Nordic Alliance for Sequencing and Personalized Medicine

NASPM 5TH CLINICAL WORKSHOP, APRIL 2018

Workshop Summary Report

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Objective:

This report summarizes the 5th clinical workshop of the Nordic Alliance for Sequencing and Personalised Medicine taking place in SciLifeLab's offices, Stockholm, 23.-24. April 2018.

Rev. No.	Date	Reason for Issue	Prepared by	Contact
0	2018-07-02	First issue	Guro Meldre Pedersen Bobbie Nicole Ray Sannerud	Guro.meldre.pedersen@dnvgl.com

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1 EXECUTIVE SUMMARY

This report summarises the 5th workshop of the Nordic Alliance for Sequencing and Personalised Medicine held at SciLifeLab offices in Stockholm, 23.-24. April 2018. The workshop was organised to focus on the main work streams of NASPM as outlined below. The full agenda is available in Appendix 1: Agenda. The workshop gathered participants from Norway, Sweden, Denmark, Finland, Iceland and Germany as detailed in Appendix 2: List of participants.

Table 1-1 Agenda outline

<table>
<tr><th></th><th colspan="2">23. April</th><th colspan="2">24. April</th></tr>
<tr><td rowspan="3">Morning</td><td colspan="2" rowspan="2"></td><td>Development of project applications</td><td>Bioinformatics tools development</td></tr>
<tr><td rowspan="2">Establishing vehicles for sharing</td></tr>
<tr><td colspan="2">Welcome
National updates</td><td></td></tr>
<tr><td></td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td rowspan="3">Afternoon</td><td rowspan="3">Enhancing quality of data and processes</td><td rowspan="3">Bioinformatics tools development</td><td colspan="2">Establishing vehicles for sharing</td></tr>
<tr><td colspan="2">NASPM white paper</td></tr>
<tr><td colspan="2">Planning of next workshop and closing</td></tr>
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Key decisions and conclusions from the two days included:

- NASPM will seek to continue to expand the alliance to include new members, while seeking to maintain the meeting format of interactive workshops.
- NASPM will enter into dialogue with other relevant initiative such as the Nordic Initiative for Personalised Medicine to explore opportunities for collaboration and coordination of activities.
- NASPM partners will collaborate to develop projects and seek appropriate funding to catalyse the alliance's work within identified working group streams. NASPM partners will focus on core interests of the alliance and seek additional partnerships where relevant. The group agreed that NASPM will work to share experiences from the meetings through papers that would reflect shared viewpoints.
- The next NASPM meeting will take place in Copenhagen 20.-21. November.
- The Hackathon session in the Bioinformatics tools development Working Group was highly successful, and the format is likely to be tried again.
- The topic of variant prioritization will need further exploration and follow-up across this and the other working groups.
- The Enhancing Data Quality and Processes Working Group ran a productive in-depth session for improving the quality of clinical reports, as well as two exploratory sessions to gather input for future in-depth sessions on requisitioning and structural variants.

2 ABOUT NASPM

The Nordic Alliance for Sequencing and Personalized Medicine is an independent, non-governmental, not-for-profit, Nordic association. Its mission is to share trustworthy genomics data and technology competence for improved diagnosis and treatment, and to be a resource for research. Following three initial workshops, the inaugural meeting of the alliance took place in Oslo in November 2017 where a transitional steering committee was elected, secretariat appointed and leads for the clinical working groups were identified.

The Nordic Alliance for Sequencing and Personalised Medicine has defined the following goals:

- 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

The NASPM organization is presented in Figure 1 and Tables 2-1, 2-2 and 2-3. NASPM summary reports and presentations shared from the meetings are available for NASPM members through the community SharePoint. The community website is currently under construction.

2.1 NASPM organisation

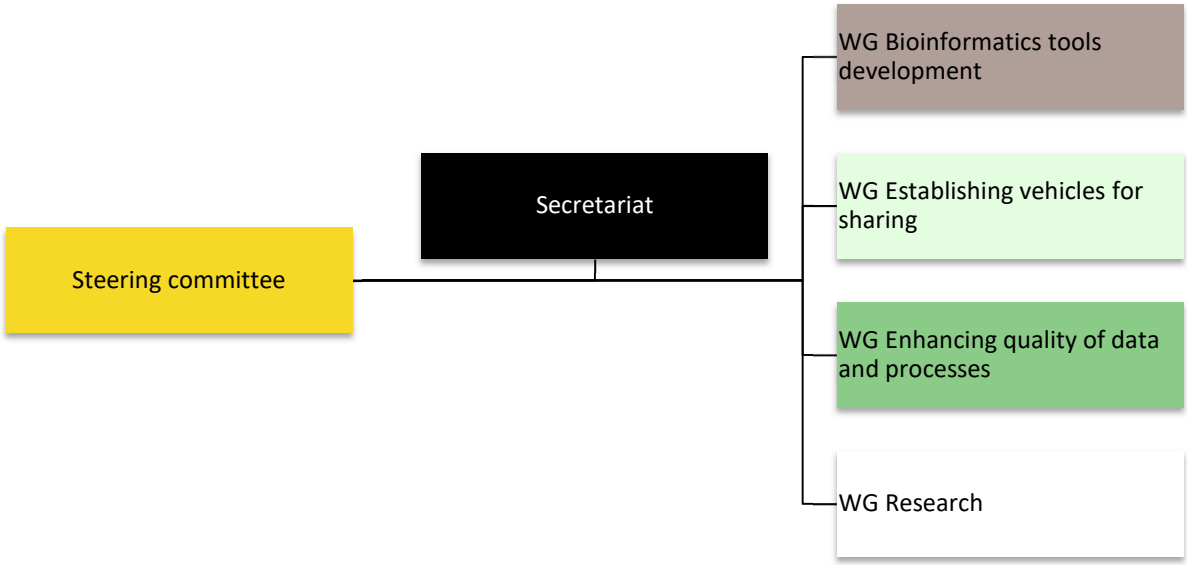

Figure 1 NASPM organization

Table 2-1 Steering Committee members

Role	Name	Affiliation	Country
SC Chair	Dag Undlien	Oslo University Hospital	Norway
SC Vice Chair	Valtteri Wirta	Clinical Genomics facility, SciLifeLab Department of Microbiology, Tumor and Cell biology, Karolinska Institutet School of Chemistry, Biotechnology, and Health, KTH Royal Institute of Technology	Sweden
SC Vice Chair	Karin Wadt / Morten Dunø	Department of Clinical Genetics, Rigshospitalet	Denmark
SC Member	Joakim Lundeberg	SciLifeLab	Sweden
SC Member	Jón Jóhannes Jónsson	Dept. of Genetics and Molecular Medicine, Landspitali - National University Hospital / Dept. of Biochemistry and Molecular Biology, Faculty of Medicine, University of Iceland	Iceland
SC Member	Maria Rossing	Center for Genomic Medicine, Rigshospitalet	Denmark
SC Member	Stephen McAdam	DNV GL	Norway

Table 2-2 Secretariat

Role	Name	Affiliation	Country
Secretariat	Guro Meldre Pedersen Guro.meldre.pedersen@dnvgl.com	DNV GL	Norway

Table 2-3 Working group leaders

Working group	Working group leaders	Affiliation	Country
Bioinformatics tools development	Kjell Petersen / Tony Håndstad	University of Bergen Oslo University Hospital AMG	Norway
Establishing vehicles for sharing	Henrik Stranneheim / Chiara Rasi	SciLifeLab	Sweden
Enhancing quality of data and processes	Sharmini Alagaratnam / Courtney Nadeau	DNV GL	Norway

3 NASPM 5TH CLINICAL GENOMICS DATA SHARING WORKSHOP

The 5th clinical NASPM workshop was kicked off by vice-chair Valtteri Wirta and chair Dag E. Undlien, welcoming the group and setting the stage for the meeting. The group was informed about ongoing processes to develop joint projects between NASPM partners, and to extend the alliance with further partners and potential collaborations with other initiatives. Representatives from Finland were invited to join the steering committee. The group agreed that NASPM will work to share experiences from the meetings through papers that would reflect shared viewpoints.

