Research Core Unit Genomics (RCUG)

Terms and Conditions

1) Submission of sample information in the „Submission form"

Please completely fill out our "submission form" and send the completed form by email to rcu.genomics@mh-hannover.de before handing over the samples. This is a prerequisite for processing either DNA or RNA samples. The current version of the form can be downloaded from our homepage (www.mh-hannover.de/genomics-submission-form.html).

2) Handing over DNA and RNA samples

Upon receiving the samples described in the submission form we perform quality control, microarray analysis or sequencing according to standardized protocols, depending on the project requirements.

a) DNA samples

For sequencing of the genome, exome, metagenome or methylome you should give us preferably 3 µg of genomic DNA per sample in a volume of less than 150 µl. For smaller amounts of DNA (> 1 ng) or other sequencing projects, we ask for a consultation, since the realization of such projects with project-related adjustments is usually also possible. In the case of methylome sequencing, the sample is subjected to bisulfite conversion.

b) RNA samples

For sequencing of the transcriptome or microarray analyzes, we should optimally be supplied with 1 µg total RNA per sample with a concentration of at least 100 ng/µl.

If only lower yields (or concentrations) are achievable, the required amount of DNA or RNA can be reduced to as low as 1 ng by using alternative protocols (assuming sufficient quality and, depending on the selected technology platform).

3) Recommendations for the purification of DNA and RNA

a) DNA sequencing

For DNA isolation, we recommend a phenol/chloroform extraction according to 'Current Protocols in Molecular Biology' (www.mh-hannover.de/genomics-methods.html). By agreement, alternative purification methods (kits) can be used, but usually result in a lower yield and poorer DNA quality. Isolation by means of magnetic beads is preferred to isolation by using columns.

b) RNA sequencing or microarray analyses

For RNA isolation we recommend the RNeasy Micro Kit (Qiagen, # 74004) or, if the option is kept open to analyze small RNA species (eg microRNAs) from the respective approaches, the mirVANA miRNA Isolation Kit (Life Technologies/Ambion, AM1560). Even if only small RNAs are to be analyzed (small RNA sequencing), the mirVANA kit should follow the protocol variant for the isolation of total RNA including small RNAs, not the variant which focuses solely on small RNAs.

4) Dealing with insufficient or limited quality of the starting material

If the quality of the sample material is insufficient or limited, users will be informed immediately. If it is foreseeable on the part of RCUG that the quality of the input material is not sufficient for the project, replacement is usually requested from the user. If this is not available, the continuation of the project can either be rejected by the RCUG or a modified framework can be defined in a discussion. Should the RCUG come to the conclusion during the quality control of incoming samples or at the initial project meeting that there are methodologically significant risks for a successful implementation of the project, these projects are classified as 'high-risk projects'. Such projects require an additional written confirmation and full assumption of responsibility by the client.

5) Initial consultation on experimental design

To define a specific experimental design (suitable application, technology platform, sequencing parameters, selection of suitable controls, ...), we offer a consultation to explain the advantages and disadvantages and to identify solutions to potential difficulties in the generation or processing of the sample material.

6) Standard technology platforms

Sequencing is generally performed on Illumina equipment (NextSeq500 or MiSeq). Depending on the question and concrete agreement, sequencing can also be performed on an Ion Torrent (Thermo Fisher Scientific), on a Sequel (Pacific Biosciences, now part of Illumina), or a MinIon (Oxford Nanopore Technologies).

7) Commissioning of external sequencing companies or cooperating core units

In case of high RCUG device utilization, particular issues, specific device requirements, or at the client's specific request, orders may be placed with external sequencing companies or cooperating core units. In this case, the time frame for the completion of the analyses depends on the commissioned partner, the corresponding costs are calculated separately and the procedure is agreed with the client prior to commissioning.

8) Applicable kits for library generation and sequencing

For library production, RCUG offers a range of standard applications. For the sequencing all 'catalog kits' of the manufacturers of the respective sequencing platforms are available. If kits and required methods deviate from these standards and new procedures have to be established or required reagents are not permanently in stock, conditions and prices must be individually agreed.

9) Notes on the number of samples per sequencing run

The standard kits from Illumina allow for the analysis of multiple samples (multiplexing) per sequencing run. The number of multiplexed DNAs or RNAs is determined together with the client (point 4). This number depends on the selected sequencing method (genome, exome, methylome, transcriptome, metagenome) as well as the targeted quality of the sequence data (sequencing depth, coverage). We attempt to offer sequencing as cost-effective as possible! However, this also means that your order has to be processed together with samples of another project if the number of samples is too low. In this case, no precise time frame for implementation can be set or guaranteed. Alternatively, it can be agreed to carry out incompletely utilized sequencing runs and bill them (at a correspondingly higher cost), so that no extended waiting period arises.

