Genes and **Development**

Kevin A. Strauss, MD*

*No Disclosures

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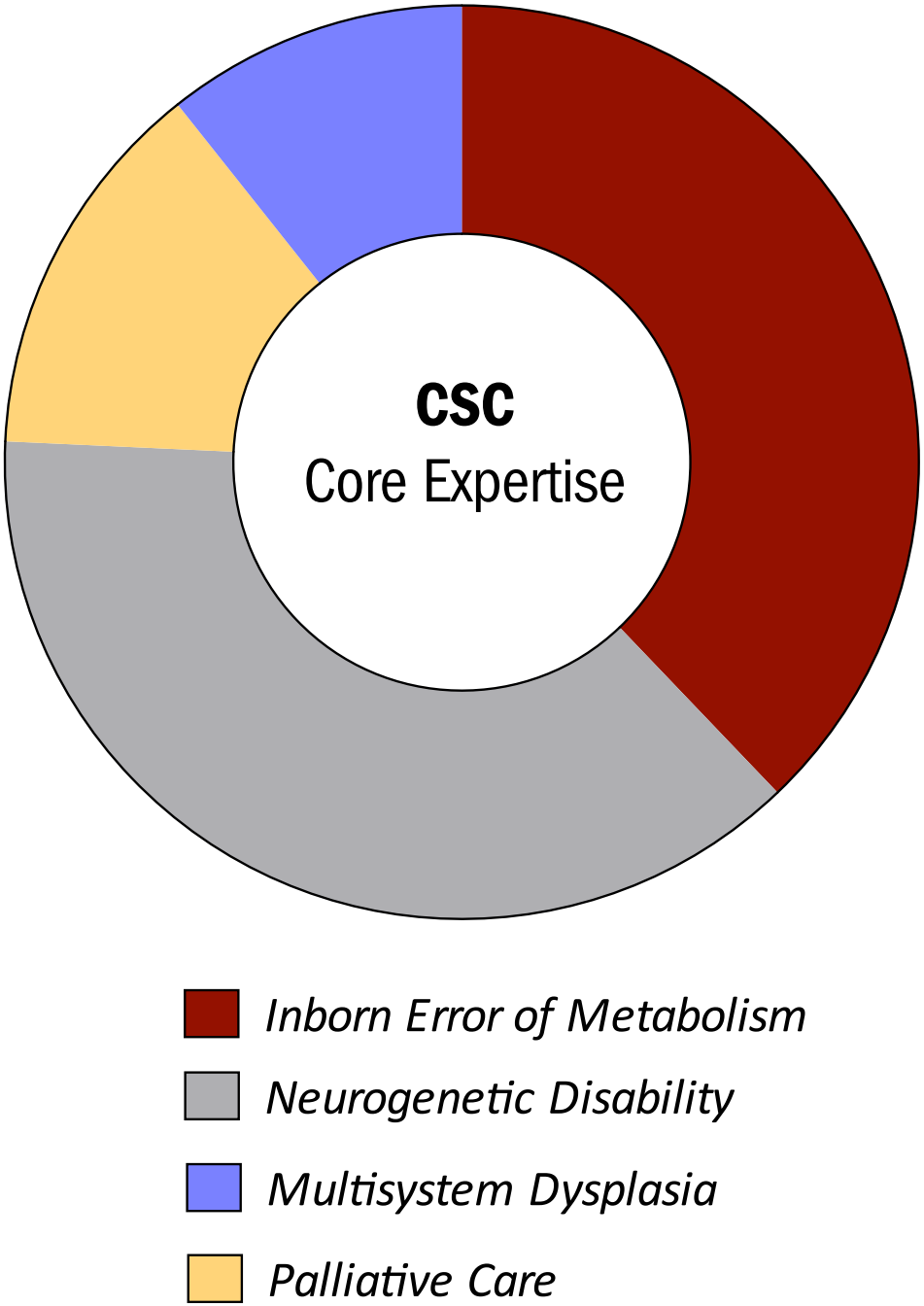
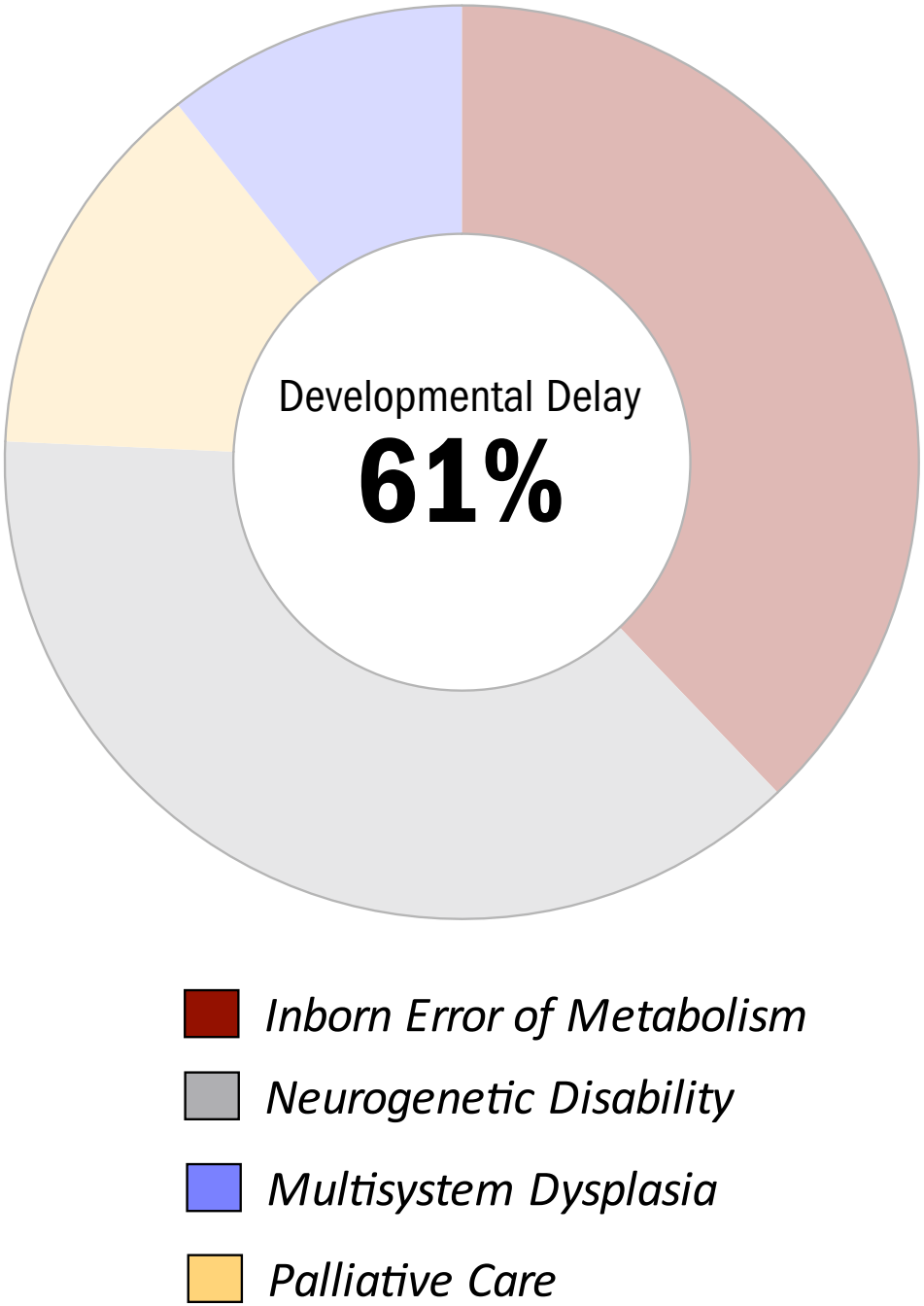
Common Disorders, Uncommon Causes

CLINICAL DIAGNOSIS	DISORDER	GENE
Cerebral palsy	Glutaric aciduria, type 1	*GCDH*
	Propionic acidemia	*PCCB*
	Gap junction deficiency	*GJA12*
	Crigler-Najjar syndrome	*UGT1A1*
	Hereditary spastic paraplegia	*SPG20*
	Segawa dystonia syndrome	*TH*
	Idiopathic dystonia	*DYT1*
Mental retardation	MTHFR deficiency	*MTHFR*
	Maple syrup urine disease	*BCKDHA*
	Phenylketonuria	*PH*
	Salla disease	*SLC17A5*
	Tyrosinemia	*HPD*
	Bardet-Biedel syndrome	*BBS1*
	Fragile X syndrome	*FMR1*
Epilepsy	Biotinidase deficiency	*BTD*
	CDFE syndrome (CASPR2)	*CNTNAP2*
	GM3 synthase deficiency	*ST3GAL5*
	LYK5 defiency syndrome	*LYK5*
Stroke and Hemorrhage	Hypercholanemia, TJP type	*TJP2*
	Hypercholanemia, BAAT	*BAAT*
	Factor V Leiden	*F5*
	Sitosterolemia	*ABCG8*
	Alpha-1-antitrypsin deficiency	*SERPINA1*
Sudden death	SIDDT syndrome	*TSPYL1*
	Hypertrophic cardiomyopathy	*SLC25A4*
Lethal infection	Properdin deficiency (X-linked)	*PFC*
	SCID, IL7 receptor type	*IL7R*
	SCID, Omenn type	*RAG1*
	Adenosine deaminase	*ADA*

