Results: Almost half of the CNVs was classified as random noise based on the underlying SNP intensities. Moreover, comparing the position of parents and children in the distribution revealed false negative calls in parents resulting in *de novo* CNVs that were actually inherited.
Conclusions: The proposed *in silico* validation approach allows rapid detection of many false positive CNV calls smaller than 100 kb, which could thus be excluded from labor intensive and expensive experimental validation approaches. Ongoing research will validate included and excluded CNVs by qPCR to determine the sensitivity and specificity of the method.

P14.096
Checking the experts: compliance with author instructions regarding HGVS nomenclature and variant submission to databases in genetics and genomics journals

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Introduction: Several genetics and genomics journals list requirements for use of HGVS nomenclature and/or submission of variants and phenotype information to public databases in their author instructions. The rationale is to improve the quality of variant descriptions in manuscripts and access to variant information in databases. We have investigated the January 2016 issue of several journals to determine how effective this is.
Materials and Methods: We used the list of genetics and genomics journals created by the Human Variome Project (HVP) (See http://www.human-variomeproject.org/resources/genetics-and-genomics-journals.html). A group of students has checked the publications first for the basic requirements: mentions of the reference sequence used to describe variants and the presence of the variants in public databases. The next step was to check variant and phenotype descriptions with specific attention for predicted protein effects.
Results: Authors include statements suggesting variants have been submitted to databases, but the variants were not found or phenotypic information was missing. Often, predicted protein effects in publications cannot be verified in case of altered splice sites without supporting RNA-level evidence or in case of insertions of unspecified nucleotides. Lack of supporting evidence complicates the assessment of disease-causing effects for diagnostic use.
Conclusions: In multiple cases, information missing in the publication was specified in public databases, indicating that submission of variants to databases prior to manuscript acceptance might improve the quality of publications. Reviewers and journal editors could help improving manuscript quality by enforcing the existing guidelines and insisting on compliance by authors prior to acceptance of manuscripts.

P14.097
Robustness of next generation sequencing-based preimplantation genetic screening (PGS) of chromosome aneuploidies from various cell types with a very low amount of template DNA

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Introduction: Reliable chromosome aneuploidy detection in a single cell or from very limited amounts of template DNA is a prerequisite for preimplantation genetic screening (PGS) of chromosome aneuploidies. The aim of the study was to assess the minimum amount of DNA in terms of diagnostic robustness and time to diagnosis in next generation sequencing-based (NGS) PGS.
Materials and Methods: Single oocytes, polar bodies, blastomeres, trophoectoderm, somatic ovarian cells, cultured choriocytes / amniocytes and isolated DNA were used to assess the diagnostic reliability of whole genome amplification (WGA; SurePlex), followed by the VeriSeq NGS assays (Illumina; USA). Single sperm were examined using a modified WGA protocol (PMID: 23565289).
Results: All samples with known karyotype were accurately replicated by our diagnostic approach. Novel findings, previous undetected, were confirmed by MLPA and/or array CGH. During the course of the study we detected a broad variety of aneuploidies, one chaotic embryo and one error in second meiotic division. The ability to detect mosaicism was assessed by artificially mixing DNA derived from blood or cultured choriocytes / amniocytes with known chromosomal constitution. We are able to detect mosaicism in aberrant cells down to 40%, while lower mosaicism could be due to WGA/NGS artifacts.
Conclusions: The utilised NGS-based assay is robust and reliable for routine detection of aneuploidies in clinical PGS in DNA derived from various single cell types and is able to unambiguously detect eventual mosaicism.

P14.098
Whole Exome NGS at the Geneva Genome Clinic: Example of successful translation to diagnostics through a multidisciplinary team

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The advances of next generation sequencing (NGS) technologies enable their application in clinical care. However, there are several significant challenges for their implementation in clinical diagnostics.
In Geneva, we use whole exome sequencing (WES) followed by targeted bioinformatics analysis of individual gene panels for the diagnosis of Mendelian disorders and we have created a multidisciplinary working group, the Genome Clinic Task Force which meets once a week. During these meetings, clinical cases and results are presented, the class of variant pathogenicity is debated and the final laboratory reports are critically discussed. Reimbursement and ethical issues such as informed consent, disclosure of incidental findings and/or variants of unknown clinical significance (VUS) are also addressed. In Switzerland, reimbursement of diagnostic NGS tests is integrated in the public health insurance since January 2015.
During the pilot year 2015, a total of 144 cases (41 with developmental delay (DD) and 103 with various other mendelian diseases (VDM)) were analyzed. We found pathogenic variants (class 4 or 5) in 27% of patients with DD and in 41% with VDM; the average detection rate of (likely) causative variants was 37 %. The decision to report VUS was made on an individual case basis.
In order to render our diagnostic use of NGS even more efficient and patient-friendly, our current aims are to 1) improve different steps of the workflow in order to accelerate the analysis process 2) continuously update the variant interpretation methods 3) continuously learn from the challenges we encounter during the genetic counseling sessions.

