Clinical Validity Scoring Guides Updates to Expanded Secondary Findings from Diagnostic Exome Sequencing; Comparison with BabySeq Scores

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BACKGROUND

Expanded Secondary Findings (ESF) can be ordered for parents and probands undergoing Diagnostic Exome Sequencing (DES).

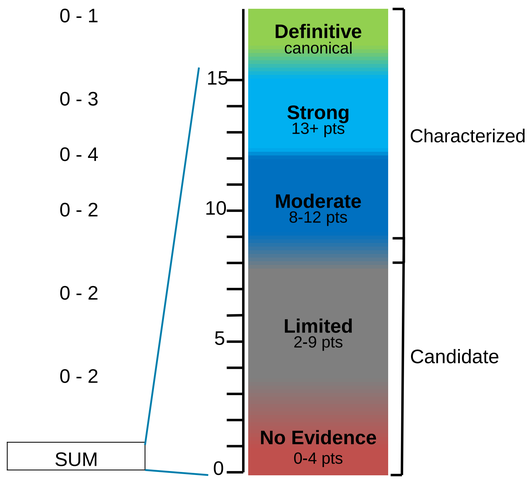
ESF panels offer healthy individuals the opportunity to learn more about their recessive disease carrier status or cancer predisposition, for family planning or early intervention purposes.

Unlike DES, screening panels cannot use the presence of clinical features to corroborate the relevance of genetic aberrations identified. Therefore, screening panels must be based on sound, up-to-date scientific knowledge.

Evaluating the clinical validity of gene-disease relationships using a standardized scoring system can help prioritize genes. Additional considerations are: the intended target population, disease penetrance, and actionability.

CLINCAL VALIDITY SCORESHEET

Number of unrelated patients *1 pt: 1-2; 2 pt: 3-4; 3 pt: 5-9; 4 pt: 10-24 patients*	1 - 4
Other Statistical Evidence *1 pt: AD disease with significant excess of de novos* *1 pt: AR disease with LOD score > 3*	0 - 1
Number of publications reporting independent probands *1 pt per publication*	0 - 3
Number of pathogenic variants *1 pt per VLP or mutation*	0 - 4
Gene Function *1 pt function/expression consistent with disease* *1 pt physically interacts with gene characterized for same disease*	0 - 2
Gene Disruption *1 pt relevant pathology in vitro after similar genetic modification* *1 pt determination of mutational mechanism*	0 - 2
Model Organism *1 pt gene function in vivo related to pathology of human disease* *1 pt phenotype and genotype match human disease*	0 - 2
SUM	



METHODS

1227 genes were originally selected for the ESF panel offered to individuals undergoing DES at Ambry Genetics based on reported evidence for a role in disease in various public databases in 2013.

To ensure the ongoing clinical relevance of Expanded Secondary Findings panel content at a diagnostic laboratory, the list of 1227 genes was updated using ESF panel.

- Recently published clinical validity criteria from Ambry (Smith, et al., 2017)
- Comparison with published scores for newborns BabySeq cohort (Ceyhan-Birsoy, et al., 2017)

Clinical Validity scores were compared for matching gene-disease pairs between the two systems.

Gene-disease pairs present on one list but missing from the other were identified.

RESULTS

Upon review of the 1227 genes originally on the ESF panel.

- 52 genes were removed due to low clinical validity

BabySeq list included 510 genes not on the ESF panel.

- 31% (159 genes) were considered reportable by BabySeq Category A, with definitive or strong evidence to cause a highly penetrant childhood-onset disorder
- Many were new Mendelian loci discovered after 2014

Final ESF panel included 321 genes that were not on BabySeq.

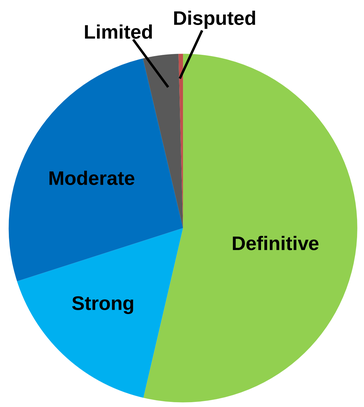
- 88% (284 genes) childhood-onset disease
- May be relevant for BabySeq.