3.1 Updates on national status and initiatives

To set the stage for the NASPM workshop, representatives from each of the Nordic countries provided updates on recent national developments.

3.1.1 Norway

Dag Undlien, Oslo University Hospital (OUS)

The Norwegian strategy for personalized medicine was released June 2016, and the work on implementation of the national strategy is slowly progressing. The first goal was to establish a national variant database but pace has been limited by legal discussions around defining anonymization. The national guidelines for the use of genomic diagnostic tests are about to be released for comments from interested parties.

BigMed is one of the major project funded by the Norwegian Research Council focussing on precision medicine. In February, the project released the report "Big data management for the precise treatment of three patient groups", providing an overview of the current status in three clinical groups and bottlenecks for the implementation of precision medicine and use of big data analytics in healthcare. The report is available through www.bigmed.no or https://www.dnvgl.com/publications/bigmed-112754.

3.1.2 Denmark

Maria Rossing, Center for Genomic Medicine, Rigshospitalitet

The national strategy for Precision Medicine was released in 2016 by the Government and the Danish Regions. A major task was the establishment of the National Genome Center, funded in the public sector while respecting patient's autonomy. The National Genome Center has been developed to include a patient board, an international advisory board, an ethics board, and a research board with working groups to focus on data sharing, & benchmarking.

The Capital Region of Denmark and Region Zealand have established *"The East Denmark Center for Whole Genome Sequencing"* in Center for Genomic Medicine. Additional lab space required will be located at the Kennedy Center in Glostrup.

Currently, there is a public debate amongst legislation regarding data sharing. Specifically, consent management around genetic testing of which the legislation has put forth that if consent is given, data could be used broadly for research purposes. This has been heavily debated due to concerns of where data is shared. This begs the question to how and if patients should have the option to opt out.

3.1.3 Sweden

Valtteri Wirta, SciLifeLab

Valtteri provided an update on the Genomic Sweden developments. All Swedish regions are in the process of forming Genomic Medicine Centres. Sweden currently has six large universities – this project will link them together and facilitate coordination. Clinical reference groups have been established with

selected technical work groups. The pre-study phase is approaching its end (August 2018) and therefore there is work oriented towards securing additional funding. Key activities include:

- National rare disease pilot on intellectual disabilities, 1000 cases, in planning (no funding yet)
- Large gene panels for cancer (trials, diagnostics) in development
- WGS for all pediatric cancers (15 MSEK, year 1 funded)
- WGS for hematological malignancies retrospective pilot funded (9 MSEK, SciLifeLab) and starting
- National surveillance project for MRSA, microbial WGS
- Formed technical groups to start addressing: 1) national db for variant sharing, 2) national computing and data storage, 3) coordination of bioinformatics
- Scout has been installed in Region Skåne, presented for Västra Götalands Region (Gothenburg), expressions of interest from Region Östergötland (Linköping)
- Work on national informed consent template started (named, work not started yet).
- Legal working group recently established to address expected key challenges

3.1.4 Finland

Janna Saarela, FIMM

There are ongoing changes within the regulatory environment in Finland. The National Genome Strategy has been established and the Biobank act is currently being revised. One of the issues under consideration is opt-out rather than opt-in consent, connected with discussions around secondary usage of register data for academic research and for commercial companies that will have more restrictions.

The National Genome Center will be an administrative entity and competence centre. It is expected that the National Genome Center will not have separate sequencing capacity but rather be supported by sequencing facilitates. HUS and FIMM are setting up a joint clinical genome sequencing unit, which will be operational this year.

The FinnGen project is a collaboration with partners from biobanks, universities, hospitals, hospital districts, healthcare industry and the Finnish Funding Agency of Innovation. Between the FinnGen project and the SISU (Sequencing Initiative SUomi) project, there is an ambition to sequence 500 000 individuals, 10% of the population in Finland. Legacy collections provide 200 000 samples while the 300 000 prospective collections will be collected via biobank with broad consent that enables industry collaboration.

3.1.5 Iceland

Jón J. Jónsson, Dept of Genetics and Molecular Medicine, Landspitali – National University Hospital and Dept. of Biochemistry and Molecular Biology, Faculty of Medicine, University of Iceland

In Iceland, focus is on clinical / variant correlation (interpretation) and application. Genealogy is a focus due to thoughts around its important implications for precision medicine. As a result, work around megapedigrees have been a focus to improve risk assessments, examples on cancer genetic counselling were provided. Relevant publications on genealogy include:

- Stefansdottir V, Johannsson OT, Skirton H, Tryggvadottir L, Tulinius H, Jonsson JJ. The use of genealogy databases for risk assessment in genetic health service: a systematic review. *Journal of Community Genetics*. 2013;4(1):1-7. doi:10.1007/s12687-012-0103-3.
- Stefansdottir V, Johannsson OT, Skirton H, Jonsson JJ. Counsellee's experience of cancer genetic counselling with pedigrees that automatically incorporate genealogical and cancer database

information. *Journal of Community Genetics*. 2016;7(3):229-235. doi:10.1007/s12687-016-0271-7.

- Stefansdottir V, Skirton H, Johannsson OT, Olafsdottir H, Tryggvadottir L, Olafsdottir GH, Jonsson JJ. Clinical impact of using electronically generated megapedigrees in cancer genetic counseling, incorporating Cancer Registry information. Submitted.

Jon expressed a deep concern regarding how GDPR affects genetic services in many ways, especially regarding data of relatives to the patient. The GDPR is strict and does not seem to have taken its effect on clinical genetics into consideration. NASPM should review this situation.

4 WG ENHANCING DATA QUALITY AND PROCESSES

WG lead: Sharmini Alagaratnam / Courtney Nadeau, DNV GL

A workshop was conducted with focus on enhancing quality of data and processes. The group discussed how results from NASPM workshops could be captured and shared with the broader scientific community. It was agreed that it would provide value to document current practices in the labs, to examine relevant external guidelines, and to identify consensus best practices as well as areas where discussions are ongoing. The group agreed that dissemination of these activities via opinion pieces or position papers was valuable, and that it was likely of greater value to limit discussions to a subset of topics rather than addressing many topics in less depth.

4.1 Clinical reporting

Session lead: Sharmini Alagaratnam / Courtney Nadeau, DNV GL, Eidi Nafstad, OUS AMG and Maria Rossing, Rigshospitalet

There are widely differing practices around the clinical reporting of genetic analysis. Group discussions were organized to map out similarities and differences, and the more challenging aspects of reporting. Examples of real world sample reports were evaluated, before a summary of guidelines for reporting of germline sequence variants was presented.

