20 I 23 JUNE 2022

Liège I Théâtre de Liège I Belgium

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70th ESCVS

International congress of the European Society for Cardiovascular and Endovascular Surgery

7th IMAD meeting

European Reference Network

for rare or low prevalence complex diseases

Network Vascular Diseases (VASCERN)

Member UZ Gent – België

Curating genes and variants for heritable thoracic aortic disease
A dynamic process!

Julie De Backer, MD, PhD

Laura Muiño Mosquera

Ghent University Hospital, Belgium

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Gene curation: rationale

More genes:

- Higher detection rate
- More VUSs

Gene curation: what?

ClinGen
Clinical Genome Resource

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qualitatively define gene-disease validity using a classification scheme based on the strength of evidence supporting the relationship

standardized semi-quantitative approach to evaluate available evidence and arrive at such a classification

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Rehm, H.L. et al., 2015. *The New England journal of medicine*

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Gene curation: how?

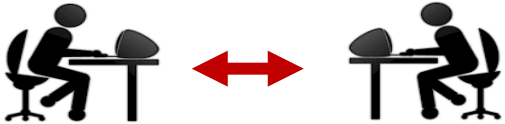
Figure 10: Clinical Validity Summary Matrix

GENE/DISEASE PAIR:				
Assertion criteria	Genetic Evidence (0-12 points)	Experimental Evidence (0-6 points)	Total Points (0-18)	Replication Over Time (Y/N)
Description	Case-level, family segregation, or case-control data that support the gene-disease association	Gene-level experimental evidence that support the gene-disease association	Sum of Genetic & Experimental Evidence	> 2 pubs w/ convincing evidence over time (>3 yrs.)
Assigned Points	A	B	C	D
CALCULATED CLASSIFICATION		LIMITED	0.1-6	
		MODERATE	7-11	
		STRONG	12-18	
		DEFINITIVE	12-18 & Replicated Over Time	
Valid contradictory evidence (Y/N)*	List PMIDs and describe evidence: E			
CURATOR CLASSIFICATION		F		
FINAL CLASSIFICATION		G		

Process

One-on-one teams

(ClinGen) Curator — (familiar with curation framework)



Clinical Domain Expert — (familiar with disease and genes)

literature search

enter data and create draft classification

Search terms

Select relevant publications

Advise as needed (e.g. experimental data)

Expert group review + approval

Definitive	Role has been repeatedly demonstrated in research & clinical diagnostic settings • Upheld over time (in general, at least 3 years) • No valid contradictory evidence
Strong	Excess of pathogenic variants in cases vs. controls OR • Multiple pathogenic variants in unrelated probands •Several different types of supporting experimental data • ≥2 independent studies • No valid contradictory evidence
Moderate	≥3 unrelated probands with pathogenic variants • Some supporting experimental data • No valid contradictory evidence
Limited	<3 unrelated probands with pathogenic variants OR • Multiple variants reported in unrelated probands but *without* sufficient evidence for pathogenicity per 2014 ACMG criteria
No Evidence Reported	No evidence reported for a causal role in disease (candidate genes, etc.).
Disputed	Valid evidence *refuting* a role for this gene in this disease is equivalent to or stronger than existing evidence *supporting* this role.
Evidence Against	Evidence refuting the role of the gene in the specified disease has been reported and significantly outweighs any evidence supporting the role.

How might one use “clinical validity”?