P14.099
Dual genetic diagnosis as a valuable feature of whole exome sequencing

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Introduction: When establishing a molecular diagnosis, we usually search for a single genetic variant which clarify the full phenotypic spectrum of the patient. However, many patients present with complex clinical features not allowing the clinician to make a clinical diagnosis. In these cases with unusual and blended clinical presentations whole exome sequencing (WES) is especially useful.
Results: Here we report 21 families for whom whole exome sequencing provided a clear dual genetic diagnosis. These cases presented with a broader or atypical phenotype that could not be explained by the finding of one unique variant.
In 5 of these families, the diagnoses were based on pathogenic/likely pathogenic variant for both disorders. The rest received a molecular diagnosis based on a pathogenic/likely pathogenic variant, and a second probable diagnosis based on a variant of unknown significance, with significant supportive evidence. These diagnoses are likely due to high compatibility of the gene-related disease with the clinical details and the mode of inheritance provided by the clinicians. Some relevant examples of dual diagnoses were spastic tetraplegia and intellectual disability (*SLC1A4* and *HNRNPU*) as well as Donohue syndrome and immunodeficiency type 28 (*INSR* and *IFNGR2*). Other cases included: cerebellar ataxia - deafness, distal hereditary motor neuronopathy type VI - atypical Krabbe disease and primary microcephaly type 3 - Leber congenital amaurosis.
Conclusion: WES allows complete and dual diagnostic analysis and a better dissection of gene specific phenotypic characteristics positioning WES as a first line diagnostic tool.

P14.100
Clinical sequencing: WGS is the better WES

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Introduction: Current clinical next-generation sequencing makes use of gene panels and exome analysis, both of which involve selective capturing of target regions. However, capturing has limitations in sufficiently covering coding exons, especially GC-rich regions. Materials and Methods: We compared whole exome sequencing (WES, SureSelect Human All Exon v5+UTR) with the most recent PCR-free whole genome sequencing (WGS, Illumina TruSeq) for five female samples. We assessed the proportion of completely and sufficiently covered (>13×) RefSeq coding exons. Thereby we analyzed (i) the entire exome and subsets of clinically relevant exons, i.e. (ii) genes recommended by the American College of Medical Genetics or (iii) exons with mutations recorded in the Human Gene Mutation Database.
Results: PCR-free WGS appears to be insensitive to GC content and is thus able to provide hitherto unprecedented complete coverage of the coding region of the genome. Although the average read depth was less than half (65× in WGS vs. 154× in WES), the proportion of completely and sufficiently covered coding exons was significantly higher in PCR-free WGS for all analyzed set of exons.
Conclusions: The advantage of WGS does not only include the potential of identifying non-coding pathogenic variation but, in view of its more homogenous and complete exomic coverage, WGS is the better WES, thereby outweighing the higher costs. Thus, from a clinical/technical point of view capturing is no longer necessary for the most comprehensive genomic testing of Mendelian disorders.

P14.101

Whole genome amplification effect on segmental copy-number changes and copy-number neutral loss of heterozygosity analysis by oligonucleotide-based array comparative genomic hybridization

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Introduction: Whole genome amplification (WGA) is an approach designed to overcome small amounts of DNA for genome-wide genetic tests. Various strategies of WGA have been developed; however, none of them can guarantee the absence of amplification bias.
Materials and methods: A total of 4 multiple displacement amplification (MDA)-based and 2 PCR-based WGA kits were compared in their effect on segmental copy-number (CN) changes and copy-number neutral loss of heterozygosity (cnnLOH) detection by 3 microarray platforms: CGH/4×44K (Agilent), CGH+SNP/4×180K (Agilent) and CGH+SNP/4×180K (OGT). Genomic imbalances-rich cell line U266 was used as material.
Results: The main outcomes are as follows: 1) MDA-based WGAs showed higher tendency to generate false positive imbalances in contrast to PCR-based WGAs with higher risk of false negativity; 2) the specific risk of false positivity and/or negativity increased with decreasing CN segments size; 3) single-cell WGAs showed significantly worse effect on results in comparison to WGAs with nanogram level of DNA as input; 4) PCR-based WGAs were incompatible with cnnLOH analysis based on SNP in restriction digestion sites and also showed higher risk of cnnLOH false negativity when combined with analysis based on simple hybridization. Detailed data of each point are presented.
Conclusions: The results of this study help to choose WGA according to individual user requirements and options. Moreover, we have shown a strategy to verify and validate segmental CN changes detection by DNA array protocol including any WGA for any purpose to attain the highest efficiency without an unnecessary WGA bias. Supported by MHCZ-DRO (FNBr-65269705).

