ACMG GENE LISTS: SECONDARY FINDINGS AND CHILDREN

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February, 2017

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.**

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

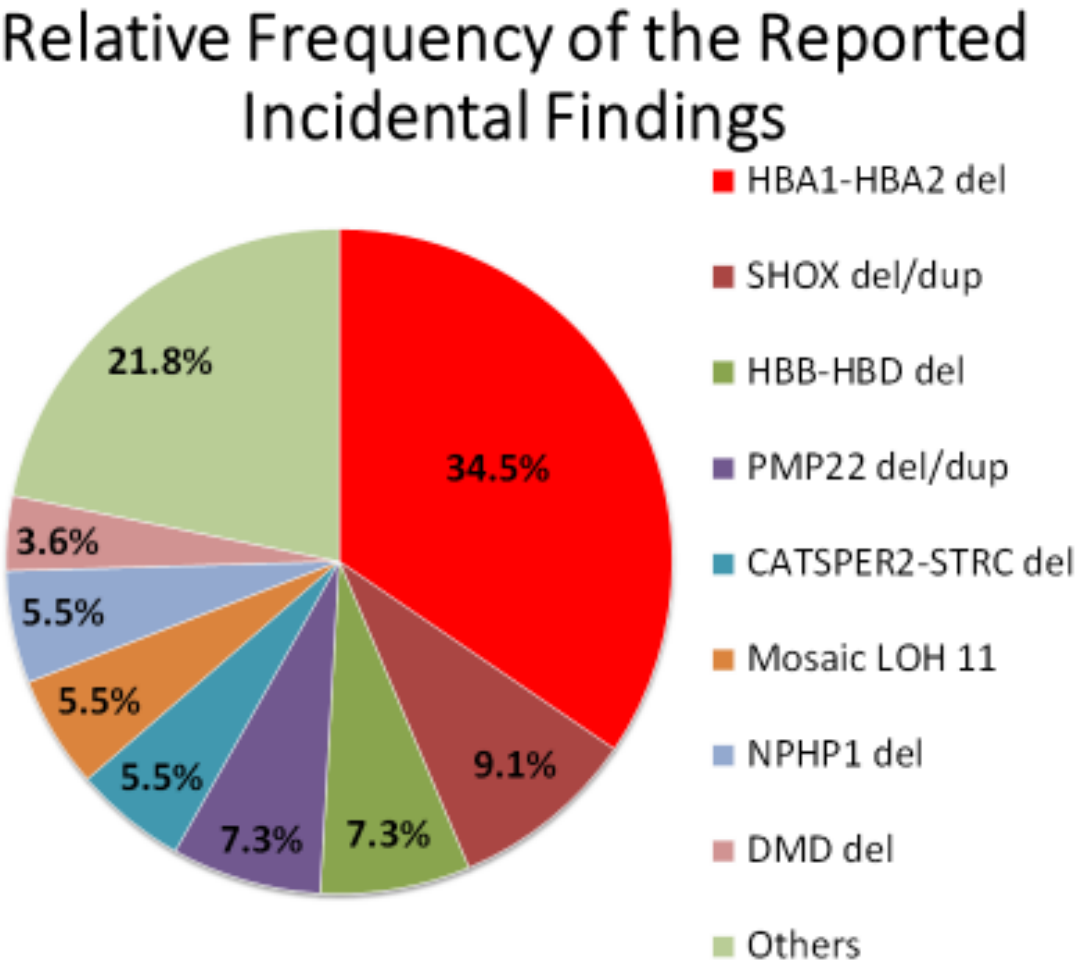
2016:

- **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%

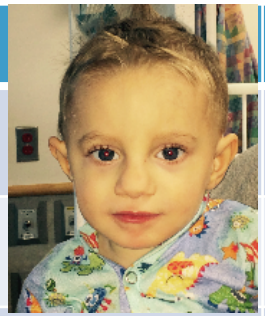


CHOP SECONDARY FINDINGS INCLUSION LIST

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?)

