Nordic Alliance
for Clinical
Genomics

WORKSHOP REPORT

NACG 15th Workshop, 27-28 September 2024, Oslo, Norway

Thank you for contributing to the content of this workshop report:

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- Ksenia Lavrichenko
- Gry Asker
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EXECUTIVE SUMMARY

This report provides a summary of the 15th workshop of the Nordic Alliance for Clinical Genomics (NACG). The workshop took place at Oslo, Iceland, 27-28 September 2024, bringing together 139 participants from 34 organizations in 8 countries.

The workshop invitation including agenda is included in Appendix 1.

The theme for this workshop was Long Read Sequencing.

KEYNOTE

Keynote speaker & affiliation	Title	Key topics
Prof. dr. Christian Gilissen, Radboud university medical center, The Netherlands	Experiences from long read sequencing	Prof. dr. Christian Gilissen has extensive experience with different kind of long read technology, mainly in the field of rare genetic diseases. He gave an introduction of the clinical application of the technology, and showed interesting results both from research and clinical use.

NATIONAL UPDATES

Session chair: Dag Undlien, Dept. of medical genetics, Oslo University Hospital

Country	Presenter	Key updates
Norway	Dag Undlien	- National strategy for personalized medicine 2023-2030. - A national genome centre is being planned (as presented earlier), with the focus on a national ICT infrastructure. - National data sharing solution for classified genetic variants in hereditary diseases has been established (separate workshop presentation, VARDE) - Impress - national clinical study in cancer
Sweden	Valtteri Wirta	- The use of NGS in Swedish healthcare extensively increases, numbers from rare diseases and cancer were presented. - Towards adapted legislation regarding secondary use of health data for the purpose of care. - Governmental funded pilots for precision medicine 2024 was presented. - National budget 2025 suggest a strong increase in funding towards research and innovation, pointing at precision health. - Pilot om data standards for genomic data
Denmark	Søren Vang	- National organization, national ICT infrastructure and turnaround time. - The national genome database has the content of >35 000 genomes/RNA samples. Cancer patients and children with rare diseases are the largest patients groups of performed samples. - The national genome centre has recently established a research computational service.

Iceland	Eirikur Briem	- Draft National Plan for Rare Diseases published in March 2024. - Developments in Precision Medicine in Iceland in 2024. - Relocation of the Dep of Genetics and Molecular Medicine. - A large study of actionable genotypes and their association with life span in Iceland published in NEJM, was presented.
Finland	Anna-Kaisa Anttonen	- In 2023 there was a major reform of public health care funding. - NIPT was established as first trimester screening in public healthcare since 2023 in to sites. - Results from genetic testing of prostate cancer and breast cancer was presented.

WORK SHOP: Long read sequencing

PARALELL SESSION 1 Bioinformatics

Session chair: Ksenia Lavrichenko, Dept. of medical genetics, Oslo University Hospital and Jesper Eisfeldt, SciLifeLab, Karolinska Hospital

Introduction
LRS as Diagnostic frontier: Framed as the future of diagnostics, expectations are high for LRS to surpass existing methods.
Current adoption: Most participants have implemented or are considering LRS, focusing on applications related to repeats, phasing, and methylation.
Concerns: Primary concerns include cost, resources, and data storage.

Jesper Eisfeldt: Phasing
Definitions: To phase is to cluster variants into cis or trans groups; phase set/block is a group of variants such that all variants within the block are phased.
Application: Aide in the resolution of compound heterozygotes and understanding epigenetic effects (e.g., imprinting and skewed X inactivation).
Tools: Various phasing tools are available, including Longphase and Hiphase.
Findings: Longphase has the fewest errors when using trio data as a truth set. All tools show similar performance. The phase block lengths correlate well with read length.

Anuradha Ravi: SV calling
Focus on ONT: Applications involve adaptive sampling. Suggested to rerun basecalling with higher accuracy model
Analysis pipeline: Utilizes Minimap2, Clair3, Sniffles2, and Whatshap, with data aligned to GRCh38.
Case Studies:
Case Study 1: Identified insertion of mobile elements in the MSH6 gene through de novo assembly using long reads.
Case Study 2: Involved adaptive sampling for complex rearrangements, requiring manual inspection based on caller indications.