P14.102

Whole-genome sequencing based strategy for diagnostics of rare inherited diseases - a collaboration between the academia and the Swedish healthcare

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Clinical Genomics at Science for Life Laboratory is a research infrastructure providing access to clinical-grade (ISO 17025) sequencing services. Our vision is to support precision medicine initiatives in the Swedish healthcare by providing a cutting edge infrastructure for clinical-grade NGS work, and through multi-year collaborative projects to prospectively demonstrate the utility of NGS-based tests. The infrastructure includes automated strategies for preparation of samples for sequencing on HiSeq X, HiSeq 2500 or MiSeq systems. Data analysis is carried out using primarily in-house developed software solutions.
Focus has been on establishing diagnostic strategies for rare inherited diseases. Briefly, exome or whole-genome sequencing is followed by identification and annotation of variants, followed by ranking based on expected pathogenicity. Variants associated with a pre-defined list of genes relevant for the specific disorder are reported.
During the last 24 months we have processed >1100 samples (700 cases) with suspected inborn errors of metabolism, skeletal dysplasia, primary immunodeficiency, unknown syndromes, and neuromuscular disorders. During the last six months a transition to whole-genome sequencing has been carried out and currently 40 to 100 samples are analysed monthly. The median turnaround time was 15 days in 2015. The impact has been dramatic with life-changing therapies initiated and several novel disease genes being identified. This collaboration has allowed clinical labs both with and without in-depth NGS and bioinformatic knowhow to implement WGS-based testing in routine settings.
We present a detailed description of the setup and the successful collaboration between the academia and the healthcare system.

P14.103

Is FISH and conventional chromosome analysis essential in genomic array era?

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Introduction: Whole-genome chromosomal microarray is recommended as a first-tier clinical diagnostic test in cases of intellectual disability and/or multiple congenital anomalies. In the era of genomic arrays, a role for conventional karyotyping and FISH is widely discussed.
Results: High-resolution genome-wide array analysis using Affimetrix Cytoscan™ HD array platform was applied in 28 probands with abnormal phenotype. In each case genome imbalance was detected. FISH for every microarray results was performed not to confirm rather a visualization of the abnormal chromosomes. Double segmental imbalances was detected in 17 cases (61%) and in 15 of them a typical microarray pattern for an unbalanced translocation was shown. Parenatal carriers of reciprocal translocations were estimated by targeted FISH or conventional karyotyping. In two cases a gain and loss were located on the same chromosome and non-recurrent inv dup del (10q) and (5p) have been identified by targeted FISH and mBAND. Single segmental imbalances (or loss either gain) was detected in 11 cases (39%) and confirmed by targeted FISH in 9 cases. In one case a 8,7-Mb loss in 15q11.2q13.3 was revealed to be unbalanced translocation due to adjacent-2 malsegregation of paternal translocation (13;15)(q11.1;q13.3). In case, although microarray testing revealed a loss of entire chromosome , FISH combined with chromosome analysis diagnosed mosaicism 45,X/46,X,psu idic(X)(p11.2)/46,X,r(X)(p11.2q13).
Conclusions: FISH evaluation revealed more complex rearrangements than suspected based on the array results. The value of genome imbalance structure by FISH and conventional karyotyping is essential for identifying the type and origin of chromosomal rearrangement, providing accurate genetic counseling.

P14.104

Standardizing the quality control of any DNA isolation to safeguard the success of genetic testing

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Genetic tests become ever more powerful, yet also more complex and costly, which is why it is prudent to include quality control steps throughout the preparation process to ensure the quality of the downstream data obtained. To make an informed go/no go decision and avoid analytical failures, a good assessment of the yield and purity of DNA/RNA isolations is essential, including the detection of carry-over constituents that may interfere with downstream tests. Here, we validate a novel approach for DNA quality assessment using a large DNA sample set derived from a variety of human tissues combined with a wide scale of extraction methods. This new QC tool employs the micro-volume spectroscopy on the Xpose™ 'Touch & Go' reader by Trinean combined with its spectral content profiling software to specifically quantify the isolated DNA as well as the amount of contaminating constituents in the sample contributing to the measured UV/Vis spectra.