4.1.1 Step 1: Mapping of information categories

Groups were asked to list information categories to be included in clinical reporting and tag them as "must have", "nice to have" or "challenges". Groups were also asked to provide information that should be excluded. The discussions are summarized in Table 4-1 and Table 4-2.

Table 4-1 Summary of group discussions on clinical reporting of genetic analysis

Category	Group 1	Group 2	Group 3	Group 4
Must have	- Indication - Sample type - Patient ID - Referring physician - Date of report - Author(s) with department affiliation - Technical description - Genes analysed - Aberrations analysed - Description of technical limitations - HGNC gene name (HGVS nomenclature, protein translation) - Genomic coordinates, transcript, genome build - Classification - Implications of the results - Comment on validation confirmation - How inheritance is reported - Statement on genetic counselling	- Title – type of analysis - Requesting source, Patient ID, Indication, clinical information - Sample detail - Results (table) - Evaluation of result - Conclusion result - Signature (electronic, paper), date, contact information In the back - Method sequencing - Quality, coverage - Software - Human Genome reference - In the method; if no class 4/5 variants, data recommended re-analysed from FASTQ in 3 years' time. - ACMG gene list for secondary findings - Short disclaimer - Family studies, co-segregation	- Easy to understand, not too much text - Reason for referral - Interpretation – short explanation with references - Results (HGVS, cDNA + reference transcript.) - Brief method description ○ Platform / kit limitations - Statistics / QC / coverage	- Summary - Indication (HPO, XRAY?) - Result and interpretation - Recommendation - Method (caveats) - Transcript – genome build
Nice to have	- Phenotypes detailed HPO - ACMG - (Some) evidence basis for classification	- Ethnicity - Colour coding - Recommendation e.g. genetic counselling + follow-up	- Include genes / gene sets - Results / interpretation (ACMG codes & criteria) - Family studies – co-segregation	- Detailed phenotype (HPO, …) - Quality report - interactive?
Exclude			- "Text-book" information - Non-treatable / low-penetrant / VUS / incidental finding - Exclude "vague" VUS and reanalyse the data in 3 years	- Speculations (limit at least) - Pages 2-15 (too lengthy reports)

Table 4-2 Summary of group discussions on clinical reporting of genetic analysis - challenges

Category	Group 1	Group 2	Group 3	Group 4
Challenges	- No agreement that genomic coordinates should be reported.	- VUS	- No findings - AR carrier - Avoid unnecessary clinical follow-up - Inform about possibility for reanalysis … or not? What time window?	- Phenotype uncertainty - Liability and limitations (panel, method description, positive inclusion, non-exclusion mentioned) - Consent information, actionable results - VUS (Subjectivity, Classification of medical use) - Data delivered to patient - Incidental findings ("medically relevant" – who should decide?)

4.1.2 Step 2: Evaluation of real world sample reports

The groups were presented with seven clinical reports from various sources, which had all consented to sharing. Building on the discussions from group work step 1, the groups evaluated the reports to identify positive and negative aspects of the different reports. Following the evaluations, the groups each presented one preferred and one least favourite report, and discussed the rationale.

Table 4-3 Discussion – best and worst practices

Organization	Positive aspects	Negative aspects
A	- Conclusion (great!) clear and stated at start of report. - Good flow: Good info to start (very interpretable) and info becomes more technical towards in, so patient can choose to continue. - Explanation of class scale (if you are to include it, this is a nice format)	
B	- Tables - Good flow¨ - Clear indication of results	- Small font - *In silico* interpretation - Start with methods (not good start)
C	- Disclaimer section - Good flow: starts with conclusion and latter part is not something clinician would focus on - Gene panels available upon request (good statement)	- Disclaimer to heavy - RNA analysis not included
D		
E	- Good flow «short & sweet»	
F		- «Conclusion» does not reflect a proper conclusion.
G		- Conclusion section: difficult to locate and poorly placed at the end of report.

As a practical exercise, groups were also tasked with interpreting a report within a one minute timespan, similar to what physicians are required to do in clinical practice. No group successfully completed the task. The key findings were non-comprehensible by experts under conditions that are standard for physicians in practice, and indicate that work remains to be done on current reports.

4.1.3 Summary of guidelines for reporting of germline sequence variants

Courtney Nadeau / Oleg Agafonov, DNV GL

A summary of guidelines regarding the reporting of germline sequence variants (Figure 1) in the context of rare disease was presented as the basis for further discussions on reporting. Guidelines were drawn from a set of >400 recommendations issued by 21 sources by restricting the analysis to only recommendations regarding reporting and consolidating overlapping guidelines.

In summary, these guidelines discuss the importance of the initial impression of the report and the importance of promoting clinician understanding, items which should be included or excluded, tools and ontologies for standardization, how to report quality control and assay validity, and issues surrounding secondary findings.

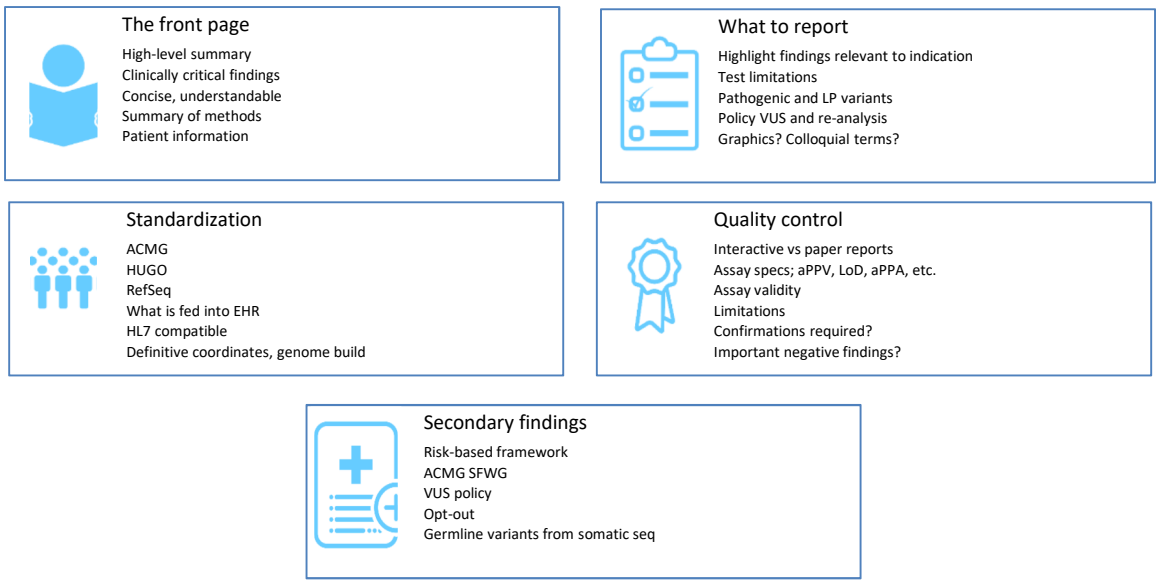

Figure 2 Summary of guidelines for reporting of germline sequence variants

4.1.4 Clinical reporting – summary of discussion

A plenary discussion between the workshop members took place following the group discussions and the summary of guidelines for reporting of germline sequence variants.