Matching gene-disease pairs showed 64% exact concordance for clinical validity scores.

Gene content may differ according to targeted population.

- Intended population for BabySeq is newborns
- Ambry ESF is offered to anyone undergoing DES

Updated Clinical Validity of 1227 Genes on Ambry's ESF panel, created 2013



→ Remove genes that are not characterized
→ Periodic clinical validity review is beneficial

Comparison of clinical validity for 878 gene-disease pairs matching between Ambry and BabySeq

BabySeq Score \ Ambry score	Disputed	Limited	Moderate	Strong	Definitive
Conflicting	0	0	0	0	0
Limited	1	14	12	2	0
Moderate	1	5	69	9	0
Strong	0	0	90	93	134
Definitive	0	0	16	43	381

0
1-100
101-200
201-300
301-400

155	Ambry more conservative
557	Total agreement
157	BabySeq more conservative

→ Matching gene-disease pairs showed 64% exact concordance for clinical validity scores
→ Many genes can cause multiple diseases – the disease scored must be carefully selected

Genes scored as definitive and not currently on Ambry ESF panel

ACTN4	Glomerulosclerosis, focal segmental, 1	*KRAS**	Noonan syndrome
ADAR	Dyschromatosis symmetrica hereditaria	*PEX6**	Zellweger syndrome
*BBS12**	Bardet-Biedl syndrome	*PFKM*	Glycogen storage disease 7
*BBS2**	Bardet-Biedl syndrome	*SLC25A38*	Anemia, sideroblastic, pyridoxine-refractory
BBS4	Bardet-Biedl syndrome	*SLC26A3**	Chloride diarrhea, congenital
*DNAH11**	Primary ciliary dyskinesia	*SLC34A3*	Hypophosphatemic rickets with hypercalciuria
*DNM2**	Charcot-Marie-Tooth disease, axonal, type 2M	*SLC39A4**	Acrodermatitis enteropathica
*GATA4**	Congenital heart defects	*SLC5A2*	Renal glucosuria
*GCK**	Hyperinsulinemic hypoglycemia	*SPTB*	Spherocytosis
H19	Beckwith-Wiedemann syndrome	*STS*	Ichthyosis, X-linked
*HPS4**	Hermansky-Pudlak syndrome 4	*THRB*	Thyroid hormone resistance

** Plan to add these genes*

Genes scored as definitive and not currently on BabySeq list

AGPAT2	Lipodystrophy, congenital generalized	*IL7R*	Severe combined immunodeficiency
ALDH7A1	Epilepsy, pyridoxine-dependent	*L2HGDH*	L-2-hydroxyglutaric aciduria
AQP2	Diabetes insipidus, nephrogenic	*MID1*	Opitz GBBB syndrome, type I
CASR	Hypocalcemia; Hyperparathyroidism	*NDUFV1*	Mitochondrial complex I deficiency
COQ8A	Coenzyme Q10 deficiency	*P3H1*	Osteogenesis imperfecta, type VIII
DARS2	Leukoencephalopathy with lactate elevation	*PAFAH1B1*	Lissencephaly 1
DYNC2H1	Short-rib thoracic dysplasia +/- polydactyly	*PCDH19*	Epileptic encephalopathy, early infantile
EBP	Chondrodysplasia punctata	*PDCD10*	Cerebral cavernous malformations
FOXG1	Rett syndrome	*SLC5A1*	Glucose/galactose malabsorption
HSD11B2	Apparent mineralocorticoid excess	*SOX2*	Optic nerve hypoplasia and abnormalities of the CNS
HSD3B2	Adrenal hyperplasia, congenital	*UBE3A*	Angelman syndrome

TAKE-HOME POINTS

The disease severity and mechanism need to be thoughtfully considered for inclusion on screening panels (*e.g.* will testing method detect trinucleotide repeats?)

The number of (likely) pathogenic variants previously reported may also affect clinical utility *(e.g. CACNA1S* rarely reported).

Evidence-based clinical validity analysis can help select genes for screening panels targeting various populations, and periodic clinical validity review of genes is essential.

Data sharing of both scientific evidence and clinical validity scores can guide panel creation and updates.

REFERENCES

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