1000 Patients, 115 Disorders

ABCG8 1720G>A
ACADM 985A>G
ACADM IVS4-30A>G
ADA 646G>A
ADAMTS10 17,346 bp deletion
AMN 44 bp deletion
APOA4 552_749dup
ATP8B1 923G>T
BAAT 226A>G
BBS1 1169T>G
BCKDHA 1312T>A
BTD 1459T>C
BTD 1368A>C
BTD 1330G>C
C7orf10 895C>T
C7orf27 638_639insA
CAPN3 2306G>A
CFP 379T>G
CHST3 1298C>T
CLCNKB 22,508 bp deletion
CNGA3 1126G>A
CNTNAP2 3709delG
COL1A2 2098G>T
CRADD 382G>C
CYBB 1335C>A
CYP11B1 1343G>A
CYP11B2 5 bp deletion
DNAH5 4348C>T
EDNRB 828G>T
ERCC6 IVS14+1G>T
EVC IVS13+5G>T
F11 1327C>T
F5 1601G>A
FLVCR1 361A>G
FMR1 (CGG)n expansion
GALT 563A>G
GALT 940A>G
GCDH 1262C>T
GJB2 35delG
GJC2 203A>G
GLB1 902C>T
GLDC 2186delC
GLDC 128delA
HARS 1361A>C
HFE 187C>G
HFE 845G>A
HPD 85G>A
HPD 479A>G
HPD 1005C>G
HSD3B2 35G>A
IL7R 2T>G
ITCH 394_395insA
KRIT1 47G>C
LAMB2 440A>G
LMNA 568C>T
LRP5 1225A>G
LRP5 1275G>A
MCCC2 295G>C
MCCC2 518insT
MCCC2 687A>C
MKKS [250C>T + 724G>T]
MTHFR 1129C>T
MVK 803T>C
MVK 1174G>A
NPHS1 1481delC
NPHS1 3250delG
NPHS2 413G>A
NTRK1 IVS12+1G>A
PAH 280_282delATC
PAH 782G>A
PAH IVS10-11G>A
PAH IVS12+1GA
PAH 782G>A
PCCB 1606A>G
PEPD 793C>T
PKLR 1436G>A
PYGL IVS13+1G>A
RAG1 2974A>G
RMRP 70A>G
SERPINA1 1096G>A
SGCB 452C>G
SGCB 271C>T
SLC12A3 1924C>G
SLC12A3 8,627 bp deletion
SLC17A5 115C>T
SLC25A19 530G>C
SLC25A4 523delC
SLC3A1 IVS6+2T>C
SLC3A1 1354C>T
SLC6A3 [1408T>A + 1409A>G]
SLC6A3 IVS9+1G>T
SLC7A9 201C>T
SLC7A9 1166C>T
SMN1 exon 7 deletion
SPG20 1110delA
ST3GAL5 694C>T
STRADA 7 kb deletion
TERT 1710C>G
TH 698G>A
TJP2 143T>C
TMCO1 139_140delAG
TNFRSF1A 362G>A
TNNT1 505G>T
TOR1A GAG deletion
TSPYL1 457_458insG
TUBGCP6 5458T>G
UGT1A1 222C>A
ZMPSTE24 54_55insT

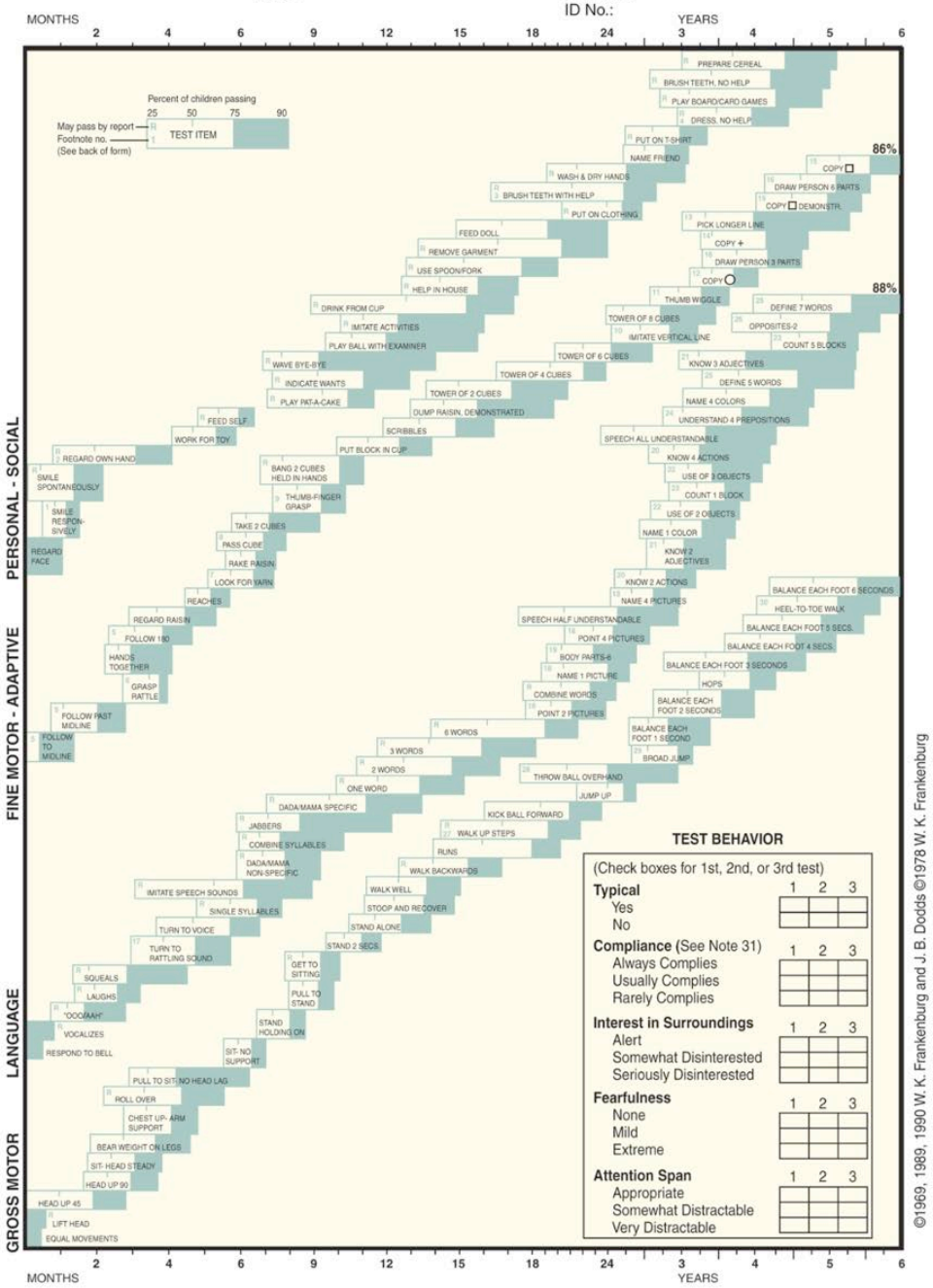

CSC
Core Expertise
Inborn Error of Metabolism
Neurogenetic Disability
Multisystem Dysplasia
Palliative Care


Developmental Delay
61%
Inborn Error of Metabolism
Neurogenetic Disability
Multisystem Dysplasia
Palliative Care

Denver II

Examiner:
Date:

Name:
Birthdate:
ID No.:

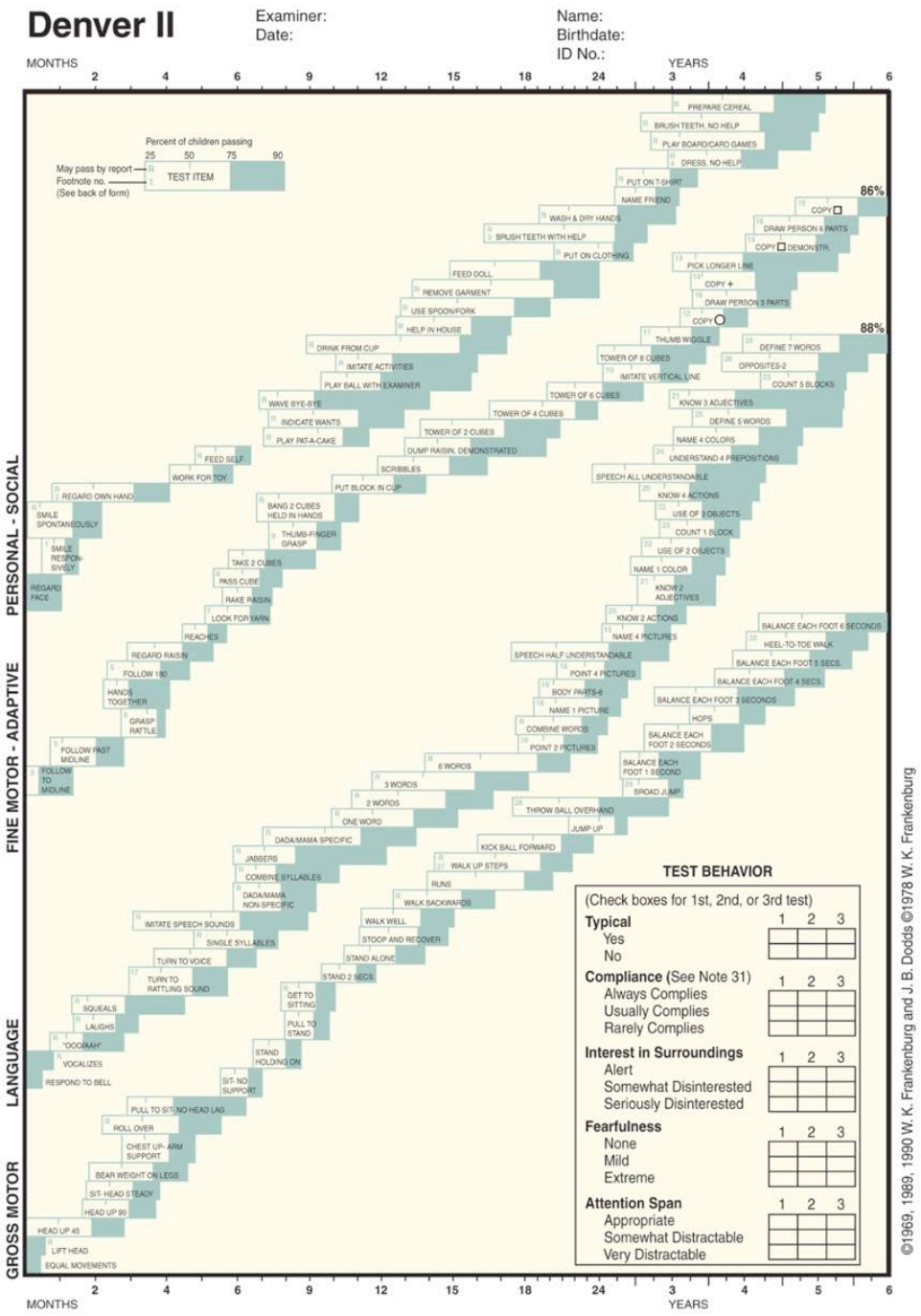


Social

Adaptive

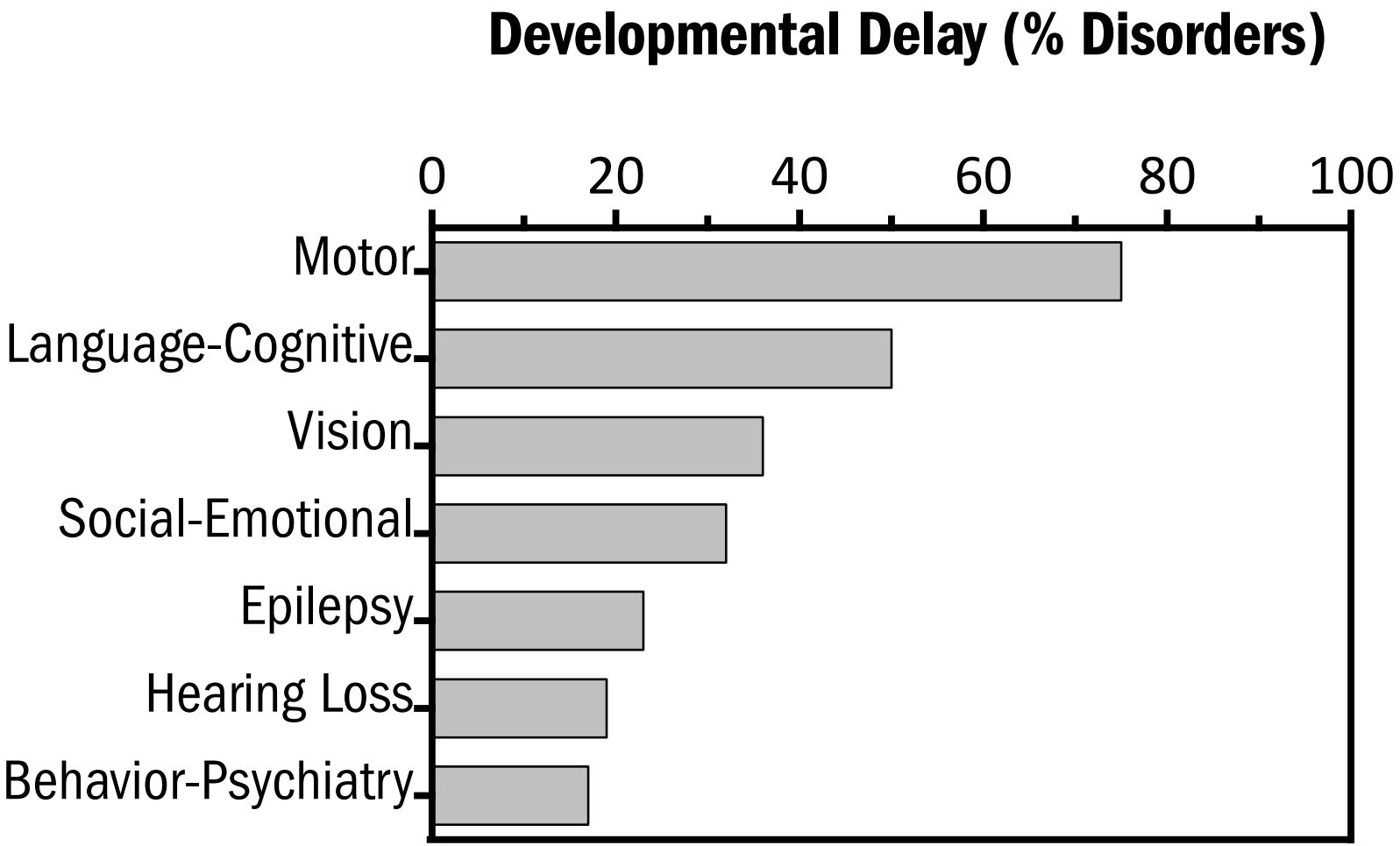
Language

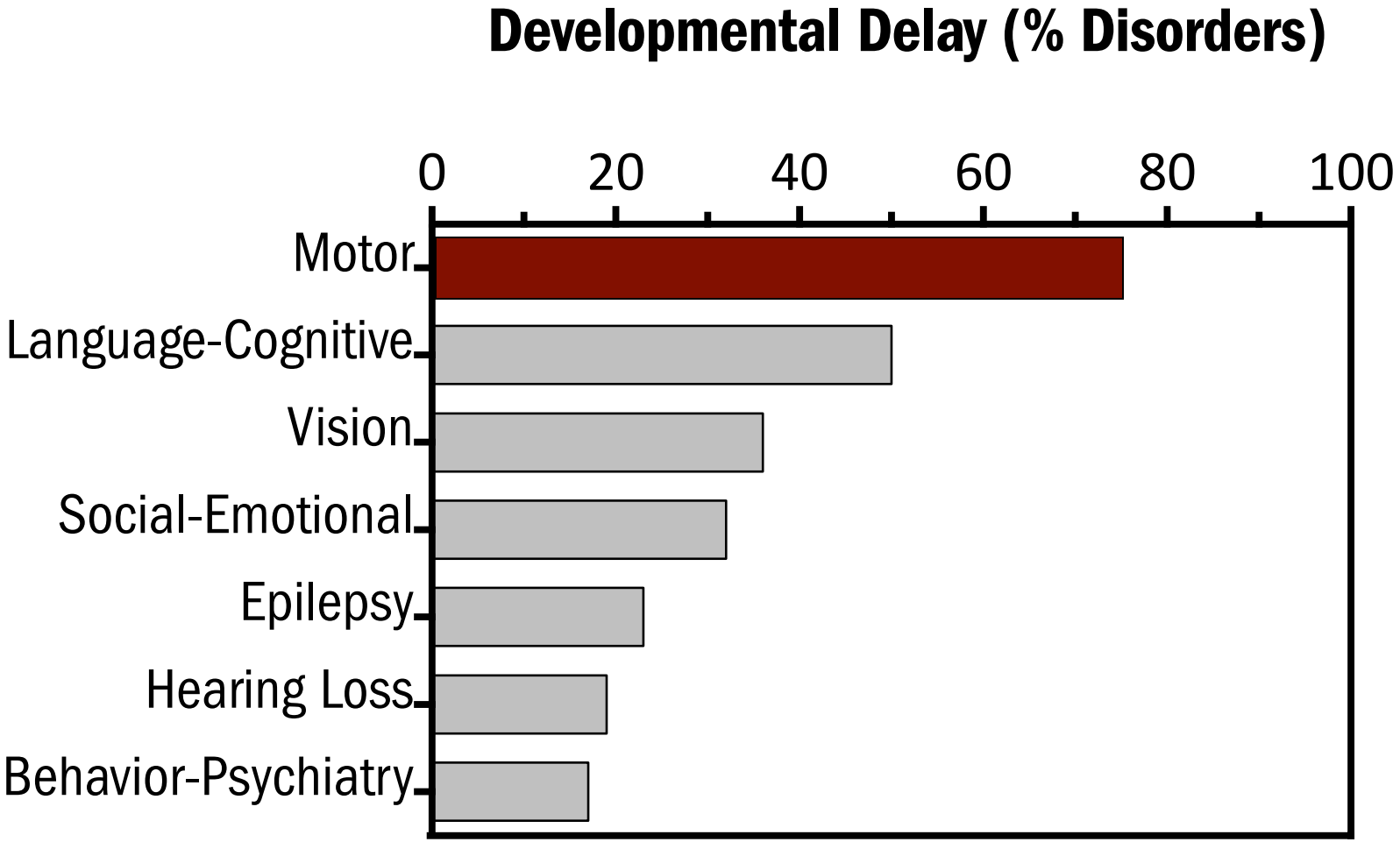
Motor



“To move things is all that mankind can do;
For such the sole executant is muscle, whether in whispering a syllable or in felling a forest.”