The group identified the following **possible follow-up actions**:

- Benchmarking of reports, with focus on content, structure and on formulations.
- Developing reporting requirements through a bottom-up process, involving end users of the reports in developing and testing.

- A broader range of stakeholders could be involved through questionnaires to ensure input from a larger and more diverse group, and learnings could be reported and presented at the November NASPM meeting.

One of the challenges identified was **the reporting of secondary findings and variants of unknown significance (VUS)**, and the group discussed pros and cons of different practices. In some departments, these are not reported, while for example the UK practice is to report VUSes in named genes and state "no follow up" with justification. Arguments not to report VUS include that clinicians and patients may misinterpret the findings. For some laboratories, there is limited graphical freedom in the reporting format to include additional information (such as VUSes) in a format that underlines that this is supplementary information.

The groups discussed the option of doing a risk assessment around reporting of incidental findings, for example using a bow tie risk assessment approach. This approach focuses on the location for the risk description, working backwards to identify risk prevention (barrier management) and risk mitigation (controls). One example case could be to explore how a clinician would interpret a given report in 30 sec and what action would she/he take.

4.2 Requisitioning

Nicole Lesko, Karolinska University Hospital

Following a short introduction to requisitioning, a discussion was prompted by posing the following questions to the workshop participants:

- How much clinical information comes in with samples for genetic analysis?
- Does anybody have a special referral form?
- Is anybody using HPO terms?
- How much follow up work is required in order to gather all necessary clinical information?

Experiences shared are summarized in Table 4-4. Workshop participants were then divided into groups to discuss ideal referrals moving forwards as summarized in Table 4-5.

Table 4-4 How much clinical information comes in with samples for genetic analysis?

Finland	Rigshospitalet	OUS	Karolinska	Iceland
Complex genotype will include a clinical analysis to look at combining phenotype info. HPOs are not used.	Requesting doctor will provide clinical information. The lab has access to EMR.	Particularly important with larger panels[1]. Requisitions include HPO list on the back. Need better information	For larger panels, interpretation is done with a physician with appropriate medical background. HPO searches are used. The lab has access to EMR.	Simple tests (e.g., factor 5) is conducted regardless of clinical information. More complicated tests require clinical information and sometime EHR review and clinical genetic consultation. HPO terms are not used as they are too cumbersome.

The plenary discussion identified that a main barrier to using HPO terms is that they are in English and not yet translated to local languages. Very few requisitions include HPO terms if any information at all. It was also pointed out that clinicians, with a very limited time available, in most cases will only be able to describe the problem rather that order a specific test. The lab should therefore be able to

[1] A quick discussion clarified that the group had different views on what was considered to constitute a larger panel; some indicated that a larger panel would include more than 25 genes, other 100 genes or more.

contact the referring physician to suggest tests that were not indicated on the requisitioning form or confirm actual needed test.

OUS AMG gave the group a brief orientation about the work taking place in the BigMed consortium, where they are collaborating with DIPS to create functionalities for requisitioning including automation of patient information inclusion. The University of Oslo will be working to develop a wizard that will assist the requisitioning doctor to provide relevant information using HPO terms through questions and suggestions.

Examples of German practices were mentioned and will be shared with the group, where they focus on clear phenotype description as this is a prerequisite for insurance payment. Requisitioning is strictly regulated with a national commission drawing up guidelines.

Table 4-5 Future ideal referrals

	What would we ideally like on a perfect referral?	**How can we ensure that we get the information that we need? What tools can we use?**
Group 1	• We want to know the previous diagnosis and the context in which it was found. • Level of consent (can we reuse data/ findings) • Ethnicity consanguinity • Phenotypical information as detailed as possible, standardized and free text.	• How: • Procedure- Requisition in conjunction with patient. • Useful to have a guided HPO fill-in form to find out what is useful. • Electronic simple requisition.
Group 2	• Would like to have HPO terms but not in too much depth. • EHR requisition form with drilled down phenotypes • consanguinity • Family disposition	• How: • Results of other biochemical tests • Patient anamnesis
Group 3	• Family history (consanguinity, ethnicity) • Pictures (X-Rays) • A section with specific features that are rarer; instead of just an overall description	• How: • Interactive tools that are easier than free text (patientarchive.org) • Patient archive approach • Clinician is led through a decision tree that does not involve hand writing. • Force inclusion of structured phenotype req.
Group 4	• Referring clinician name • Family history • Relevant structure (clinical information)	• How: • Not accept hand written requisitions. • Fill out requisition with the patient in the journal to avoid writing twice (more intermediate solution)

Suggestions for further work included a session on show & tell of requisitioning forms from different labs.

4.3 Structural variants benchmarking

Daniel Nilsson, Karolinska Institutet

The goal of this session was to design and agree on a suitable SV benchmarking exercise to be run before the November 2018 NASPM workshop. Daniel facilitated a discussion around the following perspectives:

- Review of NASPM SV pipelines
- Datasets & tools available for benchmarking
- Scope: what (data, SVs), how (comparison tools), and when

The labs presented on the topic of how the clinical implementation of structural variant analysis is being considered, as summarized in Table 4-6.

The discussions around the calling of structural variants for clinical implementation generated the following actions:

- NASPM participants would like references from Courtney and Oleg.
- NASPM participants concluded that at this time, although there is interest, due to lack of readiness of pipelines from the individual laboratories, it is too early to set up a structural variant benchmarking activity; however, requirements can for setting this up can be discussed. Participants agreed that at the next workshop, this question should be proposed again.
    - Germany: interest, but no resources
    - Finland: interest, but not ready yet, limited resources
    - Denmark (Maria): interest, work in process, November good fit. Interested in validation sets.
    - SciLifeLab: happy to participate; will share the code

Table 4-6 Structural variants – clinical approaches

Finland (HUS)	Denmark (Righospitalet)	Norway (OUS AMG)	Sweden (Karolinska)	Iceland (Landspitali)	Germany (University Hospitals Schleswig-Holstein)
aCGH used for SV CNV from WES with known caveats, also as bonus not clinical service If found SV is validated before reporting RNAseq for fusion genes Interested in CNV from WGS but no decided timeline Validate with SNParray 10X in early exploratory stages	Call CNVs from exomes then validate using SNP arrays Setting up pipeline to call SVs from WGS, so far not validated for clinical use Still exploratory	Calling CNVs on exomes but only as a bonus, not standard Working on setting up a pipeline for calling from WGS, not currently standard Lab doing MLPA and aCGH for cancer Exome and target sequencing current Looking to phase out aCGH and replace with WGS	Calling SVs for all WGS. Interpreted clinically for all but the largest panels and on strong suspicion. Interpreted in all analysis as "compounds" with SNVs. Final stages of prospective study of >100 patients comparing aCGH and WGS for ID-panel (>1000 genes) screening. Retrospective studies with 100+ samples finished with perfect recall on CNVs, but ~90% on balanced events. Research use for 400+ cases in total (A Lindstrand et al). 1000 SweGen genomes called and made available for population background (J Eisfeldt). Method development TIDDIT, SVDB, FindSV. Validation of findings by Sanger (inversions, translocations and some small CNVs), MLPA, aCGH. Occasional FISH (complex duplication). Screening is by aCGH, and MLPA for where WGS is not indicated. WGS for hematology with fusion detection on urgent cases. RNAseq in early stages of development. STR detection from WGS for a panel of clinical loci. Small pilot finished ok. Not yet in general use.	aCGH done routinely otherwise not much SV work. Considering using Saphir instrument from Bionano Geomics and 10X genomics sequencing.	MLPA in clinical setting SNParray in research setting No resources to set up SV pipelines from WES/WGS in immediate future