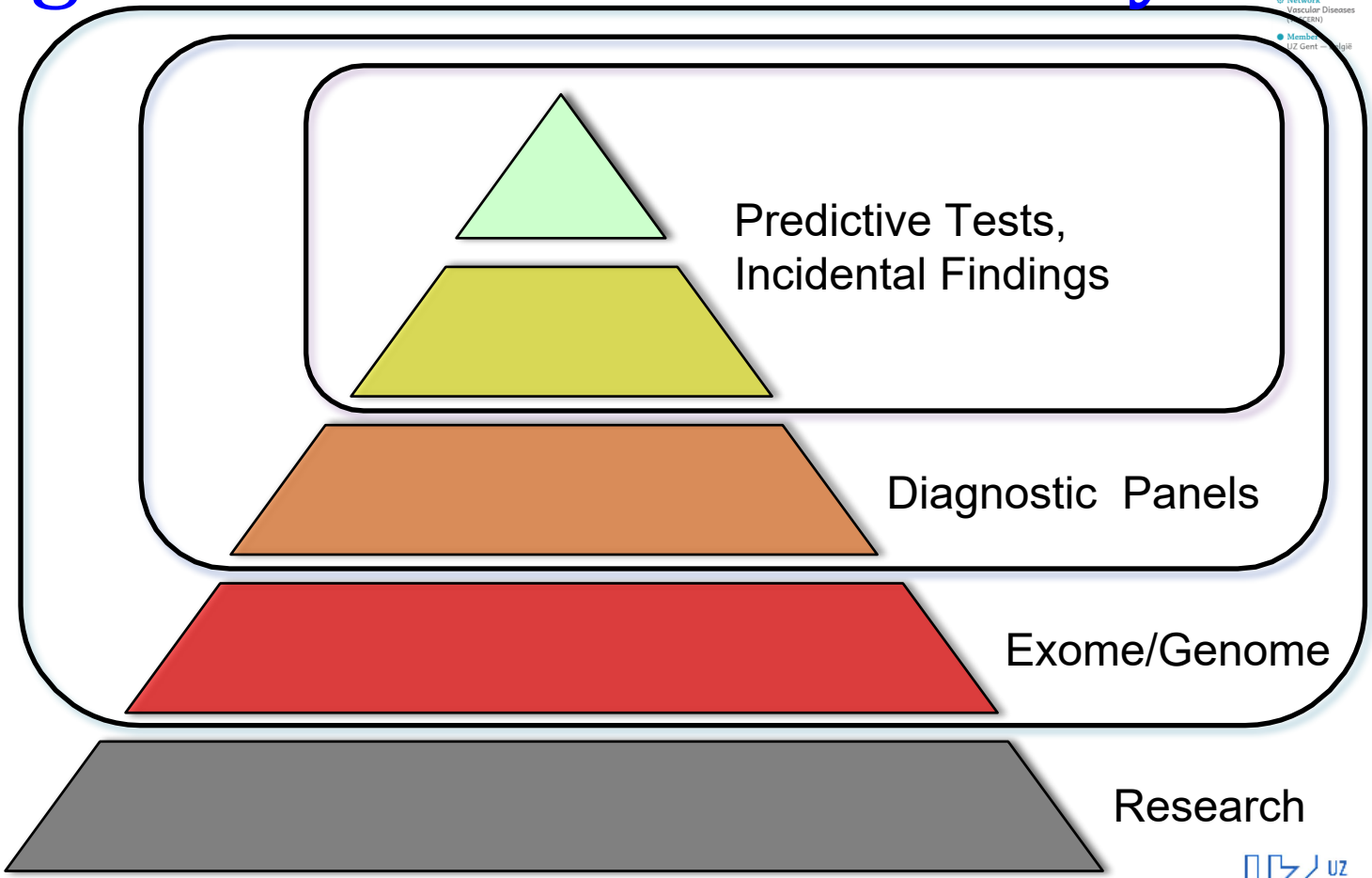
Definitive evidence

Strong evidence

Moderate evidence

Limited evidence

Disputed / no evidence



HTAAD Gene Curation 2016-2018

CENTRAL ILLUSTRATION Evaluation of the Clinical Validity of Genes for Heritable Thoracic Aortic Aneurysms and Dissections (HTAAD)

Category A

DEFINITIVE

- *COL3A1* — A1
- *FBN1* — A1
- *SMAD3* — A1
- *TGFB2* — A1
- *TGFBR1* — A1
- *TGFBR2* — A1

- *ACTA2* — A2
- *MYH11* — A2
- *MYLK* — A2

STRONG

- *LOX* — A2
- *PRKG1* — A2

Recent genes

UNCERTAIN

- *BGN*
- *FOXE3*
- *HCN4*
- *MAT2A*
- *MFAP5*
- *SMAD2*
- *TGFB3*

Category B

MODERATE

- *EFEMP2*

LIMITED

- *ELN*
- *FBN2*
- *FLNA*
- *NOTCH1*
- *SLC2A10*
- *SMAD4*
- *SKI*

Category C

LIMITED

- *CBS*
- *COL4A5*
- *PKD1*
- *PKD2*

Category D

NO EVIDENCE

- *ACVRL1*
- *ADAMTS10*
- *B3GAT3*
- *COL1A1*
- *COL1A2*
- *COL4A1*
- *COL5A1*
- *COL5A2*
- *COL9A1*
- *COL9A2*
- *COL11A1*
- *COL18A1*
- *EMILIN1*
- *ENG*
- *GATA5*
- *GJA1*
- *JAG1*
- *MED12*
- *PLOD1*
- *PLOD3*
- *SMAD6*
- *UPF3B*
- *VCAN*

Renard, M. et al. J Am Coll Cardiol. 2018;72(6):605-15.