	Patient 1: 2 yo ♂		Patient 3: 18 mo ♀	
Presenting feature	SGA, FTT, GER		Hypotonia, DD	
Development	Developmental delay		Motor delays	
Other	Seizures, proportionate short stature			

Gene 1	*SCRAP*	*FKRP*
Disease	Floating Harbor	LGMD2I
Gene	*ASL*	*ACADL*
Disease	Arginosuccinic aciduria	Long chain Acyl-CoA dehydrogenase deficiency

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

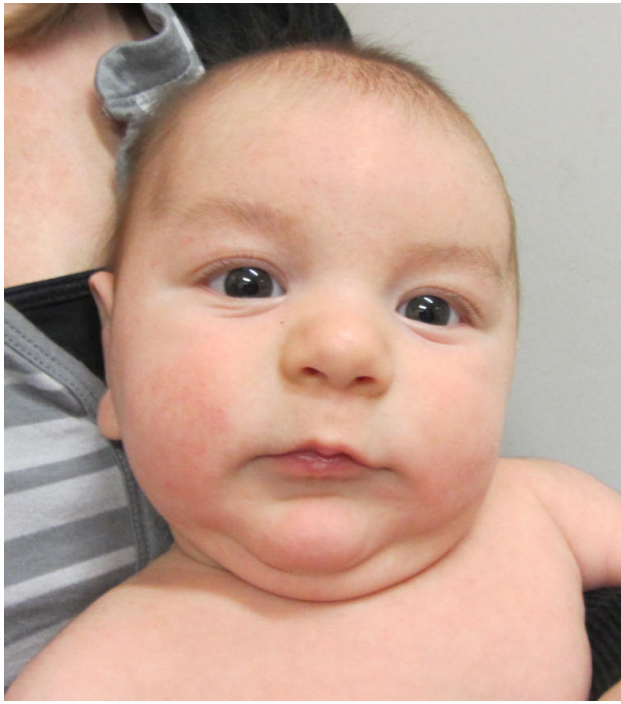
PEDISEQ EXPERIENCE: CHOICES FOR SECONDARY RESULTS

- 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

<u>PediSeq exome:</u>

Primary (all VUS):

TMC1 (AR/AD): p.Ser208Arg (mat) / p.Phe313Ser (pat)

MYO15A (AR): p.Glu209* (mat)

MYH9 (AD): p.Ser1114Pro (pat)

CHD23 (AR): p.Arg528His (pat)

Secondary:

Sucrose Isomaltase (AR): p.Val577Gly / p.Gly1073Asp – 2 most common pathogenic mutations

METABOLISM SECONDARY FINDINGS GENE LIST

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 acidemia (IVA)- IVD**
- Glutaric acidemia type 1 (GA1)- GCDH**
- Glutaric acidemia type 2 (GA2)- ETFDH, ETFA, ETFB**
- 3-hydroxy 3-methylglutaric aciduria (HMG-CoA lyase deficiency)- HMGCL**
- Holocarboxylase synthetase deficiency- HLCS**
- Biotinidase deficiency- BTD**
- Methylmalonic acidemia (mutase deficiency)- MUT**
- Methylmalonic acidemia (Cobalamin A deficiency)- MMAA**
- Methylmalonic acidemia (Cobalamin B deficiency)- MMAB**
- Methylmalonic aciduria and homocysteinuria, cblC type (Cobalamin C)- MMACHC**
- Methylmalonic aciduria and homocysteinuria, cblD type (Cobalamin D)- MMADHC**
- Methylmalonic aciduria and homocysteinuria, cblF type (Cobalamin F)- LMBRD1**
- Methylmalonic aciduria and homocysteinuria, cblJ type (Cobalamin J)- ABCD4**
- Homocystinuria (cystathionine beta-synthase deficiency)- CBS**
- Homocystinuria (Cobalamin E)- MTRR**
- Homocystinuria (Cobalamin G)- MTR**
- 3-Methylcrotonyl-CoA carboxylase 1 deficiency (3MCC)- MCCC1**
- 3-Methylcrotonyl-CoA carboxylase 2 deficiency (3MCC)- MCCC2**
- Propionic acidemia- PCCA, PCCB **
- Beta-ketothiolase deficiency- ACAT1**
- Medium chain acyl-CoA dehydrogenase deficiency (MCAD)- ACADM**
- Very long chain Acyl-CoA dehydrogenase deficiency (VLCAD)- 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
- Argininosuccinic aciduria (ASL deficiency)- ASL**
- Argininemia- ARG1
- N-acetylglutamate 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
-