5 WG VEHICLES FOR SHARING

WG lead: Henrik Stranneheim (not present) / Chiara Rasi, SciLifeLab

5.1 Beacon

Chiara Rasi, SciLifeLab

To align with continued efforts in sharing experiences regarding the set-up of Beacon for capturing opportunities for improvement, Chiara Rasi from SciLifeLab presented an overview and updates of the use of Beacon at SciLifeLab. A Beacon is a public data discovery web service containing a network of servers made possible to upload variants with the support to upload of gene panels. The following highlights were presented:

- Clinical Genomics Beacon (cgbeacon) is based on the Elixir Beacon (GA4GH partner).
- The deployment of Beacon requires MySQL 5.7 and Java Maven
- Open access requires two tables: datasets and variants
- Its simplest implementation does not include variant frequency sharing
- Risk mitigation planning and implementation is related to privacy issues especially around the sharing of the phenotypes.
- Beacon is set up to be GDPR compliant:
    - Pseudonymisation
    - Genetic data is personal data, but rules against re-identification attempts are enforced (sharing only gene panels and filtering out bad quality variants)
    - Data can be removed at any moment.

With regards to future planning at SciLifeLab, the target is to increase the number of cases in Beacon (100 in 2018); there is an ambition to switch to API.04 for its support around structural variants; would like to include variant frequency data with a possibility for registered access; and implement controlled access. To locate all available beacons, visit: beacon-network.org.

5.1.1 Lighting a Beacon: Implementation and Security

Tor Solli-Nowlan, AMG OUS

Tor reviewed three options for the implementation of Beacon;

1. Use an existing implementation
    a. ELIXIR - Java - https://github.com/ga4gh-beacon/beacon-elixir
    b. UCSC - Python - https://github.com/maximilianh/ucscBeacon
2. Write your own
    a. See published API spec: https://app.swaggerhub.com/apis/ELIXIR-Finland/ga-4_gh_beacon_api_specification/0.4.0
3. Use a hosted service
    a. DNAstack?

Implementation with Java and Python were compared. Java was described as robust but compared to Python, had less advantages. Modifications to Python are available that prevent the leaking of personalized data. This entails functionalities related to working tests along the CI pipeline by allele

frequency and minimum observations; integrated Dockerfile; makefile based controls with testing, docker container management, local server deployment, and digital ocean deployment; and lastly, VCF filtering by region.

For Beacon, security concerns are around the phenotype identification, unauthorized dataset access (outside of the cloud access, but if in the data is de-personalized), and sample re-identification (N=65, 250 queries to re-identify). Mitigations to the side effects were reviewed, these were: Restrict shared information, share only regions of interest, share only variants with at least X observations, and to lie.

5.1.2 Beacon – discussion

Chiara Rasi, SciLifeLab

An introduction to Beacons for genetic data sharing, general tips to avoid problems when you design your data sharing system, available software and the experience at Clinical Genomics, SciLifeLab Stockholm, Sweden was shared.

Workshop participants were divided into groups and participated in a discussion around Beacon implementation and security threats. Results of the discussions were presented in a plenary session and divided around the following categories for must have, challenges, nice to have, and mitigating actions related to implementation and improvement of Beacon.

Table 5-1 Implementation and improvement of Beacon

Must Have	Challenges	Nice to have	Mitigating Actions
• Variant of interest (or small list of suspicious)	• Legal • Interpretations • A strong example to how the Beacons can solve the case • Build request if there is a matching ¨ • Genealogy & risk to re-identification – Identifying relatives (searching for a lost relative – via match)	• Search by gene or region, rather than variant.	• Require a medical license to make a query • Good example of value • Web portal with login to trusted institutions • Layered access

5.2 Trusted Variant eXchange, TVX

Sharmini Alagaratnam, DNV GL

Sharmini Alagaratnam, DNV GL, gave first a brief introduction on the Trusted Variant eXchange (TVX) for the new NASPM participants, giving background for both the BigMed project and its genomic data sharing work package, of which TVX is a deliverable. She described the solution conceptually, and demonstrated features through a prototype front-end. The solution aims mainly to facilitate sharing of classified variants with their accompanying evidence between trusted partners, who maintain ownership and access control over their data. A functional solution is ready, and is in the process of being integrated with DNV GL's data platform Veracity. This allows leveraging of many modules and services, including authentication protocols, API implementation and data containers.

The architecture is in the process of being finalized, but looks to implement blob storage and APIs for submission of variant classifications from the individual labs. The classifications are then pulled into a Cosmos database for aggregation, querying and discordance identification. The resulting workflows are also being defined in detail and will determine the final implementation of the features of interest, followed by pilot user testing. Advanced feature development is also continuing.

Finally, there was a discussion around the legal clarification of anonymity of variant classifications, where indications from discussions with the legal department at OUS are that until further clarification on anonymity of variants are in place, filtering out of any observations of five or less would be a satisfactory privacy-ensuring measure. Valtteri Wirta (SciLife) felt that such a measure would strongly diminish the value of the solution, and recommended that no such measure be implemented. Additionally, he pushed for inclusion of phenotypic data which is crucial for effective clinic implementation. Tony Håndstad (OUS AMG) stressed the opinion that variant classifications were not linked to individuals, such that TVX is considered a knowledge base, containing professional opinions about the level of pathogenicity of a particular variant.

Concrete actions were proposed to further the legal clarification process, specifically proposing TVX as a concrete example for privacy evaluation in Sweden. A number of documents detailing TVX at different levels of depth has been developed in conjunction with the legal clarification process in Norway, and can be made available for use for a similar process in Sweden. Finally, a risk assessment for TVX is being planned, to enable identification, comparison and evaluation of the various potential risks posed by the creation of this data sharing solution, as well as mitigating actions. Kjell Petersen (Univ of Bergen, Elixir Norway) confirmed the necessity of performing as well as documenting the risk assessment process for attaining compliance with GDPR for non-anonymous data.

5.3 ClinVar

Chiara Rasi, SciLifeLab

Chiara introduced ClinVar, a free public database that connects genetic variants to phenotypes. It includes data from many sources (with 80% coming from clinical labs). Two Scout (SciLifeLab tool) interconnected functionalities are the ACMG classification tool and the ClinVar semi-automatic variant submission tool. The ACMG classification tool allows Scout users to classify variants according to the ACMG criteria (doi: 10.1038/gim.2015.30). The tool has an interface that mirrors the evidence framework from the ACMG document and the multiple-choice options allow to flexibly assign a variant to one of the five official classification groups (Pathogenic, Likely pathogenic, Benign, Likely benign, Uncertain pathogenicity). The ClinVar submission tool is a functionality that will be released in the next release of Scout and its aim is to simplify the sharing of classified variants according to the criteria described above. It collects the available information on Scout both at the case level and the variant level, to create comma separated files that can be used for the submission of one or more variants to the ClinVar genotype-phenotype association database (https://www.ncbi.nlm.nih.gov/ClinVar/).

