

GENYSIS: a novel core facility for clinical at the evaluation of research genomic sequence



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Introduction

Over multiple research studies, our group has developed expertise, infrastructure and protocols, and reporting of clinically-relevant variants from research-derived genetic data





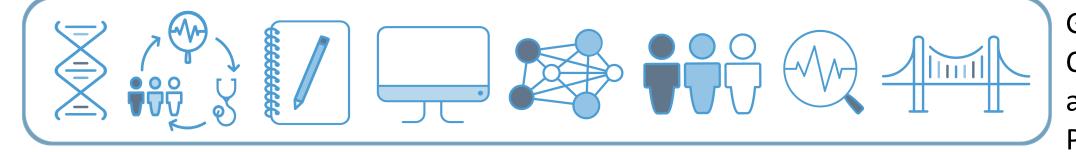
- Genetic data are increasingly incorporated into research studies by investigators whose primary expertise is outside the domain of clinical variant classification
- The Clinical GENomic AnalySIS (GENYSIS) core facility was formed to disseminate the ability to incorporate analysis and return of these results to such studies

Clinical Genomic Analysis as a Research Service

- GENYSIS uses a "research recharge center" model
- The fee-for-use model enables investigators to budget based on number of participants and expected yield of returnable findings, rather than budgeting for effort for key individuals
- We encourage study investigators to participate in the multidisciplinary conference where their cases are discussed
- Initial service rates were based on costs from historical studies and anticipated demand-rates will be reviewed annually
- Diagnostic and/or secondary findings may be returned to research participants and/or the health record, depending on study design and participant consent
- We envision that this model could be useful for development of similar services in other institutions

Ongoing Research and Development Projects

- Evaluation of study protocols and consent forms that include return of clinically-reportable results of genome-scale sequencing. We plan to produce recommended language to include as part of study documents
- Incorporation of short-read and long-read-based techniques to detect and classify copy-number and structural variants
- Development of techniques for investigators to communicate structured information about participant phenotype to incorporate in our analyses



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med.unc.edu/genysis





Post-Test Services

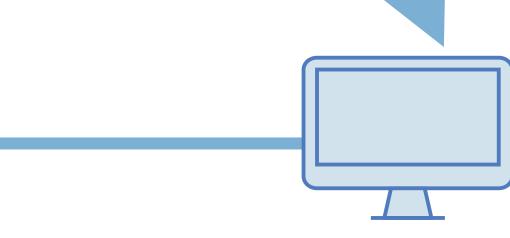
We can assist the study with disclosure of results. Depending on expertise on the study team, this may involve:

- Collaboration to prepare educational materials
- Consultation between GENYSIS genetic counselor (GC) and a study investigator who will disclose results
- Contracting with GENYSIS GC for initial results disclosure and identification of appropriate clinical follow-up.

Consultation and Project Advising

We provide initial and ongoing consultative services to investigators regarding incorporation of clinicallyrelevant genetic data in their human subjects research:

- Advice for **study protocols** and consent documents
- Estimation of **expected yield** of diagnostic, uncertain and secondary findings
- Advising of plan for production of raw sequence data



Bioinformatics

Using reproducible bioinformatic pipelines (bitbucket.org/genysis-unc) we provide:

- Alignment of sequence data
- Variant calling
- Annotation with evidence used for clinical classification



Clinical Reporting

For results determined to be reportable:

- Classification under current ACMG/AMP guidelines
- Confirmation by orthogonal technique (e.g., Sanger sequencing) in UNC Molecular Genetics Laboratory (MGL)
- Clinical report generated by MGL. Depending on study design and consent, this can be placed into the medical record (for UNCHealth patients, into the local Epic instance)



Variant Analysis

Correlation of participant phenotype and analysis of called variants:

- Initial review by core facility staff under supervision of the facility director
- Candidates for reporting are discussed at multidisciplinary conference with member expertise in Clinical Genetics, Laboratory Genetics and Genomics/Molecular Pathology and Genetic Counseling
- Study investigators are encouraged to participate in this conference!

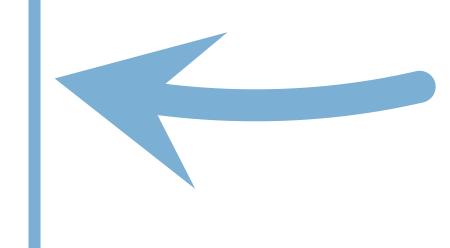


Figure: Workflow in the GENYSIS core facility. All analysis takes place for research participants in studies with appropriate consent and approval by Institutional Review Board (IRB). We focus on the analysis of these data for clinical relevance and do not duplicate services provided by other core facilities at our institution: the Biospecimen Processing (BSP) and High Throughput Sequencing Facility (HTSF) can be used for DNA extraction and production of primary sequencing data, respectively. Alternatively, investigators can provide sequence data or variant calls from their own analysis pipelines for analysis and classification. Our core services are described in light-blue boxes.