Padraic Corcoran: repeat expansions
Detection methods: STRs detected from targeted long reads (PacBio or ONT) using methods like Cas9 ONT, Pacbio puretarget, and adaptive sampling.
Data analysis: Multiple callers were employed, including Tandem Genotype, Straglr, and STRDust, with visualization aided by aSTRonut.

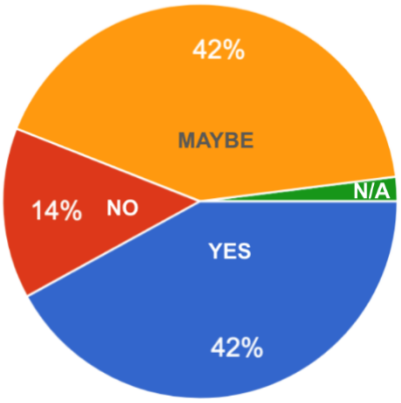
Discussion
Increased sensitivity: More extensive investigations lead to increased findings; integrating diverse information is critical for improved filtering.
Visualization needs: Calls for enhanced visualization and integration to simplify interpretation and boost diagnostic capabilities.
Competitive edge: The ease of interpretation will provide a significant advantage.
Tool stability: Stability of tools remains a concern among bioinformaticians, with a desire for graph genome methods.

Menti: then and now

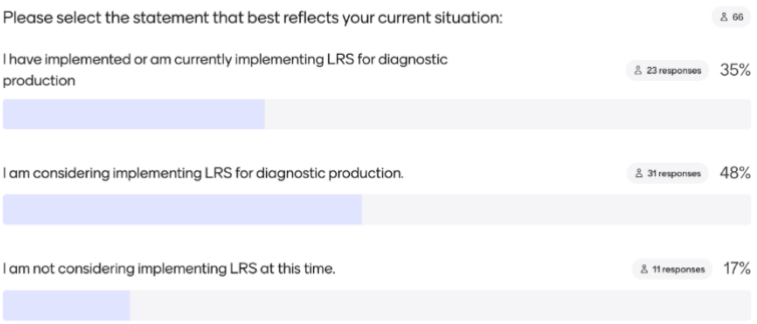
Comparing to the Menti results of 12th NACG, 2022

Q1: Adoption of the methods

Q 2022: Are you considering to implement LRS/OGM methods?



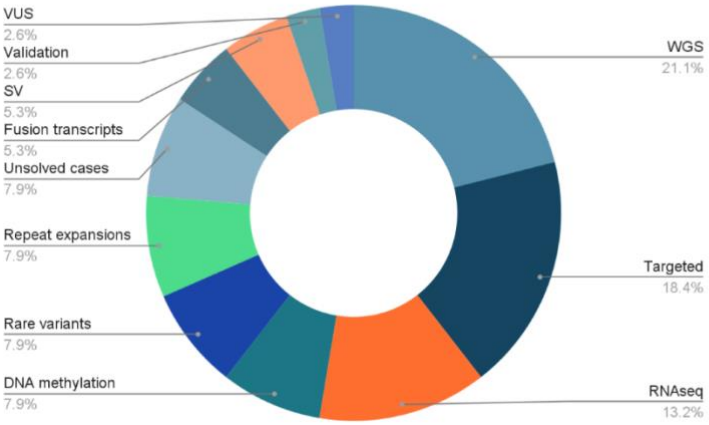
Q 2024:



Q2: Applications of interest for LRS

What are the primary applications of interest for LRS?

2022:

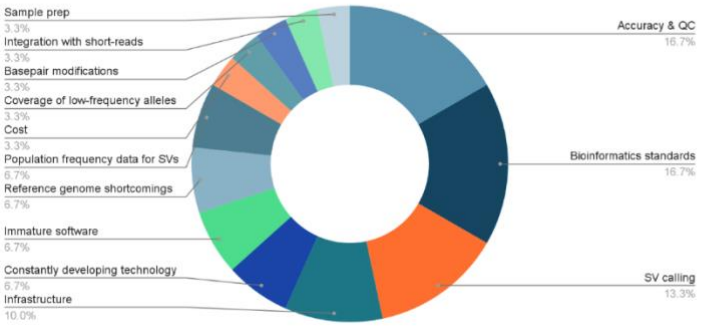


2024:

Q3: Main challenges

What challenges are you facing or anticipating in implementing LRS??