Furthermore, specialized kits or kits with short shelf life or (e.g., target enrichment and exome kits) cannot be proportionally billed to users, so consulting with RCUG is strongly advised to minimize costs before project start.

10) Notes on the number of samples per microarray study

The standard microarray slides from Agilent contain 4 (or 8) separate microarrays. These microarrays cannot be processed individually. Therefore, samples for 4 (or 8) arrays or a multiple must be put together in total for the analysis. For the single-channel system this means 4 (8, 12, 16, ...) single samples, for the two-channel system 4 (8, 12, 16, ...) pairs of samples to be compared. If a non-4 (or 8) -dividable number of arrays are to be hybridized, then we can not specify or guarantee a precise timeframe for the execution, since in this case we wait until we receive samples from other projects to be able to fully load the slides (4 or 8 arrays). Alternatively it can be agreed to calculate remaining arrays with their material cost.

11) Pricing a usage quota for commercial transcriptomics analysis software

The calculated prices for transcriptome analyses (microarrays, RNA-Seq) include costs for commercial data analysis software. For clients of such products, therefore, a principal claim results for free use of the provided software (OmicsExplorer, GeneSpring, IPA), as far as this is consistent with the claims of all other clients. This claim applies in any case and for any software until the expiration of the current one-year license. If the programs are also acquired by the RCUG in the following year (which is currently planned), the acquired right of use shall apply no later than 1 year after the transfer of the transcriptomics data.

12) Order of order acceptance and processing

Incoming project requests are usually processed in chronological order of commissioning, but exceptions are made to maintain practicability and efficiency (preference for small projects, collection of samples for the same protocol procedures, etc). If due to high utilization deadlines (see point 13) are extended, clients will be informed immediately.

13) Time frame for the completion of the analyses

After receiving all the necessary information (see point 1) and, if necessary, carrying out the initial quality control, the data will be completed within the following deadlines:

Sequencing and microarray data are usually completed and handed over within a maximum of 6 weeks (for exceptions see points 7 & 8). Pure quality controls of DNA or RNA (without a subsequently commissioned study) are carried out within a maximum of 2 weeks and the results are handed over. When ordering pure

quality controls (DNA or RNA) using more than two complete bioanalyzer chips (i.e. more than 22 or 24 samples), the processing time is a maximum of 4 weeks.

14) Processing of the raw data

The raw data is processed using appropriate standardized analysis pipelines. In DNA sequencing, the alignment of the fastq files, the variant calling and the annotation of the variants found are carried out. In the case of RNA sequencing, after the alignment of the fastq files, a quantification of the normalized read counts on gene level takes place. In addition, the extent of statistically significant mRNA expression differences is determined and presented for clarity in Excel files. Final filtering of the obtained data records takes place based on quality standards and, depending on the question, annotation-based. Other filtering strategies, such as so-called trio analyses in comparative genetics are possible by separate agreement. In addition, *de novo* assembly approaches can be requested if sufficient personnel and compute capacities are available. If necessary, resulting contigs can also be annotated automatically. Furthermore, the RCUG can assist with base calling, alignment, and the search for structural variations in Oxford Nanopore data.

Microarray raw data are processed and transferred to the internally developed RCUTAS (Research Core Unit Transcriptomics Analysis System) Excel-based analysis software. RCUTAS contains the most important values and quality parameters in clear tabular formats and allows the execution of sorting, filtering, visualization and initial analysis processes.

15) Provision of complete data

The data described in point 14 (fastq, bam, vcf, csv, and xlsx files) are provided on a hard disk, via an SFTP connection, or MHH internally via a network drive (share), if necessary also in encrypted form. If desired, the data (bam, vcf) can also be presented via our central genome browser JBrowse, if necessary with password protection.

16) Consultation on generated data formats

After handover of the data, we offer a detailed consultation on the generated data formats, which, however, does not replace a substantiated analysis of the data from the user side.

17) Exclusion of final data analysis with regards to content

A further, in-depth, content-related analysis of the generated sequence data is not included in this agreement. Depending on the order situation and capacity, however, we offer consultations and help on all topics relating to the planning, analysis, visualization and publication of the generated data.

18) Quality standards and warranty

We guarantee a high technical quality of the data according to international standards. Analyses that have significant technical impairments will, at our discretion, either be repeated free of charge or not charged. An exception to this are the so-called "high-risk projects" (see point 4). In the sequencing of libraries that have been created by the client (ready to load libraries), the responsibility lies entirely with the client. If such experiments fail, the RCUG will in no case assume any costs or carry out free repetitions.