Charles Sherrington, 1924


Developmental Delay (% Disorders)
0
20
40
60
80
100
Motor
Language-Cognitive
Vision
Social-Emotional
Epilepsy
Hearing Loss
Behavior-Psychiatry


Developmental Delay (% Disorders)
0
20
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Vision
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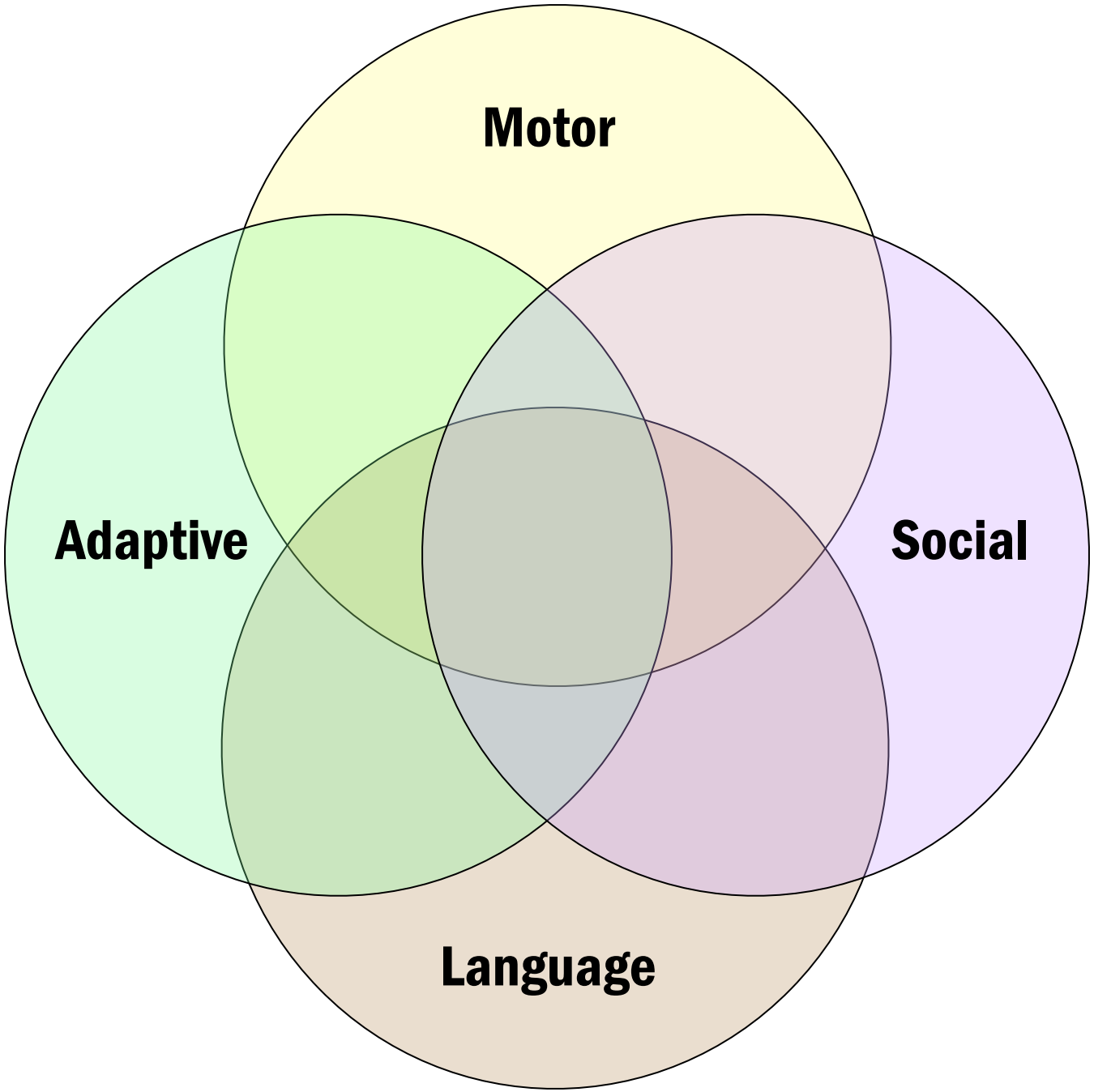
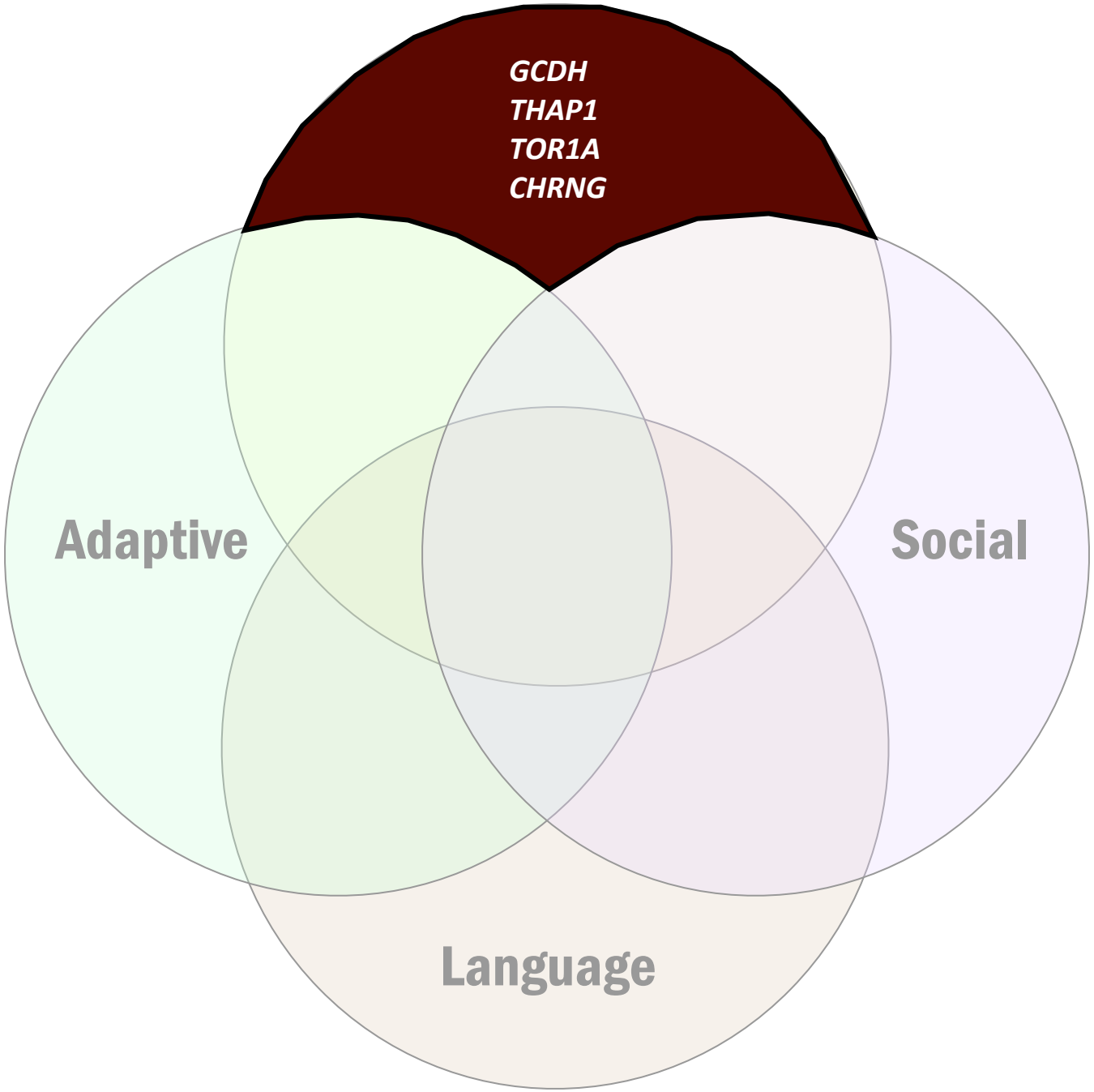
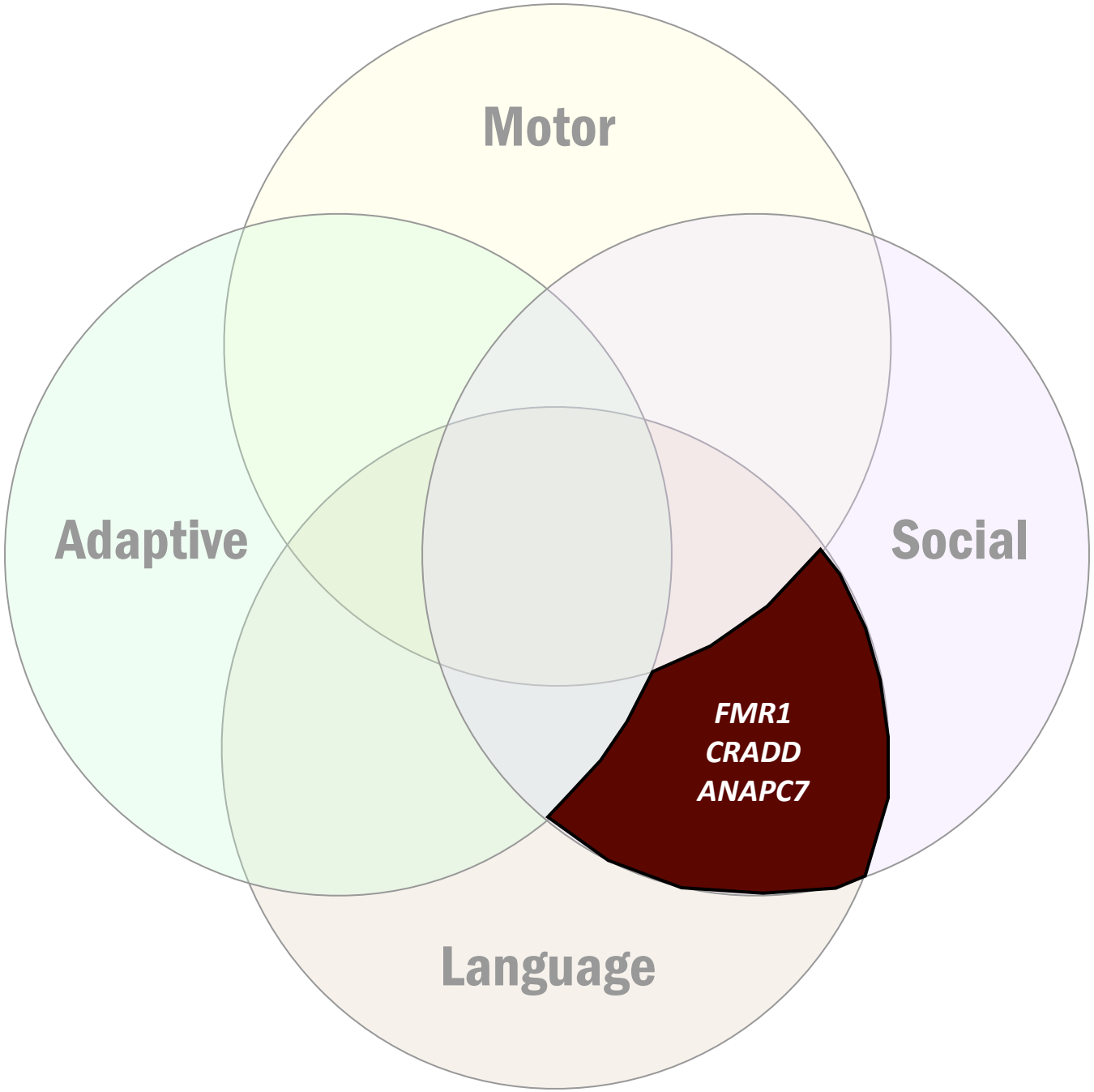
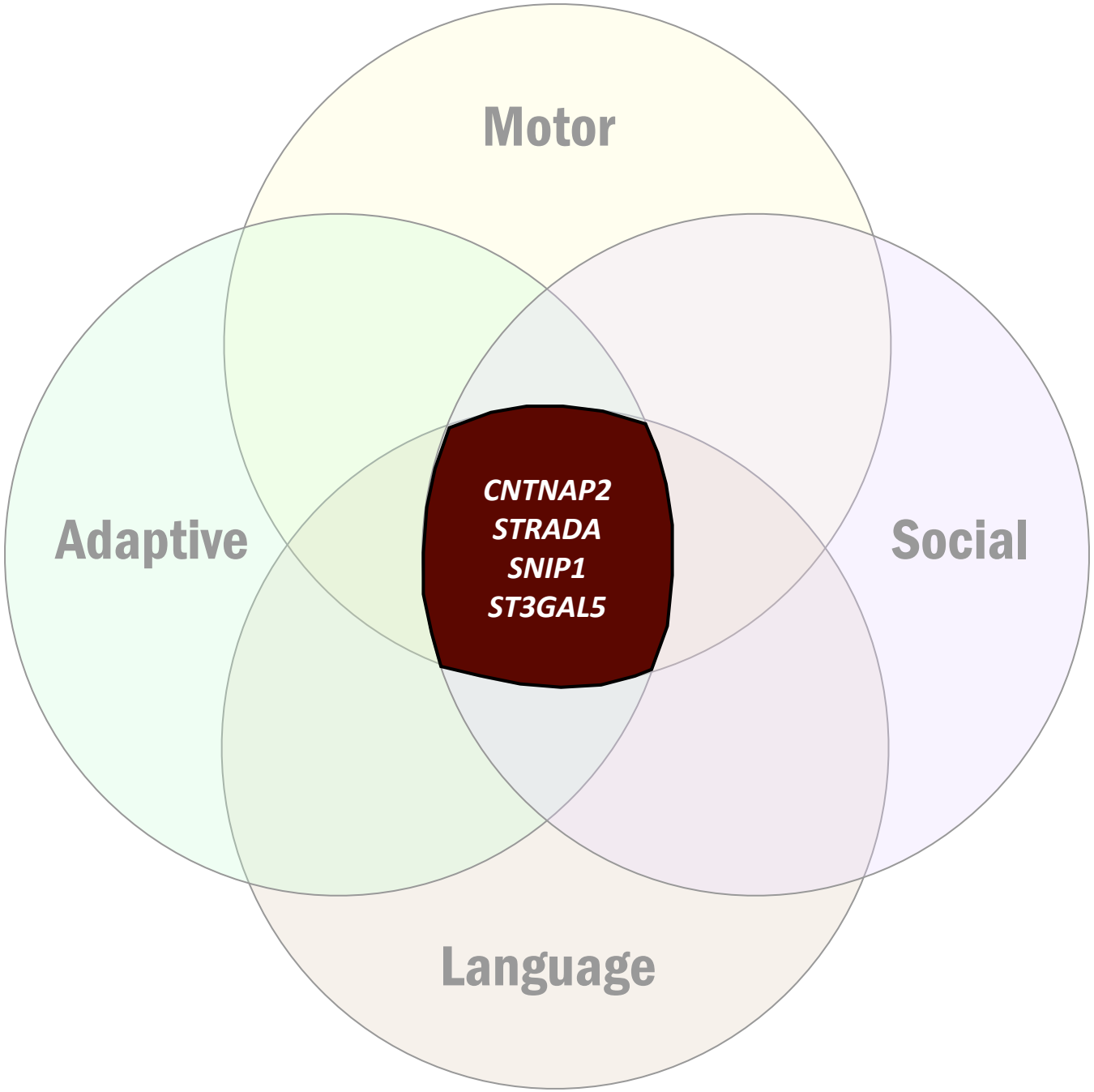
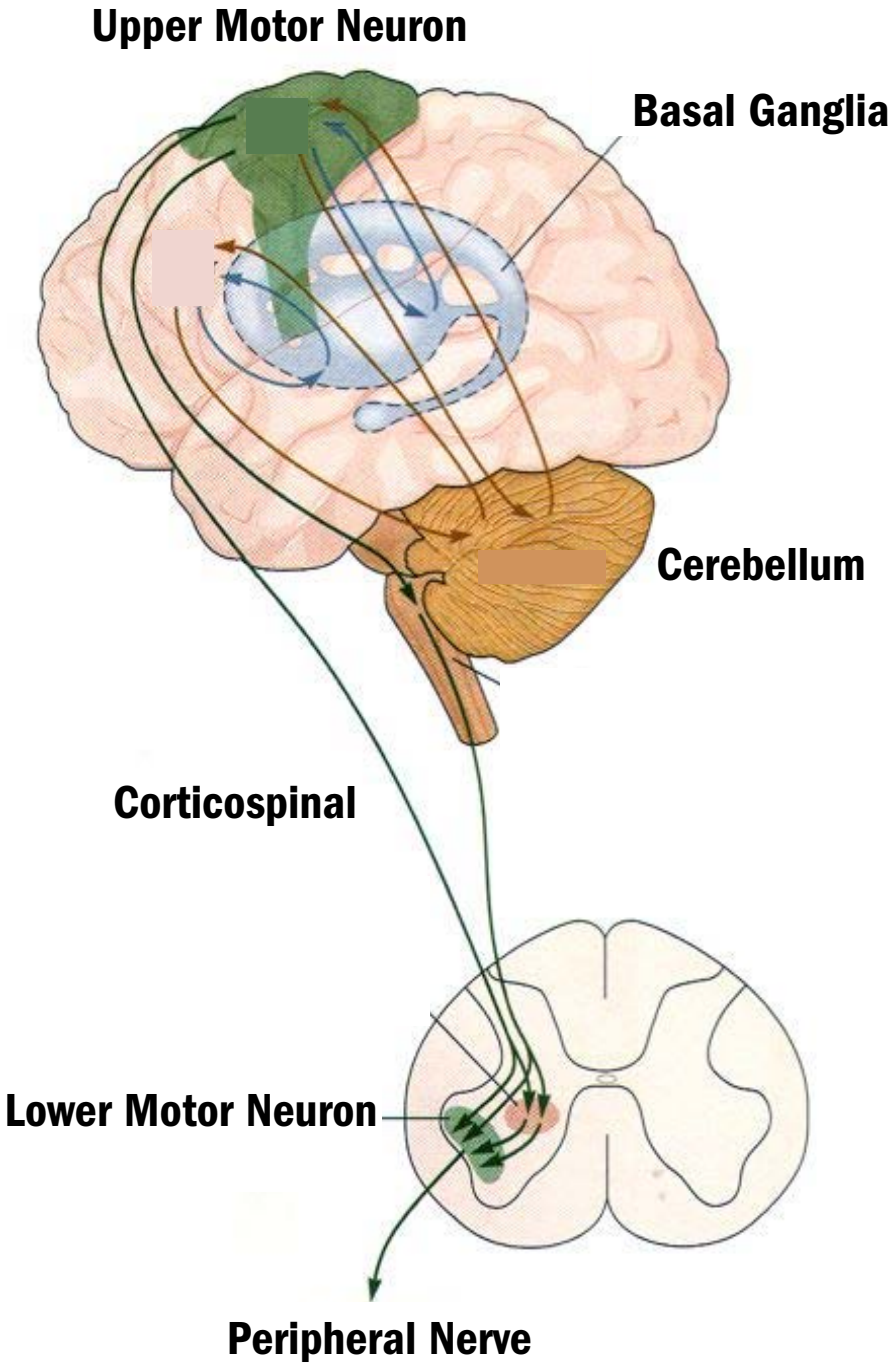
Behavior-Psychiatry