2022:



2024:

Follow up Menti

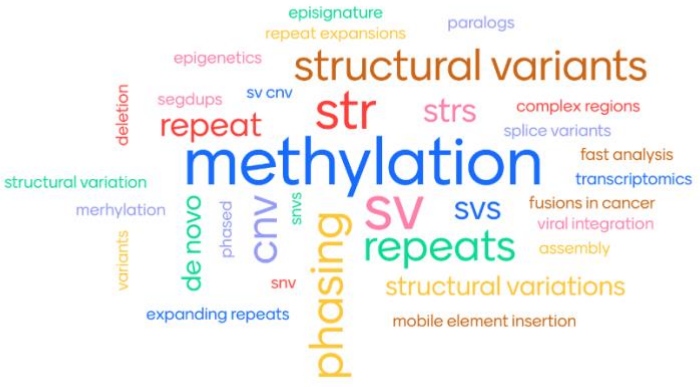
Q1: Platform

Which long-range platfrom are you implementing/testing

Q2: Applications

What analyses are you interested in?

103 responses



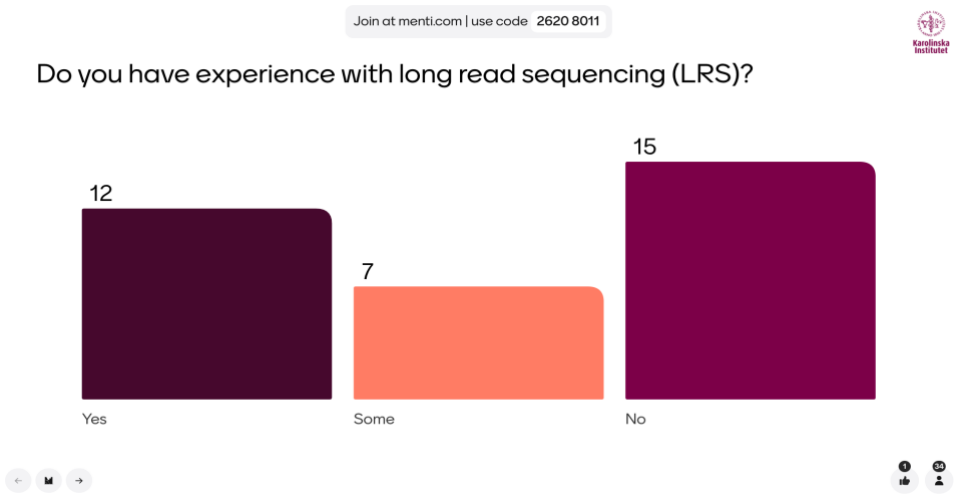
PARALELL SESSION 2 Wet lab

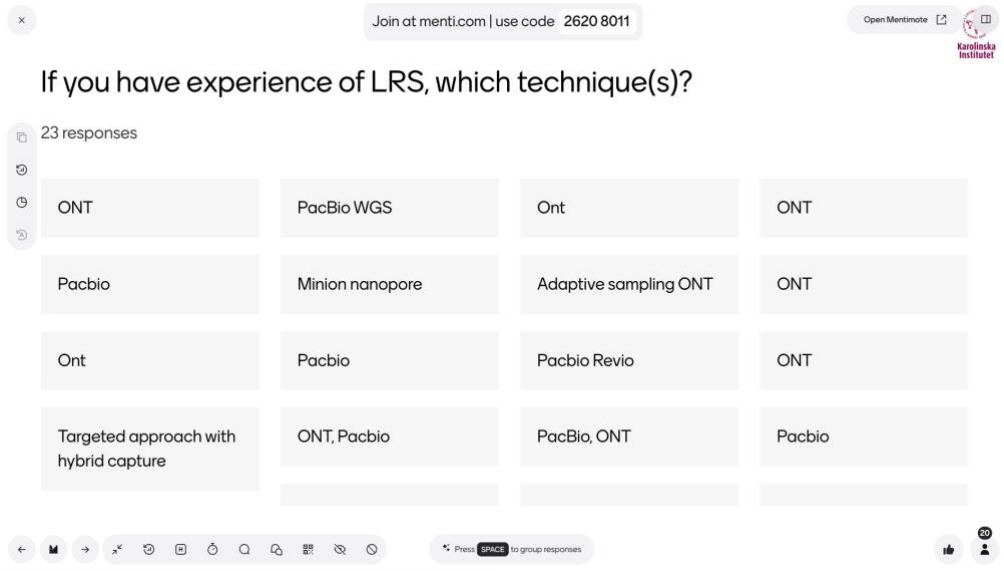
Session chair: Ida Höijer, Uppsala University, Anna Lyander, Clinical Genomics Stockholm, Karolinska Hospital, and Aino Palva, Institute for Molecular Medicine Finland FIMM Technology Centre