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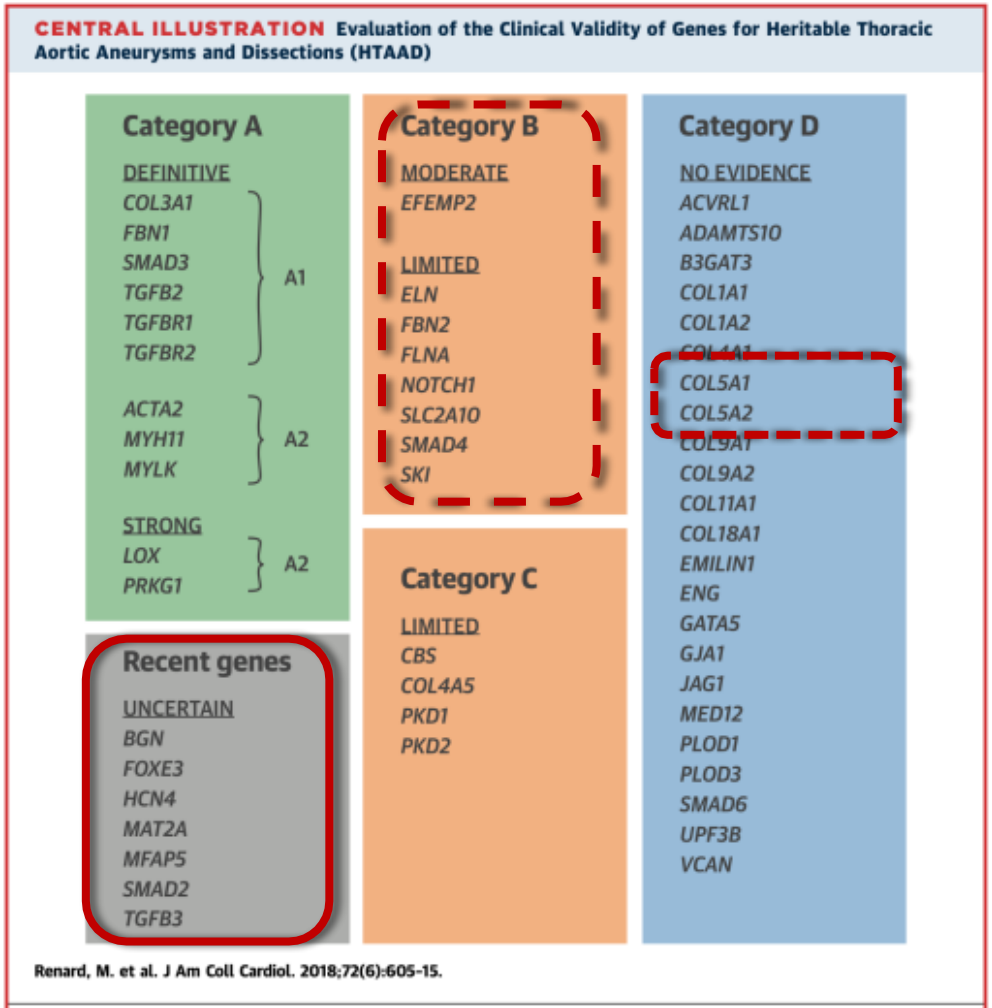

Update Needed

+ “New” genes

THSD4
LTBP3
ARIH1
IPO8

Publications!

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Gene panel quality: validity – NOT number

Curated lists:

ID patients/families at risk for thoracic aortic disease

↓ burden of uninformative diagnostic testing results by ↓ nr of screened genes

The list is Dynamic and needs update!!

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Thank you!

Paul Coucke

Laura Muiño Mosquera

Marjolijn Renard

Patrick Sips

Karen Wettinck

Liesbeth Wildero-Van Wouwe

@judbacke

Julie.debacker@ugent.be

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fwo Opening new horizons

BELGIAN HEART FOUNDATION

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