Glycogen storage diseases:

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

ACKNOWLEDGEMENTS

Project 1
Nancy Spinner, PhD
Edward Romasko, PhD
Laura Conlin, PhD
Sawona Biswas, MS CGC
Matthew Deardorff, MD PhD
Elizabeth DeChene, MS CGC
Noreen Dugan, RN
Matthew Dulik, PhD
Sowmya Jairam, PhD
Vijay Jayaraman, MS
Michele Lambert, MD
Avni Santani, PhD
Victoria Vetter, MD MPH
Alisha Wilkens, MS CGC
Leah Dowsett, MD
Jiwon Choi

Project 2
Jeffrey Pennington
Batsal Devkota, PhD
Deanne Taylor, PhD
LeMar Davidson, MS
Alex Felmeister, MS
Robert Grundmeier, MD
Michael Italia, MS
Dean Karavite, MS
Jeremy Leipzig, MS
Aaron Masino, PhD
Jeffrey Miller
Donald Naegely, MS
Juan Perin, MS
Byron Ruth

DGD
Ahmed Abou Tayoun
Bryan Krock

Project 3
Barbara Bernhardt, MS
Jon Merz, MBA, JD, PHD
Victoria Miller, PHD
Ashley Tomlinson, MA
Rena Pressman
Reed Pyeritz, MD, PHD
Connie Ulrich, PHD, RN, FAAN
Allison Werner-Lin, PHD
Samantha Wiley, MS
Sarah Walser

Roberts IMGC
Livija Medne, MS
Cara Skraban, MD
Emma Bedoukian, MS

IMMEDIATELY MEDICALLY ACTIONABLE SECONDARY FINDINGS

PediSeq ID	Cohort	Age (y)	Sex	ACMG 56	Path.	Gene	Disease OMIM	OMIM #	RefSeq ID	cDNA	Protein	Inh	Zyg
P-PSeq-0003	SCA	20.6	F	Y	LP	*RYR1*	Malignant hyperthermia susceptibility 1, autosomal dominant	145600	NM_000540.2	c.6838G>A	p.Val2280Ile	AD	Het
P-PSeq-0010	HL	44.2	M	Y	LP	*LDLR*	Familial hypercholesterolemia	143890	NM_000527.4	c.1003G>A	p.Gly335Ser	AD	Het
P-PSeq-0010	HL	44.2	M	Y	LP	*TNNI3*	Cardiomyopathy, familial hypertrophic, 7	613690	NM_000363.4	c.485G>A	p.Arg162Gln	AD	Het
P-PSeq-0028	SCA	20.9	M	Y	LP	*MLH1*	Colorectal cancer, hereditary nonpolyposis, type 2; Mismatch repair cancer syndrome	609310; 276300	NM_000249.3	c.1943C>T	p.Pro648Leu	AD	Het
P-PSeq-0029	HL	6.9	F	N	P	*RHO*	Autosomal dominant or recessive retinitis pigmentosa 4; Congenital statiory autosomal dominant night blindness 1; Retinitis punctata albescens	613731; 610445; 136880	NM_000539.3	c.491C>T	p.Ala164Val	AD	Het
P-PSeq-0034	SCA	18.3	M	Y	P	*LDLR*	Familial hypercholesterolemia	143890	NM_000527.4	c.557del	p.Gly186Vfs*2	AD	Het

MEDICALLY ACTIONABLE ADULT ONSET SECONDARY FINDINGS

PediSeq ID	Cohort	Age (y)	Sex	ACMG 56	Path.	Gene	Disease OMIM	OMIM #	RefSeq ID	cDNA	Protein	Inh	Zyg
P-PSeq-0086	HL	4	F	Y	P	*BRCA1*	Breast-ovarian cancer, familial, 1	604370	NM_000540.2	c.5503C>T	p.Val2280Ile	AD	Het