Presentations

- “Optimization of Nanopore Adaptive Sampling for rapid, cost-effective targeted native sequencing”, Ebbe Norskov Bak
- “Targeted long-read capture is both scalable and economical for population and clinical genomics”, Tina Han
- “Visual browsing vs long-read SV-calling algorithms (read the small print)”, Gregor Gilfillan

Menti





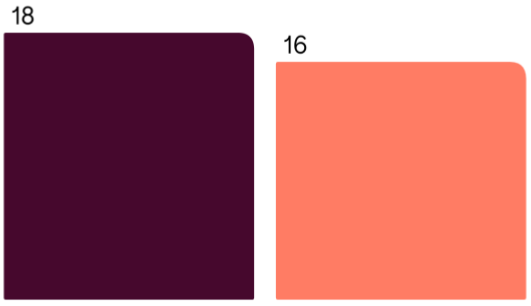
Join at menti.com | use code 2620 8011

Topics for discussion - discuss experiences, challenges, needs

- **Clinical applications**
  - Choice of technology
  - Choice of method
- **Wetlab experiences**
  - DNA extraction
  - DNA quality
  - Pitfalls in sample preparation
  - Robotics
  - Scalability in wetlab

Join at menti.com | use code 2620 8011

Which topic would you like to join for the discussion?



Discussion summary

Discussion in groups, topics clinical applications and wetlab experiences. Diverse group in aspect of LRS experience and technology.

- Choice of method depends on the application
- Turnaround time and capacity are important aspects
- Standard clinical DNA extraction methods are usually fine for long read sequencing techniques
- Clinical material might be limited - low input kits would be useful
- QC with e.g. FemtoPulse could be important but time-consuming
- Tapestation not a good alternative
- Short-read eliminator kits usually efficient but high losses
- Yield vs read-length (ONT): Yield usually more important that great read lengths