Motor
Adaptive
Social
Language

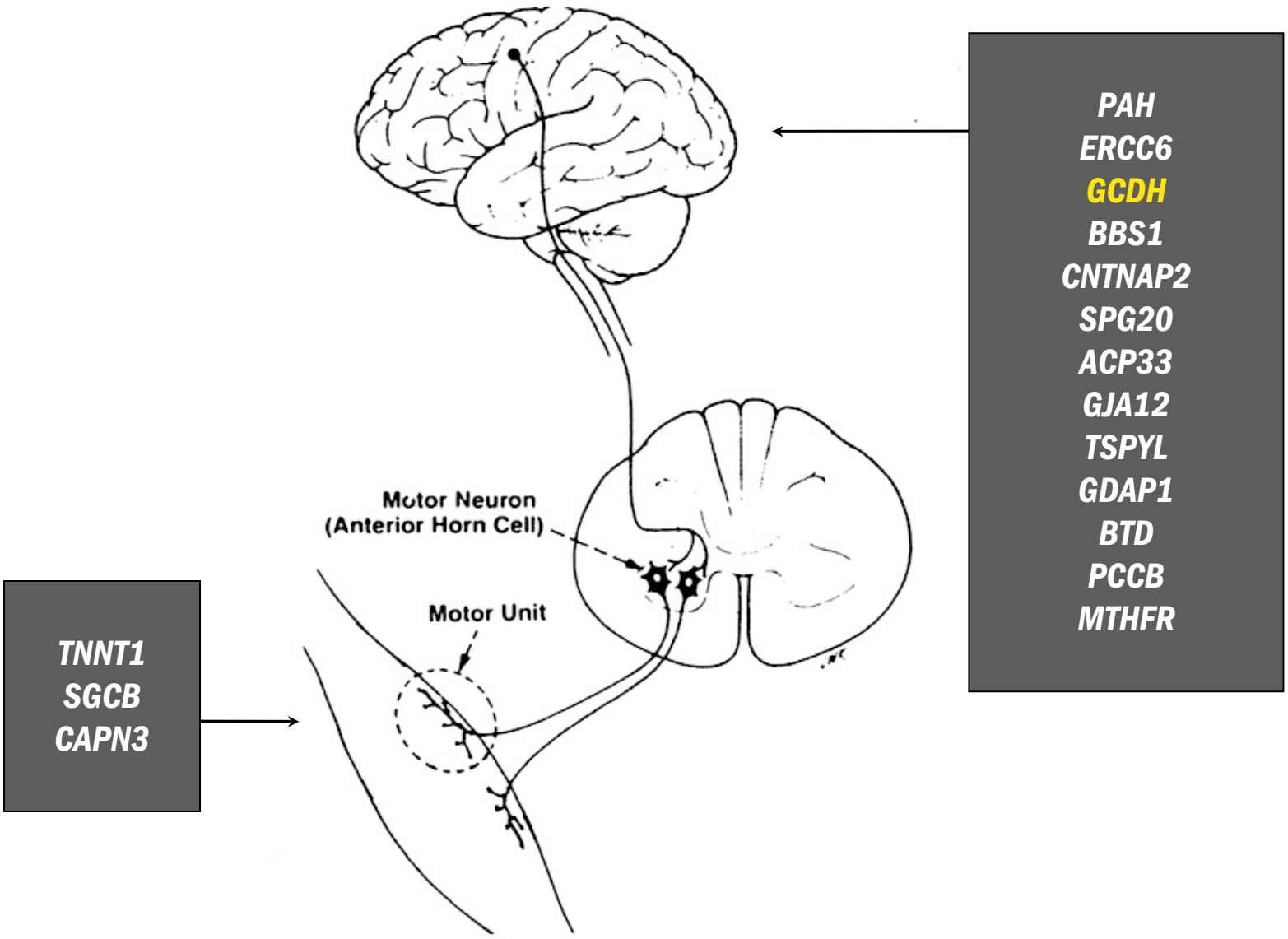

GCDH
THAP1
TOR1A
CHRNG
Adaptive
Social
Language


Motor
Adaptive
Social
Language
FMR1
CRADD
ANAPC7

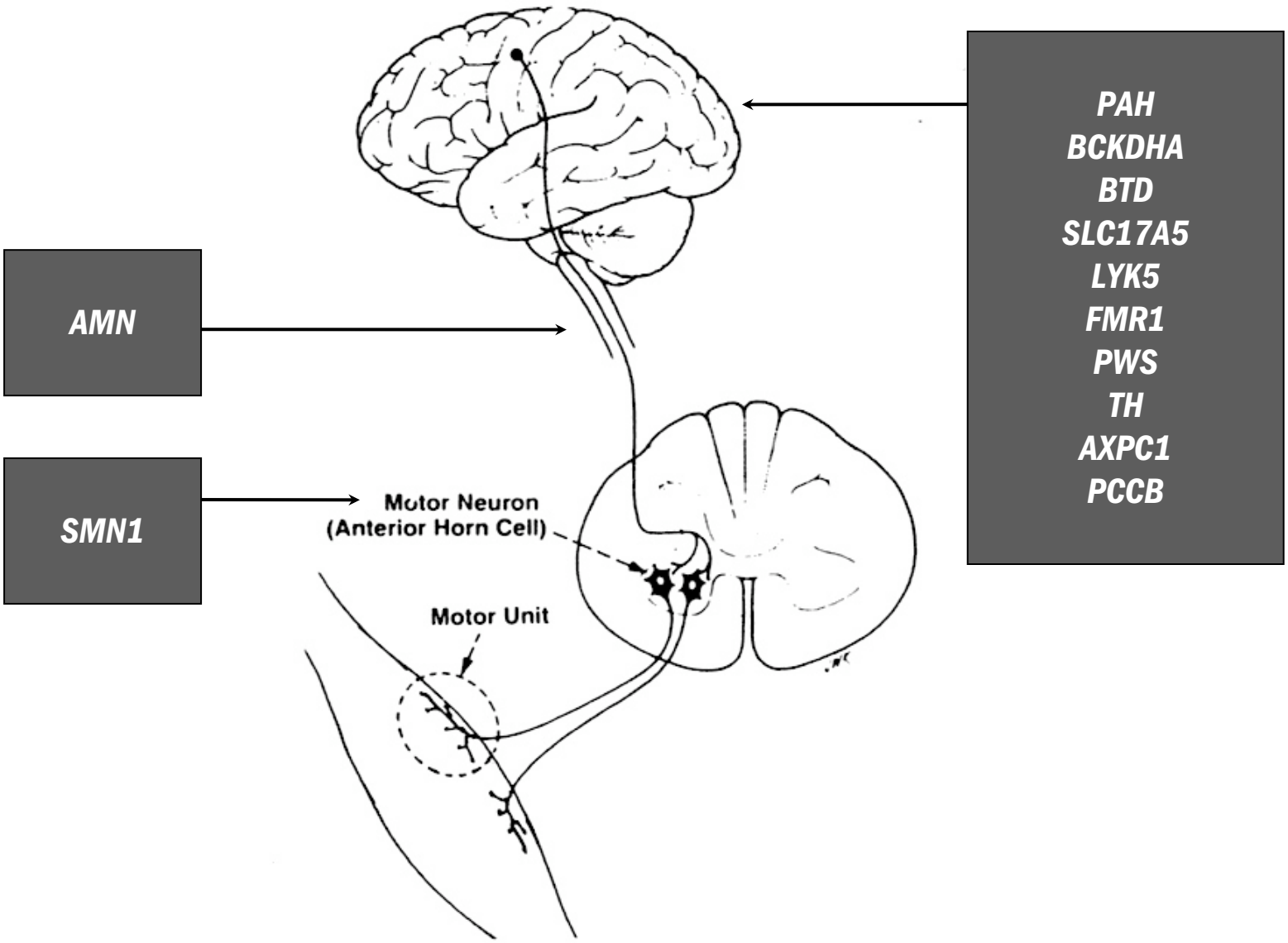

Motor
Adaptive
Social
Language
CNTNAP2
STRADA
SNIP1
ST3GAL5

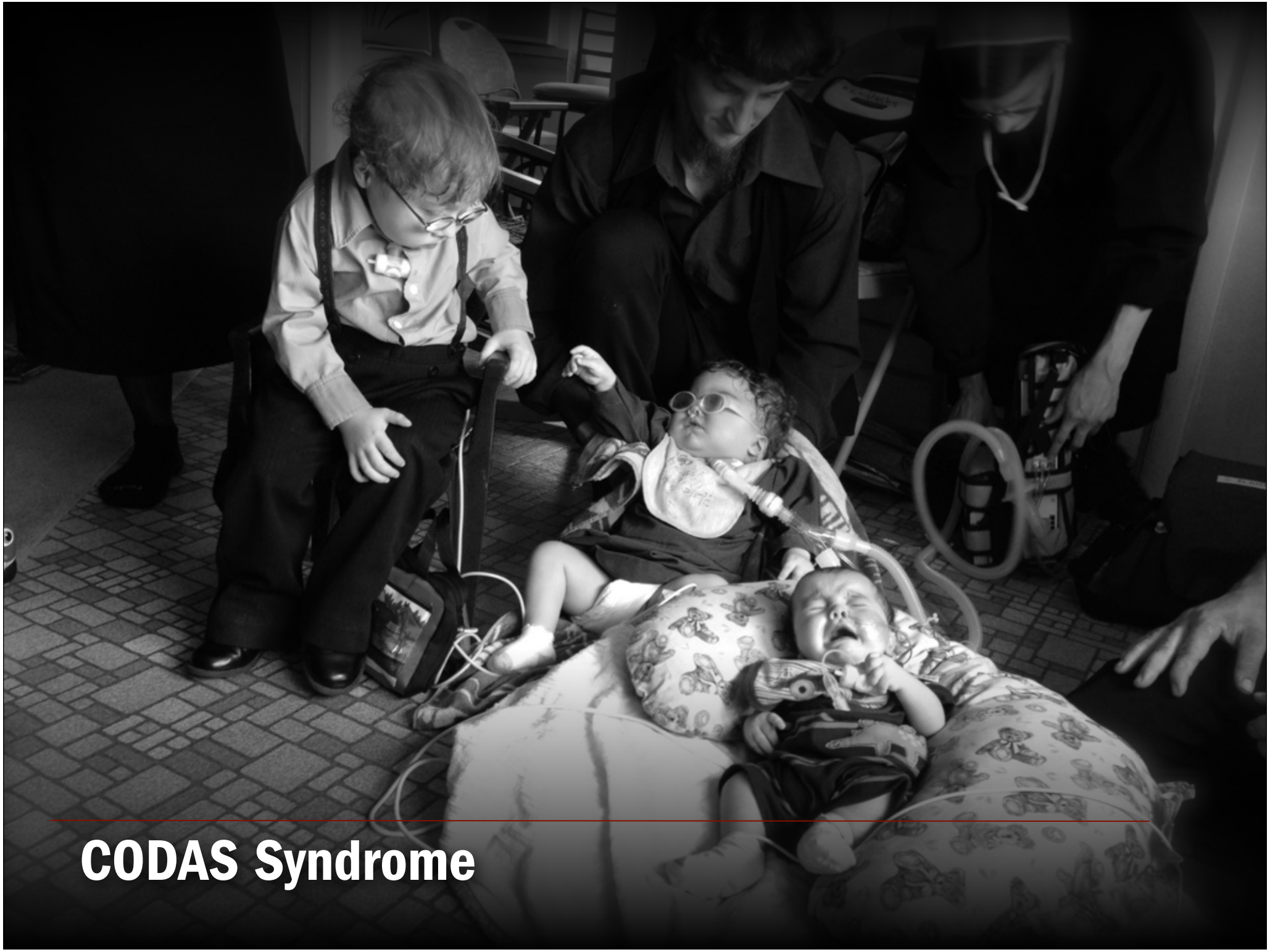

