

Supplement 2: Counseling topics discussed with family/patient prior to initiation of whole genome sequencing

Counseling topics

Introduction

- Explore parental/patient expectations/understanding of genome-wide sequencing (refers to both whole exome sequencing [WES] and whole genome sequencing [WGS])
- Review parental/patient understanding of disease under investigation
- Explore family support systems
- Provide overview of genome-wide counseling sessions
 - Parent(s)/legal guardianship established as needed
- Explain that counseling designed to inform, not a commitment to test
- Discuss process of results disclosure in-person with recommendation of long-term genetics
- Follow-up if no diagnosis established (at least annually or as determined by geneticist)

Evaluation

- Review or generate four-generation pedigree
- MD geneticist physical examination documenting phenotype (if not already done/or recent)
- Medical/psychological risk assessment and referral(s) (if not already done)
- Propose mode(s) of inheritance
- MD geneticist proposes possible genetic disorder or group of disorders (e.g., genetic seizure disorders)
- MD geneticist prepares list of possible genes based on hypothesized genetic disorder(s) (if appropriate)
- Discussion of proposed disorders with family

Counseling genetic concepts needed to understand genome-wide sequencing

- Cells, genes, chromosomes, and inheritance
- About 20,000 genes in humans, about 3000 associated with disease(s), some with more than phenotype
 - <http://www.omim.org/statistics/geneMap>
 - Some genes well understood, most poorly understood, improving constantly
 - Genetic disorders treatable versus not treatable
 - Age of onset of disease varies (Tay-Sachs vs. Alzheimer's)
- Patterns of inheritance reviewed including autosomal recessive, autosomal dominant, mitochondrial, X-linked inheritance, and multifactorial
 - Genetic change called a variant (pathogenic, VUS, benign) instead of a mutation
- De novo versus inherited genetic changes
- Variable penetrance and variable expressivity
- Epigenetic etiologies
- Modifier genes
- Health affected by genetic factors and nongenetic factors such as lifestyle, diet, and medications

Counseling genome-wide sequencing

- WES vs WGS—explain test, exome is 1% of genome (coding regions, understand most about these regions)
 - WES and number of samples included for sequencing (single, duo, trio, quad, etc.)
 - Parental and family member specimen use and reporting
 - Definition of result (sequence vs. report)
- WES and WGS consent form and resulting protocols are laboratory specific
 - Consent form
 - One time result versus reanalysis available

No return of incidental findings versus required return of certain incidental findings
versus patient/family choice of return of incidental findings
Sequence available versus not available for research use
Sequence data may be requested by family versus not available
Only certain types of variants generally reported by laboratories (pathogenic, likely
pathogenic, and variants of uncertain significance)

Limitations of genome-wide sequencing

WES and WGS coverage is incomplete, certain types of variants not detected (e.g.,
trinucleotide repeat diseases, copy number variants)
Comparison to reference genome, no “normal” genome
About 15% of genes associated with a phenotype based on medical literature
Many uninterpretable variants

Limitations of genetic test results

For a given pathogenic variant, the phenotype is affected by penetrance, expressivity,
modifier genes

Decision making

Goal of genome-wide sequencing is to establish diagnosis
Patient/family decide which incidental findings they wish to have reported if allowed by
laboratory
 Childhood onset treatable (some laboratories report automatically)
 Childhood onset not treatable
 Adult onset treatable
 Adult onset not treatable
 Carrier status for genetic disorder
 Variants affecting drug metabolism
 Variants associated with risk for a common disorder (e.g., hypertension)
Variants confirmed by Sanger sequencing will go into the medical record
 Remainder of genome does not go into the medical record

Risk of genome-wide sequencing

Find out about genetic disorders/predisposition that family did not want to know
Results may find untreatable conditions
Nonpaternity/nonmaternity
Consanguinity
Ethnic origin
Test likely to be negative (75% of testing at present does not find the diagnosis)
May have psychological distress associated with unfavorable result
May find out information about a close biological relative that patient did not wish to
know (e.g., ethnic background, BRCA1 in a relative)
Workplace and health insurance discrimination addressed by GINA legislation 2008.
Life insurance, disability insurance, and long-term disability insurance discrimination
may still occur. Consider obtaining policies before testing
Error in data or interpretation that can occur with any laboratory test
Privacy concerns. Information in medical record protected by HIPPA
Once information revealed cannot retract

Benefits of genome-wide sequencing

Establish a diagnosis
Personal utility
Positive psychological impact

Review timeline of testing for blood draw to results disclosure

Laboratory retains sequence data that is protected information like all medical information

Laboratory may use data for laboratory quality improvement

No rights or compensation to family for use of deidentified
Where possible patient and parents drawn for segregation analysis
All commercial insurance companies will be sent a preauthorization request before testing started
due to cost of testing
Financial responsibility of patient