RAPID FIRE SESSION

Session chair: Dorte Lildballe, dept. mol. med, Aarhus University Hospital

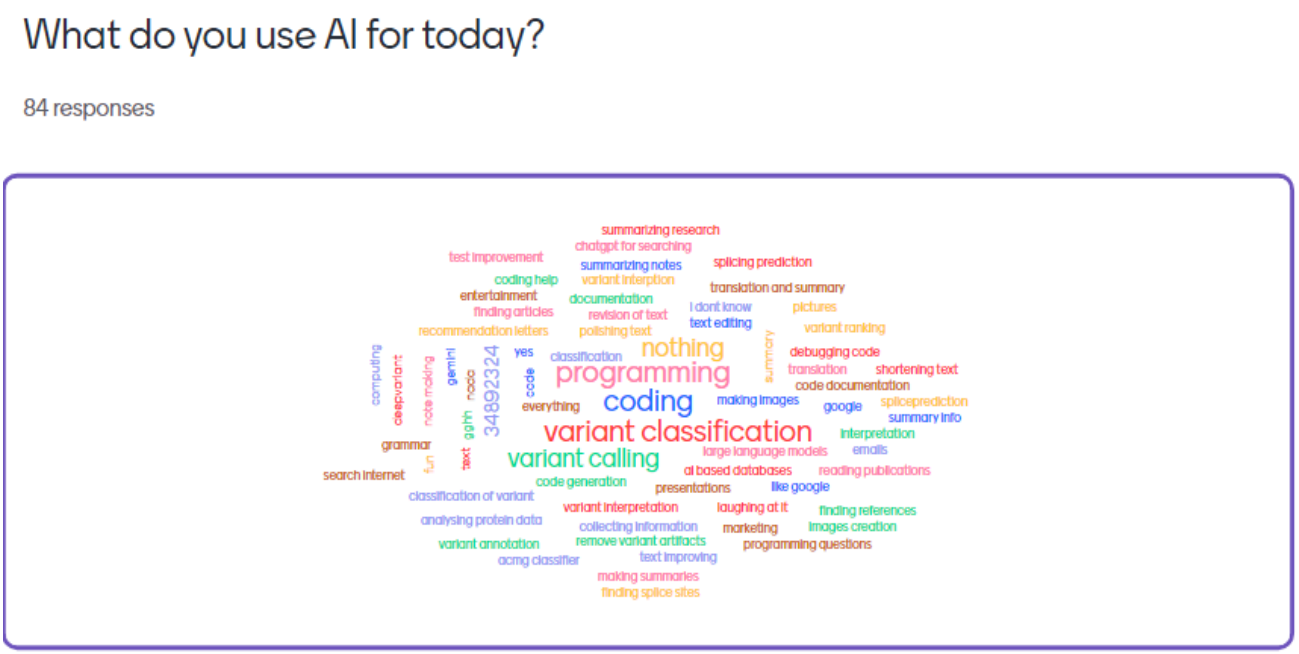
Site	Presenter	Key updates
Laboratory of Genetics; Helsinki University Hospital (HUS); Finland	Outi Monni; PhD, Adj. Prof. Cancer Genetics, Laboratory Supervisor	Comparison of cancer gene panels for somatic mutation detection in solid tumors
Clinical Genomics Stockholm; Karolinska University Hospital; Sweden	Beatriz Sá Vinhas ; Bioinformatician Marcela Gallardo; Research Engineer	Reducing turnaround times: optimising lab preparations and bioinformatics workflows
Tyks Genomics; Turku University Hospital; Finland	Minna Paavola; PhD, clinical laboratory geneticist	Prenatal exome sequencing at Turku Genomics Laboratory
Clinical Genomics Uppsala, SciLifeLab; Uppsala University; Sweden	Malin Melin; PhD, Head of Clinical Genomics Uppsala	Genomic Medicine Sweden: Three national long-read sequencing pilot projects
Genomics Unit; University of Helsinki/FIMM; Finland	Henrikki Almusa; Msc, Bioinformatician	Automations arrival to lab and it's effect to CNV analysis
Limbus Medical Technologies GmbH; Germany	Ben Liesfeld; PhD, Managing Director	What it took to get an IVDR class C device approved for genetic diagnostics
Clinical Genomics Stockholm; Karolinska Institutet; Sweden	Linnéa La Fleur, ; PhD, Research Engineer Felix Lenner and ; Bioinformatician Susanne Månér; Research Engineer	Experiences from implementing two long read platforms
HUS Diagnostic Center ; Helsinki University Hospital; Finland	Salla Rusanen; PhD, Clinical laboratory geneticist	Ring chromosome in exome sequencing
HUS Diagnostic Center ; Helsinki University Hospital; Finland	Ronja Hotakainen; Bioinformatician, PhD student	Features of gnomAD v4

AI IN CLINICAL GENOMICS

Session chair: Beate Skinningsrud, Dept. of medical genetics, Oslo University Hospital

The content of the sessions was dominated with presentations from industry. Limbus Medical Technologies GmbH gave an introduction to the use of AI in genetic diagnostics, and also a presentation of limitations and challenges with training set and validation data. SeqOne and Nostos Genomics focused on the aim of variant classification, while DNV introduced the EU AI Act and its consequences for deployers of AI devices.