5.4 PanelApp

Daniel Nilsson, SciLifeLab

Daniel Nilsson from SciLifeLab, presented an introduction to PanelApp and facilitated a discussion with workshop participants around the management of *in silico* gene panels. Daniel reported that there is expected to be many panels with opportunity to more gene discovery, resulting in an annual demotion of the old. As it was noted lone clinical experts (and bioinformaticians) tend to tire a little after the first few versions. Daniel provide a demonstration of PanelApp, specifically for its function around *gene searching*. The question was then posed to workshop participants, "how do you currently manage in silico gene panels?" Workshop participants were divided into groups and presented results of this discussion as it pertained to the management of Silico Panels (tools, APIs, Trusted Sources) into the following categories: Not Public and Public (Table 5-2).

Daniel facilitated a discussion around the criteria of trust regarding the inclusion of genes on a panel. An exercise was conducted in which workshop participants were asked to identify the criteria needed

to trust a crowdsourced gene panel without extensive internal review. Workshop participants were divided into groups and mapped information from *Nice to have* to *Very Critical* related to Own, Crowd Sourced, and combined gene panels. Results of the discussion were presented in a plenary session and consolidated.

Table 5-2 Tools for managing in silico gene panels

Not public	Public
Scout Excel Word Manual text files Excel sheets with version included in name PanelApp Text curated (inheritans, phenotypes, inclusion criteria) GIT (versioning, pipeline) Other clinical labs Internal R&D Meetings Publications DDD-List – to try follow updates	PDF (website, genetikkportalen.no, homepage)

Table 5-3 Trust criteria for inclusion of genes on a panel

Criticality	Nice to have	Intermediate	Very critical
Own panels			• Disease causing with defined phenotype
Crowd sourced panels			• We would not accept crowdsourced panels • Trust /transparent with expert review • Explorative (include all suggested genes)
Both panels		• Published • >2 independent families (w/ extensive evidence) • Functional / family studies • Diagnostic panel (document why gene is in)	• Scientific evidence • Green status • Commercial Panel • Segregation • Independent findings

Workshop participants were positive to the exercise and suggested that the next NASPM meeting focus on a discussion related to the sharing of gene panels. It was concluded that in principal, all NASPM stakeholders currently have mechanisms that allow the sharing of their panels; therefore, we can consider a way of which we can harmonize the panels.

6 WG BIOINFORMATICS TOOL DEVELOPMENT

WG lead: Kjell Petersen, UiB / Tony Håndstad, OUS AMG

6.1 MultiQC/ MegaQC intro and hackathon

Phil Ewels, SciLifeLab

Phil introduced MultiQC (http://multiqc.info/), a bioinformatic tool which aggregates results from bioinformatics analysis across many samples into a single report. A hackathon was arranged to adapt the MultiQC tool to local pipelines and develop MegaQC into a tool suitable for trend analysis and possibly continuous benchmarking.

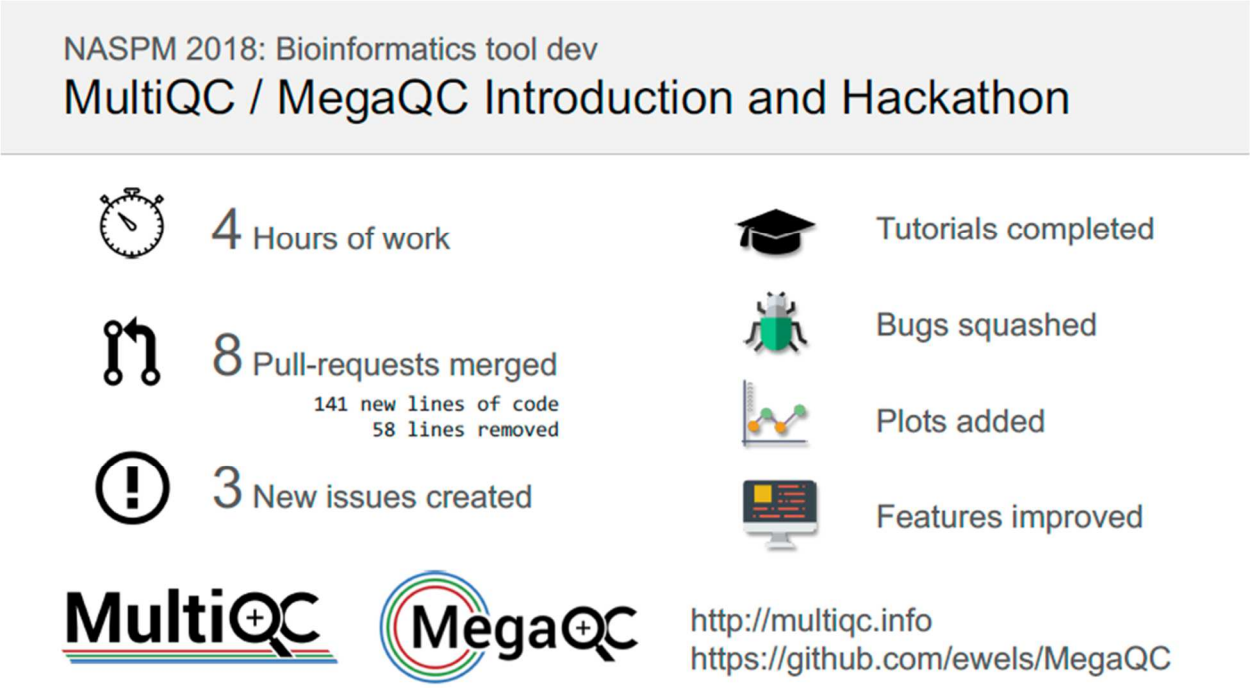

Figure 3 Summary of MultiQC / MegaQC hackathon achievements

6.2 Variant prioritization

Tony Håndstad, OUS AMG

Variant prioritization is described as the process of ranking variants observed in an individual genome on the basis of factors such as the predicted consequence of each variant and the observed frequency in a population. Approaches to prioritization include using annotation and reference data to prioritize individual variants, using genotype data (also from other samples) to prioritize genes, and using phenotype/knowledge-driven gene prioritization.

Annotation prioritization includes:

- Variant Effect Predictors: (VEP, SnpEff, etc.)
- Phylogenetic/ protein conservation: (SIFT, polyphen-2, MutationTaster)
- Allele population frequency, statistical gene/region-wide constraint models, haploinsufficiency regions: (ExAC, RVIS, etc)
- Integrative/Machine learning methods: (CADD, fitCons)

Tony pointed out that gene prioritization tools use information such as variant allele frequencies, genotype frequencies, inheritance models, family histories and patient phenotypes to identify and prioritize likely damaged genes associated with a phenotype, as opposed to simply identifying potentially damaging variants. To use this effectively, it must be integrated in the workflow. Some free and open source tools are also being published and/ or worked on such as:

- Phenopolis integrates some variant prioritsation methods into a web-based interface
- seqr from Broad Institute
- GEMINI

Scout; however, has for some time now included HPO support and variant ranking and OUS AMS is currently working to add a similar functionality to Ella. Tony highlighted that the future of gene prioritization will entail integrative approaches, not linear filtering approaches.