Upper Motor Neuron
Basal Ganglia
Cerebellum
Corticospinal
Lower Motor Neuron
Peripheral Nerve

Amish Child

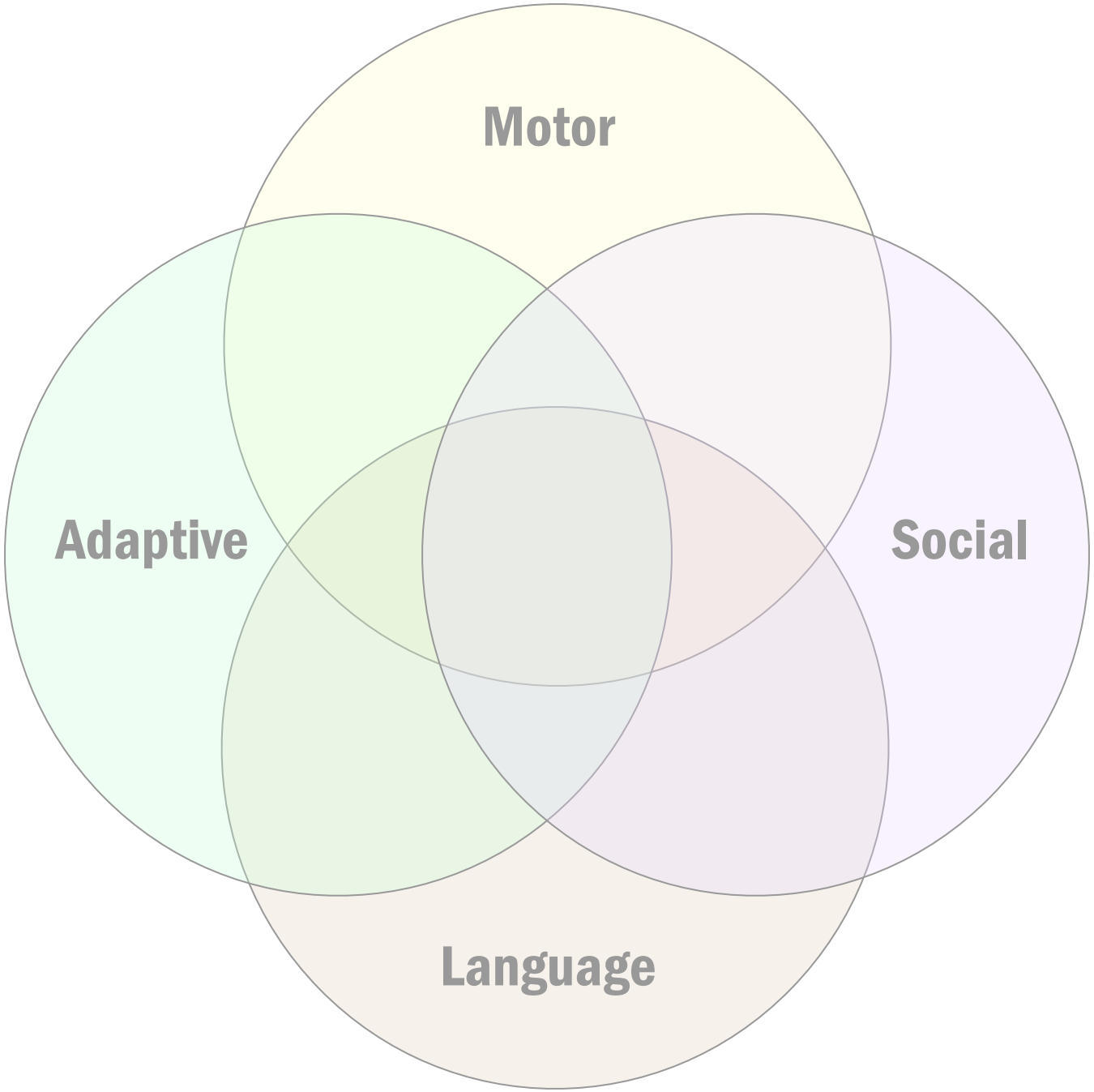

PAH
ERCC6
GCDH
BBS1
CNTNAP2
SPG20
ACP33
GJA12
TSPYL
GDAP1
BTD
PCCB
MTHFR
Motor Neuron
(Anterior Horn Cell)
Motor Unit
TNNT1
SGCB
CAPN3