DNV and Oslo University Hospital also presented a joint project with the aim of comparing different solutions for AI-based variant prioritization tools. The planned benchmarking is aiming to assess the effectiveness of commercially available AI-based solutions in prioritizing genetic variants using real-world patient data within clinical settings, however, a list of hurdles were also discussed in the presentations.



LRS IN CLINICAL APPLICATIONS

Session chair: Majbritt Busk Madsen, Dep. of Genomic Medicine, Rigshospitalet, Copenhagen, Gry Asker and Ksenia Lavrichenko, Dept. of medical genetics, Oslo University Hospital

The session included nine presentations focusing on the use of long read sequencing in clinical applications.

The results from the interactive workshop is presented below.

Site	Presenter	Key updates
Dep. of Clinical Genetics, Odense University Hospital	Martin Larsen	Implementation of Long-Read Genomes for Structural Variants and Imprinting Disorders
Dep. of medicine, University of Iceland	Katrin Möller	Identifying shared DNA methylation abnormalities in mendelian disorders of the epigenetic machinery
Institute for Cancer Research, Oslo University Hospital	Mev Dominguez Valentin	Long read sequencing in hereditary cancer
Dep. of Molecular Medicine, Aarhus University Hospital	Søren Færgeman Simon Drue Ebbe Norskov Bak	From Symptoms to Diagnosis: Detection of Repeat Expansions with Nanopore adaptive sampling
Dep. of Molecular Diagnostics, Aalborg University Hospital	Jakob Holm Dalsgaard Inge Søkilde	Implementing PacBio sequencing in a clinical setting
Clinical Genomics, Uppsala University	Ida Höijer	Rapid diagnosis of leukemic aberrations using nanopore sequencing
Dep. of Clinical Genetic, Rigshospitalet in Copenhagen	Ulf Birkedal	Nanopore Sequencing in Functional Genetics – Experiences and insights two years later
Dep. of Genomic Medicine, Rigshospitalet in Copenhagen	Majbritt Busk Madsen	Testing different long-read platforms in a clinical setting
Clinical Genetics, Uppsala University Hospital	Hans Matsson	The clinical utility of whole genome long read sequencing in neonatal hypotonia diagnostics

Currently, Long Read Sequencing (LRS) is most useful

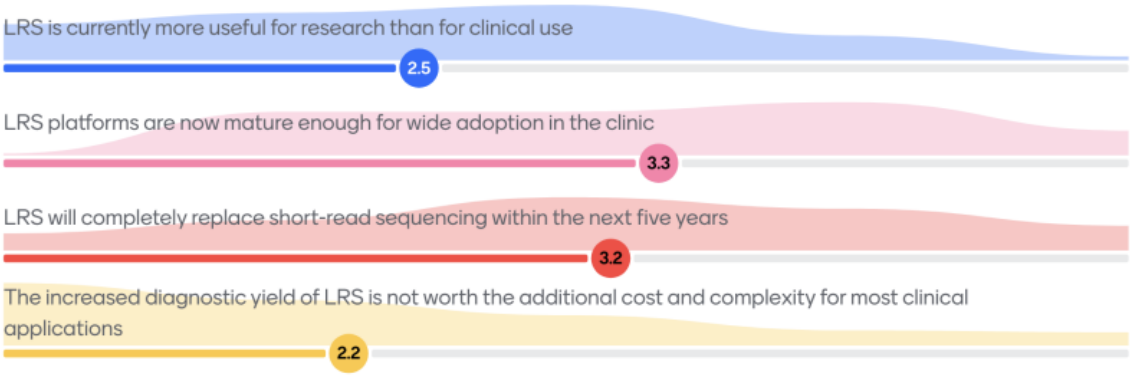
Which patient groups benefit (or will benefit) the most from LRS?

125 responses

Which patient groups benefit (or will benefit) the most from LRS?