19) Citation and publication

In cases where our service is limited to pure data generation according to our standard pipelines, we do not claim co-authorship. In the case of a publication of the data, we ask for a mention in the "acknowledgment" according to the following wording:

"Sequencing data used or referred to in this publication were generated by the Research Core Unit Genomics (RCUG) at Hannover Medical School."

"Microarray data used or referred to in this publication were generated by the Research Core Unit Genomics (RCUG) at Hannover Medical School."

If it becomes clear that the contribution of our employees to a study goes beyond our offered standards and a substantial contribution to the research project is made, we endeavor to contact the client in a timely manner. Thus, a justified claim to co-authorship (genuine scientific cooperation) can be agreed early and by mutual agreement with the client.
Regarding the question of which type of participation represents a "genuine scientific cooperation" or justifies a co-authorship, we refer to the relevant recommendations of the Deutsche Forschungsgemeinschaft and the respective journals.

20) MHH internal prices, commissioning and cost accounting

The MHH internal prices of our NGS standard products can be estimated using the interactive Excel spreadsheets available on our homepage. An overview with current microarray prices is also available on our homepage. Please note that the final prices offered by us may differ from the information described above and that only the final offered prices are binding. Personnel costs are explicitly not included in MHH internals. The cost accounting takes place via the 'Interne Leistungsverrechnung' (ILV). After receiving the respective order and handing over the generated data, we will instruct the accounting department. Accounting is guaranteed to be made during the financial year, unless the fund in question is closed or generally closed at a time prior to the official MHH accounting closure. Accounts (or funds) to be debited must be managed by the MHH, otherwise conditions and prices for external orders apply.

21) MHH external prices, commissioning and cost accounting

The prices for MHH external clients are based on a full cost calculation. The corresponding prices will be calculated on specific request. The external billing is initiated by sending an invoice by post. All relevant information and transfer data are included on the invoice.

22) Discount indications for external orders

With regard to the following indications, discounts may be granted to external clients, the amount of which may be agreed individually depending on the situation:

a) A minimum scope of sequencing is achieved, which is requested and accounted as a whole (no subsequent summation over the year possible).
b) For the study in question any (standardly included) advice given by RCUG staff is explicitly waived (eg advice on study design, discussion of results, advice on final analysis and presentation options).

c) A scientific co-operation is agreed, which on the one hand requires and presupposes a significant contribution to content and on the other hand a corresponding consideration of RCUG employees as co-authors in publications.

d) The client finances the investigation through a third-party funded research project, which is part of a collaborative project (eg SFB) administered and requested at the MHH.

23) Handling of personal data and research data

Personal data that are collected in the course of commissioning services from RCUG (Incidents, Projects) will not be passed on to persons outside the RCUG. However, the RCUG reserves the right to create and present overview images for the purpose of MHH-internal events as well as for proof of performance to present to the university president, the senate, the research committee or other important MHH-internal committees. Such presentations may contain the entirety of the over a certain period of time performed services, broken down according to individual work groups and PIs or departments (only applies to MHH-internal assignments).

Corresponding presentations or overviews can also be linked by the RCUG on its own homepage, but then with access restriction to the group of people with MHH domain ID.

The research data generated in the course of the commissioning of the RCUG or the research data transmitted by the commissioner to the RCUG for this purpose remain the property of the commissioner, are processed and viewed exclusively by the employees of the RCUG and are not passed on to third parties without the express consent of the commissioner.

24) Storage of personal data and research data

Personal data and research data will be stored after collection by the RCUG for as long as this is necessary for the fulfillment of the purpose (processing and completion of the Incident) and, at the discretion of the RCUG, for ensuring appropriate subsequent traceability of all essential work and communication processes in connection with the performed service.

Existing retention obligations and periods are observed. However, the RCUG points out that the responsibility for the long-term archiving of research data in accordance with the guidelines of good scientific practice (which are generated in the course of commissioning the RCUG), as required by the DFG and third-party funders, lies solely with the commissioning project management.

The Research Core Units at the MHH follow the recommendations of the European Science Foundation for the operation of equipment centers.

Responsible for the content:
Oliver Dittrich-Breiholz
Head of Research Core Unit Genomics

Project requests:

Genomics

Dr. rer. nat. Lutz Wiehlmann
Building I10, level H0, room 7060
Phone: +49 (0)511-532 5334
E-mail: Wiehlmann.Lutz@mh-hannover.de

Transcriptomics

Dr. rer. nat. Oliver Dittrich-Breiholz
Building I3, level 1, room 1304
Phone: +49 (0)511-532 5814
E-mail: Dittrich.Oliver@mh-hannover.de

Homepage:	www.mh-hannover.de/genomics.html
Incident form:	www.mhh.de/genomics/kontakt/rcug-incident
Order form:	www.mhh.de/genomics/kontakt/rcug-project-order
E-Mail:	rcu.genomics@mh-hannover.de