6.2.1 Filtering strategy in Ella

Eidi Nafstad, OUS AMG

Eidi Nafstad from OUS AMG reported on the filtering strategy in Ella. Ella has three auto filters that are applied in the following order:

1) Frequency (> 0.5% in genes with phenotypes with only autosomal dominant inheritance (source OMIM); > 1.0% in all other genes; gnomAD populations >5000 total alleles; custom frequency cutoffs can be set for specific genes or gene panels)
2) Intron (outside exons and the consensus exonic splice sites [-20, +6] in all available RefSeq-transcripts)
3) UTR (VEP CSQ annotation with 3_prime_UTR_variant/5_prime_UTR_variant as the worst consequence in all available RefSeq-transcripts)

Eidi reviewed possible additional auto filtering /sorting that may be introduced in Ella. They will be useful, especially in large gene panels, but details must be discussed more in detail and agreed on before implementation. This included the following:

- «3hetAR» if the variant meets all the following criteria:
  - heterozygous
  - in a gene with phenotypes with only autosomal recessive inheritance (source OMIM)
  - only variant (not already filtered out by frequency, intron and UTR filter) observed in that gene
  - not LOF (loss of function VEP CSQ annotation)
  - not in HGMD and/or ClinVar (depending on status, details need to be discussed)
- Synonymous if the variant meets all the following criteria:
  - benign splice prediction (which tools, needs to be discussed)
  - not in HGMD and/or ClinVar (depending on status, details need to be discussed)

6.2.2 Prioritization of genetic variants in immune exomes

Rasmus Lykke Marvig, Rigshospitalet, Center for Genomic Medicine

At Rigshospitalet, the prioritization of genetic variant in immune exomes requires different discrete filtering steps that can be applied to narrow down the search for candidate disease-causing genetic

variants. For determining the pathogenic variant, the variant filters: effect on protein sequence, conservations of encoded amino acid, gene function, model of inheritance, and frequency. This can be conducted by the *ingenuity variant analysis*, a disease causing variant locator by searching scientific literature and indexing all known disease-causing biological processes. An example was provided using a singleton exome that typically contains 10 variants after filtering. Rasmus concluded with alternatives to variant filtration, these are: Vcfanno, SnpSift, SnpEff, and VCFtools.

Discussion around this topic proposed the following questions: How do you document what you did for the patient (i.e., you missed this variant two years ago). Answer to this was unknown but it was noted that the order of variants can change.

6.2.3 Variant Prioritization at Clinical Genomics, SciLifeLab

Chiara Rasi, SciLifeLab

Chiara introduced the Mutation Identification pipeline (MIP[2]) and GENMOD[3] software used at SciLifeLab. The MIP pipeline was developed by Clinical Genomics, SciLifeLab, and takes care of all the steps required for the analysis of whole exome and whole genome sequencing data. GENMOD is another in-house developed software and takes care of the prioritisation of variants from the MIP pipeline. GENMOD includes a weighted sum rank model to rank single nucleotide variants as well as structural variants to identify the more likely pathogenic variants.

GENMOD calculates ranking scores by taking into account factors such as variant frequencies on public and local databases, computed inheritance models (calculated by GENMOD), protein functional prediction and conservation.

6.2.4 Discussion on prioritizing of variants

Tony and Eidi from OUS AMG facilitated a discussion with workshop participants around the topic of variant prioritization. Workshop participants divided into five groups to answer a set of three questions:

- When is prioritization necessary?
- What are the most important challenges and what should be the strategy to improve current practice?
- How do we structure future NASPM work in this area?

The results of the discussions were presented in a plenary session with workshop members as summarized in tables below.

Table 6-1 Summary of group discussion - When is prioritization necessary?[4]

Group 1	Group 2	Group 3	Group 4	Group 5
Poorly represented ethnicity (African) Singletons & large gene panels WGS	Prioritization for gene panels for more than 100 genes, with use of hard filtering Always use ranking regardless of the size of the gene panel	Small gene panels you look at everything but find a number / boundary for larger gene panels.	Ranking is necessary for larger gene panels Ranking necessary by tool or Manna	Large data set will always be prioritized

[2] https://github.com/Clinical-Genomics/MIP

[3] http://moonso.github.io/genmod/

[4] «large panels» were not consistently defined among workshop participants, from >25 genes to >100 genes

Table 6-2 Summary of group discussion - What are the most important challenges and what should be the strategy to improve current practice?

Group 1	Group 2	Group 3	Group 4	Group 5
Consistency with ACMG guidelines Disease made CLOG / misuse gene False negatives Transparency and traceability	Standardization across tools and groups Missing phenotype annotation to make an informed analysis	Lack of harmonized models Liability (related to false negatives)	Lack of good clinical databases Genomes and diseases are different	Ranking by inheritance model Challenge related to ranking vs filtering Trust and transparency of the ranking system

Table 6-3 Summary of group discussion - How do we structure future NASPM work in this area?

Group 1	Group 2	Group 3	Group 4	Group 5
Another workshop to find out what we agree on List of good resources Benchmarking Agree on minimum criteria	Have more time to discuss at the next meetings Establish a sub-group to work on this	Develop a method for prioritization and rankings. (how high was the ranked variant, look at real data). How well is your method with your dataset?	Define and scope sub-areas to focus on	Develop a common understanding of definitions

It was agreed amongst workshop participants that NASPM should develop a focus group on this topic to further decide how to bring this topic forward in the next session. The following workshop members volunteered to start this process: Morten Eike and Chiara Rasi.

7 NASPM PAPER DEVELOPMENT

Courtney Nadeau, DNV GL

Courtney Nadeau from DNV GL facilitated a discussion with workshop participants with the goal of gathering input to a NASPM paper. It has been agreed that the NASPM paper should focus on issues around quality within the clinical pipeline, more specifically zoom in on a specific step within the clinical pipeline that can be more carefully examined for addressing its issues around quality to generate solutions. Workshop participants were issued five votes each to vote on where in the clinical pipeline had the most critical issues related to quality. Participants could place all their votes on one step or spread out. As displayed in Table 7-1, results of the voting exercise indicated *Prioritising and Interpretation* as the area within the clinical pipeline presenting the most issues in terms of quality.

Table 7-1 Prioritising of key topics

Topic	Votes
Prioritizing and interpretation	44
Reporting	40
Variant calling	17
Legal	17
Test requisitioning	15
Primary data analysis	9
Sample prep & sequencing	6
Regulatory	3

Workshop participants were then divided into groups where they answered the following questions for *Prioritising and Interpretation* within the clinical pipeline*:*

1. What are the main issues;
2. What are you doing about it; and
3. What would be useful to mitigate.

Discussion outcomes are summarized in Table 7-2.