125 responses

To what extent do you agree with the following statements



DATA SHARING IN NORWAY

Presenter: Dag Undlien, Head of de Dept. of medical genetics, Oslo University Hospital and project leader of VARDE.
Title: Data sharing – Experiences from national data sharing of interpreted variants in Norway

VARDE is a national wide project in Norway aiming to compare interpreted variant classifications between the five different sites in Norway doing medical genetic diagnostics. The five sites are situated at the different hospital; Oslo University Hospital, St. Olavs hospital, Telemark Hospital Trust, Haukeland University Hospital, and University Hospital of North Norway. All classifications are compared based on the usage of ACMG criteria (ref. Richards S. *et al*. Genet Med. 2015 Mar 5;17(5):405–424), and merged in a common database.

The workflow for variant classifications discrepancies, and preliminary results, were presented in the talk.

Appendix 1: Agenda

26th September, Day 1

Time	Item	Responsible
10:00 - 10:30	Registration and coffee	Oslo University Hospital
10:30 - 11:00	Welcome address	Dag Undlien
11:00 - 12:00	**Invited keynote speaker**: Prof. dr. Christian Gilissen, Radboud university medical center, The Netherlands. Experiences from long read sequencing	
12:00 - 13:00	**National updates** relating to development in national programs in genomic medicine, precision diagnostics and precision medicine	Anna-Kaisa Anttonen Søren Vang Dag Undlien Eirikur Briem Valtteri Wirta
13:00 - 14:00	Lunch	
14:00 - 15:30	**Parallel session 1** – long read sequencing. Bioinformatics Introductions: - "Long read phasing and de novo assembly", Jesper Eisfeldt - "Structural variant analyses in long read sequencing", Anuradha Ravi - "Repeat expansion detection with targeted long read sequencing", Pádraic Corcora *Methods, tools and pipelines*	Ksenia Lavrichenko, Jesper Eisfeldt
	Parallel session 2 – long read sequencing. Wet lab; Experiences and challenges Introductions: - "Optimization of Nanopore Adaptive Sampling for rapid, cost-effective targeted native sequencing", Ebbe Norskov Bak - "Targeted long-read capture is both scalable and economical for population and clinical genomics", Tina Han - "Visual browsing vs long-read SV-calling algorithms (read the small print)", Gregor Gilfillan *DNA extraction, choice of method, pitfalls in sample preparation, robotics, scalability in wetlab*	Ida Höijer, Anna Lyander, Aino Palva
15:30 - 16:00	Coffee break and visit at sponsor booths	
16:00 - 16.15	**Summary of today's workshops**	Workshop coordinators
16:15 - 17:30	**Rapid-fire session on knowledge sharing**	Dorte Launholt

	Brief presentations (6+1 min) - "Comparison of cancer gene panels for somatic mutation detection in solid tumors",Outi Monni - "Reducing turnaround times: optimising lab preparations and bioinformatics workflows", Beatriz Sá Vinhas and Marcela Gallardo - "Prenatal exome sequencing at Turku Genomics Laboratory", Minna Toivonen - "Genomic Medicine Sweden: Three national long-read sequencing pilot projects", Malin Melin - "Automations arrival to lab and it's effect to CNV analysis", Henrikki Almusa - "What it took to get an IVDR class C device approved for genetic diagnostics", Ben Liesfeld - "Experiences from implementing two long read platforms", Linnéa La Fleur, Felix Lenner and Susanne Månér - "Ring chromosome in exome sequencing", Salla Rusanen - "Features of gnomAD v4", Ronja Hotakainen	Lildballe
17:30-19:30	Time on your own – spa, sauna or free time	
19:30 – 20:00	Pre-dinner drink and social activity	Oslo University Hospital
20:00	Dinner	

27th September, Day 2

Time	Item	Responsible
09:00 – 10:00	**Bridging the gap – experiences with AI-solutions in clinical genomics** *In the 14th NACG workshop AI-solutions was the major theme.* *Brief presentations (8+2 min)* - "Introduction to AI in diagnostics", Lena Hausdorf - "Limitations of AI in genomics", Ben Liesfeld - "Benchmarking of AI-based variant prioritization tools: status update", Oleg Agafonov and Ksenia Lavrichenko - "How can AI help identify novel disease-causing mutations in diagnostics and research?", Rocío Acuña-Hidalgo - "An AI driven platform to support the diagnostic process for germline applications", Christophe Meynier - "EU AI Act and its consequences for users of AI-based IVD medical devices", Oleg Agafonov	Beate Skinningsrud
10:00 – 10:20	Coffee break and visit at sponsor booths	
10:20 – 11:30	**Long read seq; Clinical applications - sharing experiences** *Brief presentations (12+2 min)* - "Implementation of Long-Read Genomes for SV and Imprinting Disorders", Martin Larsen	Majbritt Busk Madsen, Ksenia Lavrichenko, Gry Asker

