DNV GL	Norway	Courtney	Nadeau
DNV GL	Norway	Guro Meldre	Pedersen
DNV GL	Norway	Jahn Henry	Løvaas
DNV GL	Norway	Oleg	Agafonov
DNV GL	Norway	Sharmini	Alagaratnam
DNV GL	Norway	Stephen	McAdam
FIMM	Finland	Henrikki	Almusa
FIMM	Finland	Janna	Saarela
Genomics England	UK	Antonio	Rueda
Helsinki University Hospital	Finland	Anna-Kaisa	Anttonen
Helsinki University Hospital	Finland	Eevi	Kaasinen
Helsinki University Hospital	Finland	Pia	Alhopuro
Helsinki University Hospital	Finland	Matti	Kankainen
HUSLAB	Finland	Arto	Orpana
HUSLAB / FIMM	Finland	Kaisa	Kettunen
HUSLAB Helsinki University Hospital	Finland	Minna	Pöyhönen
Karolinska Institutet	Sweden	Anders	Jemt
Karolinska University Hospital	Sweden	Nicole	Lesko
Landspitali (University Hospital of Iceland)	Iceland	Eiríkur	Briem
Landspitali (University Hospital of Iceland)	Iceland	Jon J.	Jonsson
Microsoft	Norway	Christian	Bryne
Nordic Precision Medicine Initiative (NPMI) Faculty of Medicine, University of Copenhagen	Denmark	Hakon	Heimer
Oslo University Hospital	Norway	Beate	Skinningsrud
Oslo University Hospital	Norway	Cathrine	Nordhus
Oslo University Hospital	Norway	Dag	Undlien
Oslo University Hospital	Norway	Eidi	Nafstad
Oslo University Hospital	Norway	Jim	Thorsen
Oslo University Hospital	Norway	Knut Erik	Berge
Oslo University Hospital	Norway	Lars	Retterstøl
Oslo University Hospital	Norway	Morten C.	Eike
Oslo University Hospital	Norway	Sarah Louise	Ariansen
Oslo University Hospital	Norway	Svein Tore	Seljebotn
Oslo University Hospital	Norway	Tony	Håndstad
Oslo University Hospital	Norway	Yngve	Sejersted
Oslo University Hospital	Norway	Øyvind	Evju

Rigshospitalet (Copenhagen University Hospital)	Denmark	Line	Borgwardt
Rigshospitalet (Copenhagen University Hospital)	Denmark	Lukas	Berchtold
Rigshospitalet (Copenhagen University Hospital)	Denmark	Mathias Husted	Torp
Rigshospitalet (Copenhagen University Hospital)	Denmark	Peter	Johansen
Rigshospitalet (Copenhagen University Hospital)	Denmark	Rasmus	Marvig
Rigshospitalet (Copenhagen University Hospital)	Denmark	Thomas	Hansen
Rigshospitalet (Copenhagen University Hospital)	Denmark	Ulf	Birkedal
Rigshospitalet (Copenhagen University Hospital)	Denmark	Birgitte	Bertelsen
Rigshospitalet (Copenhagen University Hospital)	Denmark	Elsebet	Oestergaard
Rigshospitalet (Copenhagen University Hospital)	Denmark	Filipe	Vieira
Rigshospitalet (Copenhagen University Hospital)	Denmark	Karin	Wadt
Rigshospitalet (Copenhagen University Hospital)	Denmark	Lotte	Risom
Rigshospitalet (Copenhagen University Hospital)	Denmark	Majbritt Busk	Madsen
Rigshospitalet (Copenhagen University Hospital)	Denmark	Maria	Rossing
Rigshospitalet (Copenhagen University Hospital)	Denmark	Morten	Dunø
Rigshospitalet (Copenhagen University Hospital)	Denmark	Jakob	Ek
SciLifeLab	Sweden	Chiara	Rasi
SciLifeLab	Sweden	Henrik	Stranneheim
SciLifeLab	Sweden	Valtteri	Wirta
St. Olavs Hospital	Norway	Christa	Schmidt
St. Olavs Hospital	Norway	Maren F.	Olsen
University of Bergen	Norway	Kjell	Petersen



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