ACMG GENE LISTS:
SECONDARY FINDINGS AND CHILDREN

Ian Krantz, M.D. on behalf of the PediSeq Project

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ACMG POLICY STATEMENT ON REPORTING INCIDENTAL / SECONDARY FINDINGS ON EXOME AND GENOME SEQUENCING

2013:
• “minimum” list – “must” report
  • 56 genes: 24 conditions: 23 AD, 2 SD, 1 AR, 1 XL: 3 adult, 3 childhood, 17 childhood/adult)

• “Have a fiduciary duty to prevent harm…supersedes concerns about autonomy…autonomy preserved as patients have the right to decline clinical sequencing…”

• “…the ethical concerns about providing…genetic risk about adult-onset diseases were outweighed by the potential benefit to the future health of the child and…parents…”

• “Incidental variants should be reported regardless of the age of the patient"

• Conditions that are part of newborn screening were excluded.
2016:

- Opt out option added
- Removed *MYLK* (thoracic aortic aneurysm)
- Added: *ATP7B* (Wilson disease - AR), *BMPR1A* & *SMAD4* (juvenile polyposis - AD), *OTC* (OTC defic. - XL)
CHILDREN ARE NOT LITTLE ADULTS (FOR THE MOST PART)

• Clinical manifestations vary by age – severe disorders may not manifest in neonate or early years.

• Many sick children may not manifest secondary diagnoses (may be masked by more severe or striking primary diagnosis)

• Issues of consent and autonomy need to be more carefully considered when returning secondary findings for late or adult onset disorders – both for the child and for the potentially affected parent.

• Prenatal (!) Healthy kids (!)
CMA SF EXPERIENCE AT CHOP: OVERALL FREQUENCY 1.7%

Relative Frequency of the Reported Incidental Findings

- HBA1-HBA2 del: 21.8%
- SHOX del/dup: 34.5%
- HBB-HBD del: 9.1%
- PMP22 del/dup: 5.5%
- CATSPER2-STRC del: 7.3%
- Mosaic LOH 11: 7.3%
- NPHP1 del: 7.3%
- DMD del: 5.5%
- Others: 5.5%

Children's Hospital of Philadelphia

PEDISEQ
Beyond the ACMG 56/59 gene list, known pathogenic or likely pathogenic mutations should be reported in genes that fit the following criteria:

1. Condition is medically actionable: successful interventions and/or screening are available for the disease (and would be implemented if the condition is known).
2. Focus on pediatric onset disease.
3. The expected phenotype(s) for each gene is clearly defined.
4. Adequate literature is available for the interpretation of the variant.
5. Significant disease is anticipated based on the variant.
6. Pharmacogenomic variants could also be considered within these criteria.
7. For autosomal and X-linked recessive conditions, carrier status would be reported if medical screening or interventions would change based on known carrier status in an individual.

(would it be useful to include exclusion criteria (such as neurodegenerative diseases?))

CHOP SECONDARY FINDINGS INCLUSION LIST
<table>
<thead>
<tr>
<th>Presenting feature</th>
<th>Development</th>
<th>Other</th>
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<tr>
<td>SGA, FTT, GER</td>
<td>Developmental delay</td>
<td>Seizures, proportionate short stature</td>
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<table>
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<tr>
<th>Gene 1</th>
<th>Disease</th>
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<tr>
<td>SCRAP</td>
<td>Floating Harbor</td>
<td>ASL</td>
<td>Arginosuccinic aciduria</td>
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<td>FKRP</td>
<td>LGMD2I</td>
<td>ACADL</td>
<td>Long chain Acyl-CoA dehydrogenase deficiency</td>
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</table>
THE CHOP CLINICAL EXPERIENCE

• 14/347 (4%) exomes with an incidental finding

• 43/390 or 11% declined to receive

• GLA*, KCNQ1*, MUTYH* x 2, NR3C2, SCN5A*, SDHB*, BRCA2*, MYL2* x 2, COL3A1*, MYBPC3*, BRCA1*, CFTR

• 12/14 were ACMG and 2 were not: NR3C2 and CF.

*ACMG SF List
PEDISEQ EXPERIENCE: CHOICES FOR SECONDARY RESULTS

• YES - Primary findings
  • Related/possibly related to clinical indication for testing

• YES – Immediately medically actionable
  • Results suggest immediate change in medical care, including screening or intervention

• YES/NO – Medically actionable (MA) childhood onset
  • Childhood onset results that could cause serious health risk with known options for improving health via changes in treatment or management

• YES/NO – MA adult onset
  • Adult onset results that could cause serious health risk with known options for improving health via changes in treatment or management

• YES/NO – Carrier status
  • Carriers of a variant for AR disease at risk for having a child with AR disease if partner is a carrier
PEDISEQ EXPERIENCE:

• Requested results
  • 94.1% (medically actionable within their age category)
  • 90.2% (carrier status)
  • 92% (children requesting adult onset findings)
  • 4.9% opted out of any SFs

• 105 SFs returned (74% pathogenic, 26% likely pathogenic) (78 variants not reported before) (avg. 1.03 SFs/patient enrolled)
  • 55.2% missense
  • 41% frame shift/nonsense/splice
  • 3.8% amino acid deletion

• 62 patients received SF (avg. 1.7 SFs / patient)

• 98/105 - carrier variants (among 56 genes)

• 6/105 (6%) – IMA variants (among 5 genes)
  • 1 variant is non-ACMG gene, RHO assoc. with night blindness and retinal abnormalities