	- "Identifying shared DNA methylation abnormalities in mendelian disorders of the epigenetic machinery", Katrin Möller - "Long read sequencing in hereditary cancer", Mev Dominguez Valentin - "From Symptoms to Diagnosis: Detection of Repeat Expansions with Nanopore adaptive sampling", Søren Færgeman, Simon O. Drue and Ebbe N. Bak - "Implementing PacBio sequencing in a clinical setting", Jakob Holm Dalsgaard Thomsen and Inge Søkilde Pedersen	
11:30 – 12:30	Lunch	
12.30 – 13:30	**Long read seq; Clinical applications - sharing experiences** *Brief presentations (12+2 min)* - "Rapid diagnosis of leukemic aberrations using nanopore sequencing", Ida Höijer - "Nanopore Sequencing in Functional Genetics – Experiences and insights two years later", Ulf Birkeland - "Testing different long-read platforms in a clinical setting", Majbritt Busk Madsen - "The clinical utility of whole genome long read sequencing in neonatal hypotonia diagnostics", Hans Matsson	Majbritt Busk Madsen, Ksenia Lavrichenko, Gry Asker
13:30 – 13:55	**Workshop** **Long read seq; Clinical applications - possibilities, limitations and scalability**	Majbritt Busk Madsen, Ksenia Lavrichenko, Gry Asker
13.55 – 14.15	Coffee break and visit at sponsor booths	
14:15 – 14.45	**Data sharing – Experiences from national data sharing of interpreted variants in Norway**	Dag Undlien
14:45 – 15:00	**Summary & farewell, announcement of next WS**	Dag Undlien

About NACG

The Nordic Alliance for Clinical Genomics (NACG) is an independent, non-governmental, not-for-profit Nordic association. 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

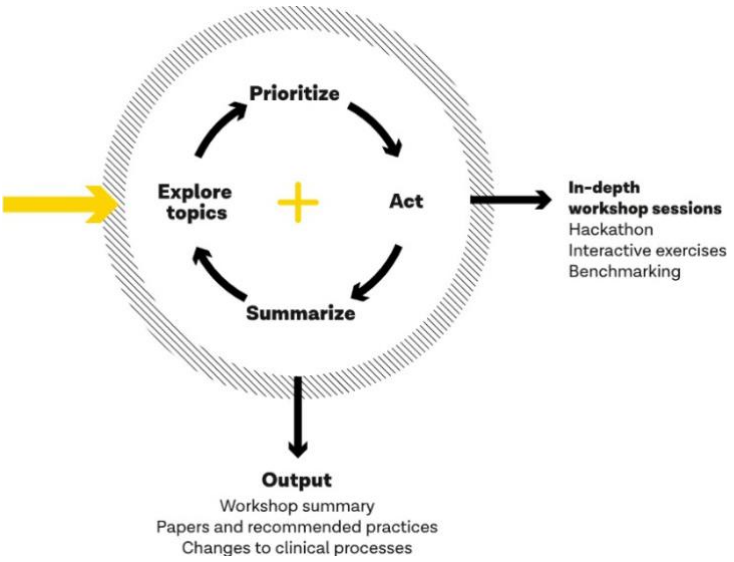
Facilitate the responsible sharing of genomic data, bioinformatics tools, sequencing methods and best practices for interpretation of genomic data.

Enhance quality of genomic data and processes and explore methodologies to provide assurance.

Understand legal barriers to the implementation of personalized medicine and to engage with key stakeholders that influence these barriers

Develop demonstration projects that challenge perceived legal barriers that limit responsible and ethical sharing of genomic and health data.

Build bridges between research and clinical communities, technologies and practices to foster innovation



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