Table 7-2 Summary of group discussion on quality issues related to prioritizing and interpretation

	What are the main issues?	What are you doing about it?	What would be useful to mitigate?
Group 1: Iceland, Finland and Bergen	Mixed group with varying practices and issues.		
Group 2: Rigshospitalet	Pathogenic first, optimize - Ranking - Filtering We want the most relevant variant at of the list, how do we get there?	Run trio	Optimize functions
Group 3: Karolinska	Today we are missing - Splice - Intronic - Intergenic - Regulation - GOF missense	RNASeq Databases RNA studies Synonymous variants RNAseq Building Data Base for causative variants	We are learning a lot and are more critical to data More critical to the data and analyse them in a different way
Group 4: SciLifeLab I	Lack of standardization due to variable amount and type of input samples, type of analysis etc.		Improving the documentation on how results were obtained would make it easier for others to understand pipelines and standards adopted at each facility.
Group 5: SciLifeLab II	Lack of standardization in how variants are prioritized due to inconsistencies around interpretation guidelines (SOPs, annotation sources, lack of standards) Risk of misunderstanding of guidelines due to expertise, for example some have experience with neuromuscular disorders whereas some do not.		Conduct a NASPM workshop for closer examination and funnel results into a NASPM paper.
Group 6: OUS AMG I	Reproducibility between analysts	Improve procedures and software (version control)	Variant classification database
Group 7: OUS AMG II	Secure structured phenotype description to guide prioritizing. Feedback; did the findings fit the phenotype? Sharing of variant interpretations	BigMed: electronic requisitioning Testing tools for HPO phenotypes (like Phenotips)	Sharing of interpretations

8 NASPM – NEXT STEPS

8.1 Next meeting

The next NASPM meeting will take place in Copenhagen 20.-21. November 2018.

8.2 Expansion of collaboration

NASPM workshop participants agreed that the collaboration should seek to expand the collaboration to include interested parties, and coordinate / collaborate with other Nordic initiatives where relevant, while maintaining the format of the workshops. The Steering Committee will follow up on this to discuss with stakeholders and develop communication channels and inclusion mechanisms.

8.3 Collaborative projects

The Steering Committee will take lead to develop project applications and seek appropriate funding for NASPM relevant topics such as quality improvement, data sharing, standardization and secondary use of data.

8.4 Open items – input to planning of further activities

As a closing exercise, the group reviewed and complemented open items and identified opportunities for further collaborations identified throughout the workshop, before placing votes on most interesting topics in the individual work streams as summarized in the tables below.

Table 8-1 General topics

Topic	Votes
GDPR and sharing of variants - Invite experts - Share experiences from the first 6 months	19
Usage of data from other patients including family. Consent from family members?	3
Genealogy	1
GDPR & Informed consent (e.g. for ClinVar submissions)	1
Expansion of NASPM collaboration (Nordic Precision Medicine Initiative, other clinical labs, clinical vs research	1

Table 8-2 Tools – hot topics

Topic	Votes
Benchmarking SV – prioritizing and interpretation	18
Share 2-5 VCFs + phenotype → do interpretation (proficiency testing / standardization)	16
Bioinformatics reproducibility & workflows	15
Structural variants - CNV annotation filtering, notation - experiences	13
User friendly tools for curation and annotation	2

Table 8-3 Vehicles for sharing – hot topics

Topic	Votes
Process for evaluation & update of panels → description; develop best practice for panels	7
Agree on minimum prioritization criteria	1
Define and scope sub-areas within variant prioritizing – establish network subgroup (Chiara, Måns, Morten E)	1
Benchmarking - Feedback like: the solved cases did have a high priority of variants	
List of good resources	
Ranking model from Finland - presentation	
#submission (ClinVar, Beacon, etc.)	

Table 8-4 Enhancing quality – hot topics

Topic	Votes
Reporting exercise and comparison	8
Long term trends / monitoring	8
New ways of viusalizing results	7
Risk Assessment / Risk based framework for secondary findings / report bowtie (examples)	4
Position Paper / Opinion Piece - Status today - Identify consequences & non-consensus	2
Lab infrastructure (LIMS) etc	1
Show & tell of requistion forms from different labs	
Cutoff small /large Panel: 100 genes	
Micheal sends examples of german requistion	
MTA template for NASPM Miceal to share	
Exchange SV pipeline code (SWE -> Dev)	
Statements, opinions, etc. pre-guidelines	

APPENDIX 1: AGENDA

Agenda Monday 23. April 2018

Time	General	Enhancing data quality and processes *WG lead: Sharmini Alagaratnam / Courtney Nadeau, DNV GL*	Vehicles for sharing *WG lead: Henrik Stranneheim / Chiara Rasi, SciLifeLab*	Bioinformatics tool development *WG lead: Kjell Petersen, UiB / Tony Håndstad, OUS AMG*
11	Welcome National updates			
12	Lunch			
13		Clinical reporting		MultiQC/ MegaQC intro and hackathon
14				
15				
16		Requisitioning		
17		Structural		Buffer

Agenda Tuesday 24. April 2018

Time	General	Enhancing data quality and processes *WG lead: Sharmini Alagaratnam / Courtney Nadeau, DNV GL*	Vehicles for sharing *WG lead: Henrik Stranneheim / Chiara Rasi, SciLifeLab*	Bioinformatics tool development *WG lead: Kjell Petersen, UiB / Tony Håndstad, OUS AMG*
9	**NASPM SC:** Project application development			Variant annotation and prioritisation
10				
11			Beacon	
12	Lunch			
13			TVX	
			ClinVar	
14			PanelApp	
15	NASPM paper			
16	Planning of next workshop and closing			

APPENDIX 2: LIST OF PARTICIPANTS

Country	Organisation	Department	First name	Last name
Denmark	Rigshospitalet, Copenhagen University Hospital	Center for Genomic Medicine	Maria	Rossing
			Rasmus	Marvig
			Savvas	Kinalis
		Department of Clinical Genetics	Karin	Wadt
			Mads	Bak
			Morten	Dunø
Finland	HUSLAB	Laboratory of Genetics	Emma	Andersson
			Kaisa	Kettunen
	University of Helsinki	FIMM	Janna	Saarela
			Henrikki	Almusa
Germany	Christian-Albrechts-Universität zu Kiel, University Hospitals Schleswig-Holstein	Institute of Clinical Molecular Biology	Michael	Forster
Iceland	Landspitali - University Hospital	Department of Genetics and Molecular Medicine	Eirikur	Briem
			Jon J:	Jonsson
Norway	DNV GL	Digital Solutions	Stephen	McAdam
		GTR Life Sciences	Bobbie	Ray-Sannerud
			Courtney	Nadeau
			Guro Meldre	Pedersen
			Oleg	Agafonov
			Sharmini	Alagaratnam
Norway	Oslo University Hospital	Department of Medical Genetics	Eidi	Nafstad
			Hugues	Fontenelle
			Morten	Eike
			Dag	Undlien
			Tony	Håndstad
			Øyvind	Evju
			Tor	Solli-Nowlan
			Lars	Retterstøl
Norway	University of Bergen, Elixir Norway	Department of Informatics	Kjell	Petersen
Sweden	Karolinska University Hospital	CMMS	Nicole	Lesko
		Department of Clinical Genetics	Kristina Lagerstedt	Robinson
			Daniel	Nilsson
Sweden	SciLifeLab		Hassan	Foroughi
			Kenny	Billiau
			Maya	Brandi
			Patrik	Grenfeldt
		Clinical Genomics	Chiara	Rasi
			Valtteri	Wirta
		National Genomics Infrastructure	Maxime	Garcia
			Orlando	Contreras
			Philip	Ewels
			Remi-André	Olsen