• 1/105 (1%) - MA adult (BRCA1 variant in 3 y/o female)

• Expanded SF approach does not result in significant increase in reporting of MA SFs
2 YEAR-OLD BOY WITH BLSNHL

• First seen at 2 mo of age:
  • Profound congenital BLSNHL
• Family history: HL in father and maternal grandmother (mild)
  • CMA: WNL
  • Waardenberg syndrome testing: WNL
• Exome denied

PediSeq exome:

Primary (all VUS):
TMC1 (AR/AD): p.Ser208Arg (mat) / p.Phe313Ser (pat)
MYH9 (AD): p.Ser1114Pro (pat)
CHD23 (AR): p.Arg528His (pat)

Secondary:
Disorders of intermediary metabolism:
- Phenylketonuria (PKU)- PAH**
- Tyrosinemia type I- FAH**
- Tyrosinemia type II- TAT**
- Tyrosinemia type III- HPD**
- Maple syrup urine disease (MSUD)- BCKDHA, BCKDHB, DBT**
- Classic galactosemia- GALT**
- Isovaleric aciemia (IVA)- TVD**
- Glutaric aciemia type 1 (GA1)- GCDH**
- Glutaric aciemia type 2 (GA2)- ETFDH, ETFA, ETFB**
- 3-hydroxy 3-methylglutaric aciemia (HMG-CoA lyase deficiency)- HMGCL**
- Holocarboxylase synthetase deficiency- HLCS**
- Biotinidase deficiency- BTD**
- Methylobalaminic aciemia (mutase deficiency)- MUT**
- Methylobalaminic aciemia (Cobalamin A deficiency)- MMAA**
- Methylobalaminic aciemia (Cobalamin B deficiency)- MMAB**
- Methylobalaminic aciemia and homocysteinuria, cbiC type (Cobalamin C)- MMACHC**
- Methylobalaminic aciemia and homocysteinuria, cbiD type (Cobalamin D)- MMADHC**
- Methylobalaminic aciemia and homocysteinuria, cbiF type (Cobalamin F)- LMBRD1**
- Methylobalaminic aciemia and homocysteinuria, cbiJ type (Cobalamin J)- ABCD4**
- Homocysteinuria (cystathionine beta-synthase deficiency)- CBS**
- Homocysteinuria (Cobalamin E)- MTR**
- Homocysteinuria (Cobalamin G)- MTR**
- 3-Methylcrotonyl-CoA carboxylase deficiency (3MCC)- MCCC1**
- 3-Methylcrotonyl-CoA carboxylase 2 deficiency (3MCC)- MCCC2**
- Propionic aciemia- PCCA, PCCB **
- Beta-ketothiolase deficiency- ACAT1**
- Medium chain acyl-CoA dehydrogenase deficiency (MCAD)- ACADM**
- Very long chain Acyl-CoA dehydrogenase deficiency (VLAD)- ACADVL**
- Long chain L-3-hydroxy acyl-CoA dehydrogenase deficiency (LCHAD)- HADHA**
- Trifunctional protein deficiency (TFP)- HADHA, HADHB**
- Carnitine uptake defect- SLC22A5**
- Carnitine palmitoyltransferase I deficiency- CPT1A**
- Carnitine palmitoyltransferase II deficiency- CPT2**
- Carbamoylphosphate synthetase 1 deficiency- CPS1
- Ornithine transcarbamylase deficiency (OTC)- OTC (X-linked)
- Citrullinemia type 1 (arginosuccinate synthetase deficiency)- ASS1**
- Citrullinemia type 2 (citrin deficiency)- SLC25A13
- Argininosuccinase aciduria (ASL deficiency)- ASL**
- Argininosuccinase- ARG1
- N-acetylglycine synthase deficiency- NAGS

Lysosomal storage diseases:
- Fabry disease- GLA (X-linked)
- Niemann-Pick A/B disease- SMPD1
- Gaucher disease- GBA
- Hurler syndrome- IDUA
- Hunter syndrome- IDS
- Morquio A- GALNS
- Morquio B- GLB1

Glycocen storage diseases:
- Glycocen storage disease type 0- GYS1, GYS2
- Glycocen storage disease type I (von Gierke)- G6PC, SLC37A4
- Glycocen storage disease type II (Pompe)- GAA**
- Glycocen storage disease type III- AGL
- Glycocen storage disease type IV- GBE1
- Glycocen storage disease type V (McArle)- PYGM
- Glycocen storage disease type VI- PYGL
- Glycocen storage disease type VII- PFKM
- Glycocen storage disease type IX- PHKA2 (X-linked), PHKB (recessive), PHKG2
- (recessive)
- Glycocen storage disease type XI (Fanconi-Bickel)- SLC2A2
- Glycocen storage disease type XII- ALDOA

**screened in PA, red: known missed NBS
SUMMARY

• Recessive and hemizygous conditions need to be included on secondary gene lists in pediatrics (e.g. CF, MCAD, DMD, OTC (now on revised ACMG list)).

• Not enough to assume picked up on NBS
  • many are not (e.g. LSDs)
  • can be missed (e.g. MCAD)
  • Populations without NBS (international patients)

• Need for more frequent updating of list

• Need pediatric specific list/recommendations

• Prenatal considerations.
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**IMMEDIATELY MEDICALLY ACTIONABLE SECONDARY FINDINGS**

**MEDICALLY ACTIONABLE ADULT ONSET SECONDARY FINDINGS**

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