A Clinical Perspective on the Need for Integration

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Disclosures

• Past-President of the American College of Medical Genetics and Genomics (ACMG)

• PI on DOD funded grant on autism

• Chair of the external advisory board for the NIH funded Mouse Genome Informatics database, The Jackson Laboratory
Precision Medicine

• Possible through disruptive technology of NGS and advances in computational biology

• Clinical utility currently
  – Diagnosis of rare Mendelian disorders
  – Cancer diagnosis and personalized therapeutics

• Future expected clinical utility
  – Pharmacogenomics
  – Multifactorial disorders
Clinical Exome Sequencing

- High diagnostic yield (~25-40%)
- Importance of studying trios – higher yields in trios of ~40% vs ~25% if study DNA from proband only (peds)
- VUS and actionable secondary findings are common (the latter in ~1-5% of cases depending on lab)
Secondary Findings

**Actionable secondary findings** – damaging variants in disease genes unrelated to the reason testing was sent for which there is significant morbidity and/or mortality and where early dx can ameliorate or prevent the disease
Secondary Findings in Clinical Sequencing

• Recommendations of ACMG & President’s Commission on Bioethics (2013) to search for and report them

• ACMG “Minimum list” of 56 actionable genes and specific mutations
  – Hereditary cancer genes, Marfan and related syndromes, inherited cardiomyopathies & arrhythmias, familial hypercholesterolemia, malignant hyperthermia

• Pathogenic variants in this gene list should be reported regardless of indication for clinical exome sequencing
  – Additional genes may be analyzed
  – Minimal list should be reported regardless of patient age
  – Patients/parents may “opt out” at time of consent
Secondary Findings

• Labs should seek and report only certain types of variants (pathogenic, likely pathogenic)
  – Low prior likelihood of disease for secondary findings
  – Labs should list quality of coverage/data which may be lower than for diagnostic genes
• Clinician/team has responsibility to provide appropriate pre- and post-test counseling [should include qualified genetics professional(s)]
• List should be refined and updated at least annually
• No consensus or recommendations on reporting of secondary findings in research WES/WGS sequencing
Who are the Best Candidates for Clinical Exome Sequencing?

- Specific phenotypes/disorders should lead to specific genetic testing (single gene, gene panel)
  - May be less coverage of specific genes/regions on WES
  - Longer TAT; higher cost; lower % reimbursement

- Testing prior to exome (peds)
  - Microarray analysis - MCA, intellectual disability (IDD), severe szs, severe ASD (low IQ, dysmorphic); may uncover consanguinity
  - Low cost screening tests where appropriate
Utility of a Genetic Diagnosis

- Prevents additional unnecessary testing
- May help predict future medical complications
- May help tailor specific interventions
- May help predict function as an adult
- Will often provide better guidance concerning recurrence risks
- Will occasionally permit specific medical therapies that may significantly improve the outcome
Models for Clinical Genomics - NCH

• All exome sequencing must be ordered or approved by a clinical geneticist
• Referrals to Genetics
  – Ongoing from multiple services, outside providers
• Case conference started with Neurology (9/14); GI (12/15); Endocrine (4/16)
• Genomics Clinic, planned 2016
Clinical Exome Sequencing Results at NCH from 10/29/12 – 8/3/15

<table>
<thead>
<tr>
<th>Exomes Completed (Baylor-Miraca)</th>
<th>160</th>
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<tr>
<td>Cause Identified</td>
<td>71 (44%)</td>
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<tr>
<td>(Pathogenic variant found related to disease)</td>
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<td>Likely Cause Identified</td>
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<td>(awaiting confirmation)</td>
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<td>Questionable Results</td>
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<tr>
<td>(VUS, pathogenicity unclear)</td>
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<tr>
<td>Actionable Secondary Findings</td>
<td>4 (2.5%)</td>
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<tr>
<td>(BRCA1, MEN I, BRCA2, KCNQ1)</td>
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Implications for Management on 1st 100 Cases

- 19/41 (46%) with positive result had change in management beyond reproductive risk
  - 16/41 change in surveillance, including increased cancer risk (DKC)
  - 3/41 specific rx such as medication, diet (Lesch-Nyhan, AR disorder of creatine synthesis, novel sz/movement disorder)

- 20/41 clearly de novo – dramatic reduction in recurrence risk (?25% to <1%)

- 3 novel genes identified (PURA, VARS2, NR1H4 that encodes FXR)
Trends in Clinical Sequencing

• Expansion to carrier and population screening

• Move from gene identification to validation of variant pathogenicity; Need rapid, robust tools to validate potential disease-causing variants, particularly missense variants

• Move toward WGS, with assessment of chr rearrangements included in analysis; increased complexity of assessing non-coding variants
• Standardized process for classifying variants
• Work group of Lab Directors and Clinicians from ACMG, AMP, CAP
• Classification Terminology – pathogenic, likely pathogenic, VUS, likely benign, and benign
An Example

- 18 mo with progressive epilepsy; speech delay
- Seizure panel – no pathogenic variants; VUS KCNQ3 c.1360C>T, p.Pro454Ser
- Gene causes AD seizure disorders – benign neonatal (BFNS), later onset szs
- 3 publications on this variant – suggestive functional data

- Eric Zmuda, Fellow, NCH Cytogenetics and Molecular Genetics Laboratory
Review of Evidence for *KCNQ3* c.1720C>T (p.Phe574Ser)

- Population frequency – Too high (?1:250 vs <1/50,000 for disease)
- Case Control Study – Enriched in disease
- Conservation- Highly Conserved
- Functional Predictions – Conflicting

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<td>FATHMM_pred</td>
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Review of Evidence for \textit{KCNQ3} c.1720C>T (p.Phe574Ser)

- ClinVar– Conflicting Interpretations
- Plug info into ACMG Checklist (modified online tool from ClinGen)….
Review of Evidence for KCNQ3 c.1720C>T (p.Phe574Ser)

Conclusion:
ACMG Guidelines “If the evidence for benign and pathogenic are conflicting, the variant defaults to uncertain significance.”
How Can Studies in Model Organisms Help?

- Demonstrate a role for protein in biological process
- (Help) demonstrate pathogenicity of a specific variant
- Examine gene-gene interactions
- Test potential therapies
Model of Choice Depends on Gene and Phenotype

- Yeast – conserved metabolic pathways
- Zebrafish – heart development, early nervous system development
- Xenopus – channel studies in oocytes
- Mouse – mammalian development (placenta, skeletal), learning & behavior
- Dog – certain tumors, behavior
- Primate – complex behaviors, language
Model of Choice Depends on Gene and Phenotype

- Yeast – conserved metabolic pathways
- X-linked mouse models of cholesterol synthesis disorders
Model of Choice Depends on Gene and Phenotype

- Mouse – mammalian development (placenta), behavior

- Damaging de novo variants in novel genes in 2 human autism pts - ?likely pathogenic based on behavioral phenotypes in KO mice
Using Mouse Model Data to Prioritize and Characterize Genes with Unknown Clinical Significance

Joanne Berghout, PhD
Outreach Coordinator
Mouse Genome Informatics

16 October 2015

• www.ACMG.net/EDUCATION
• Online Learning