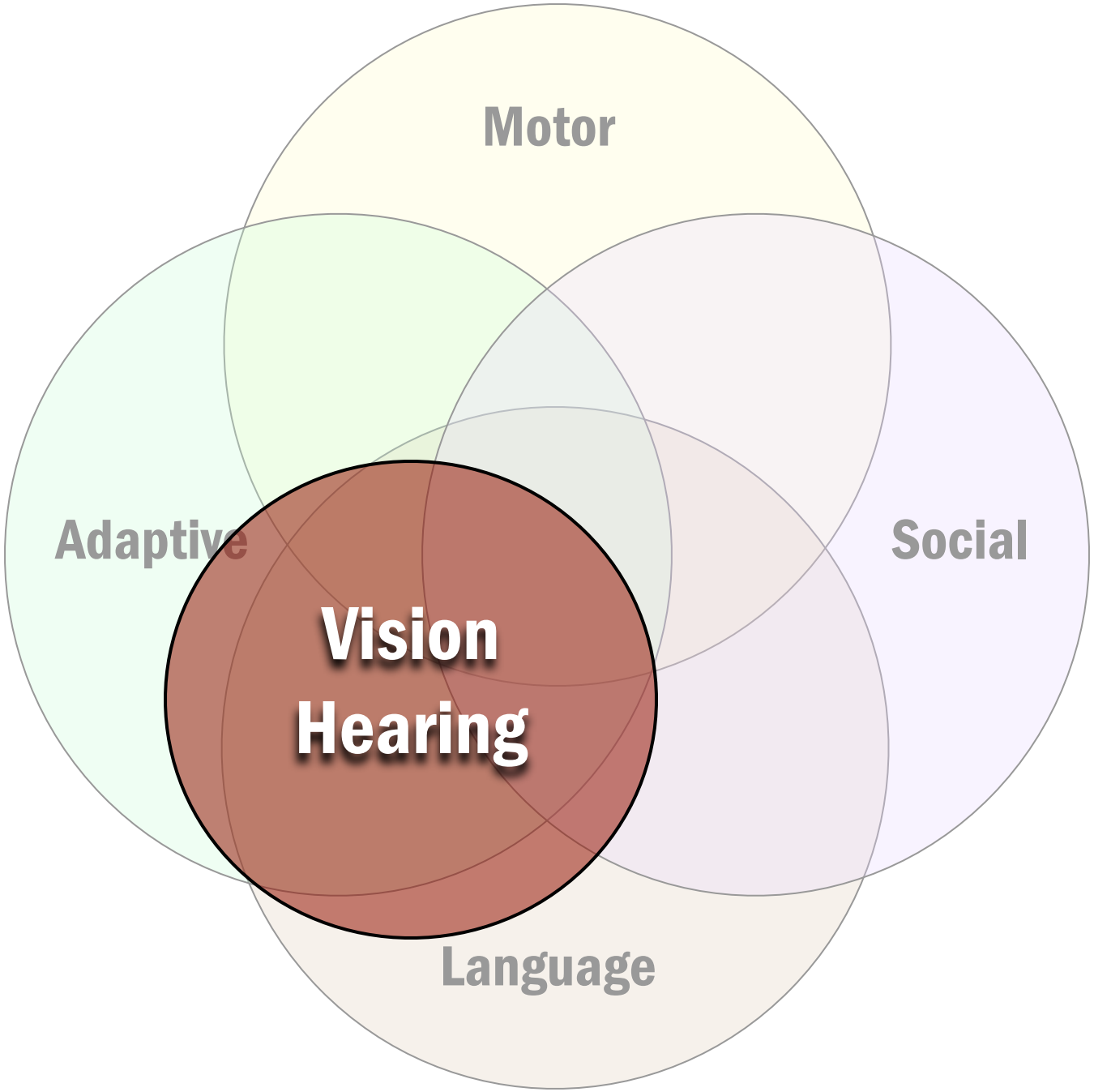
Mennonite Child

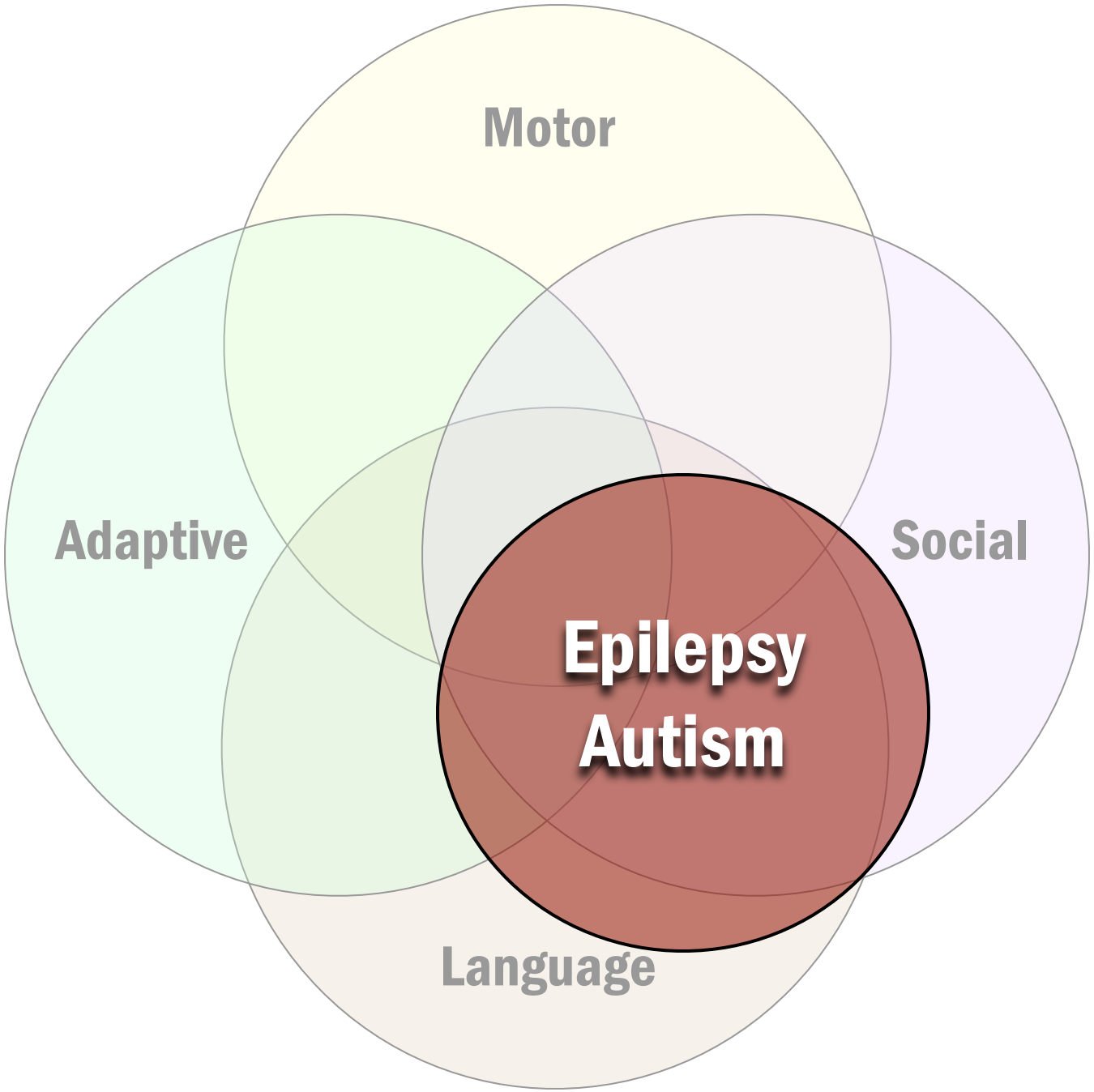


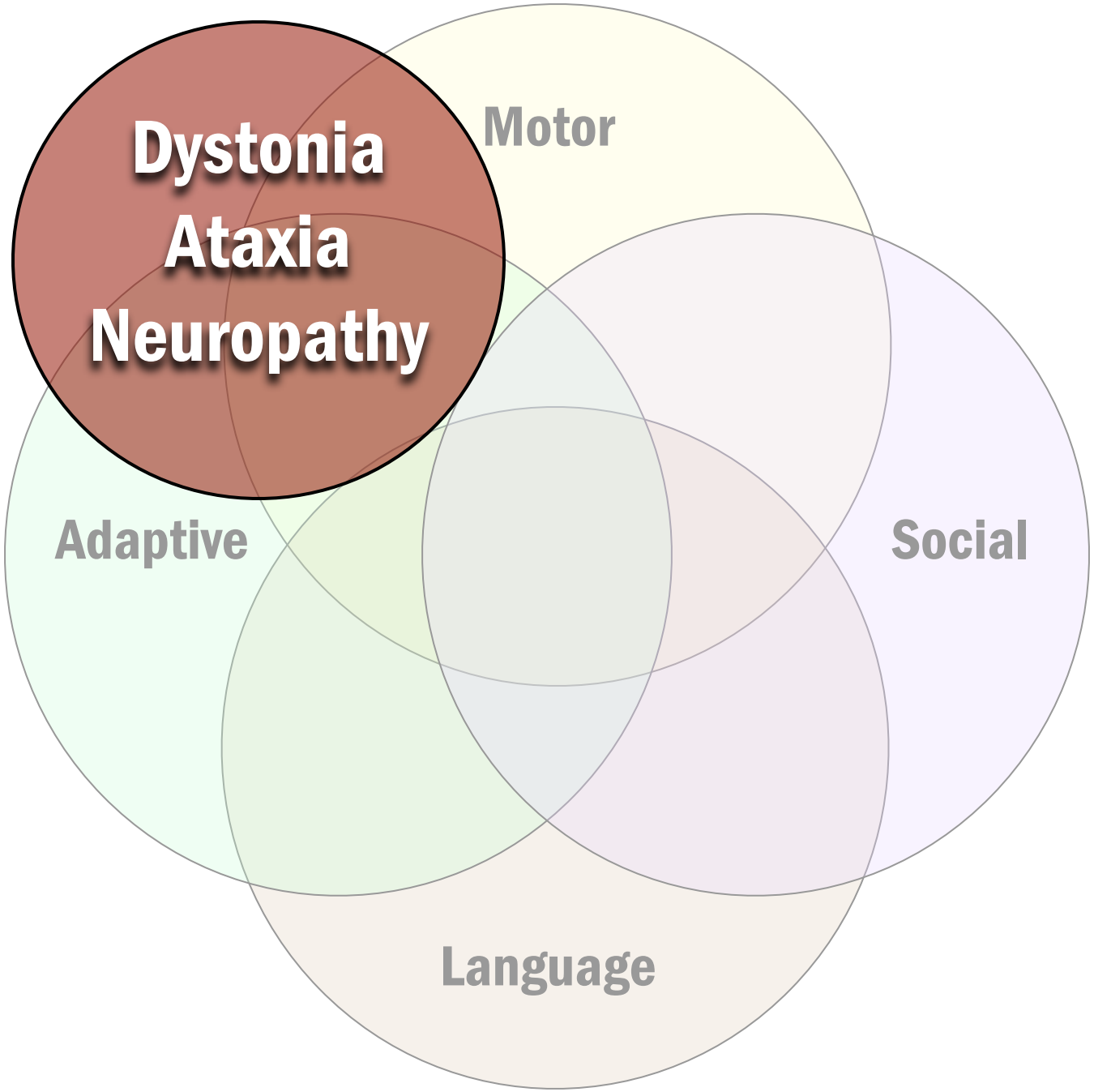


CODAS Syndrome


Motor
Adaptive
Social
Language


Motor
Adaptive
Social
Vision
Hearing
Language


Motor
Adaptive
Social
Epilepsy
Autism
Language


Dystonia
Ataxia
Neuropathy
Motor
Adaptive
Social
Language

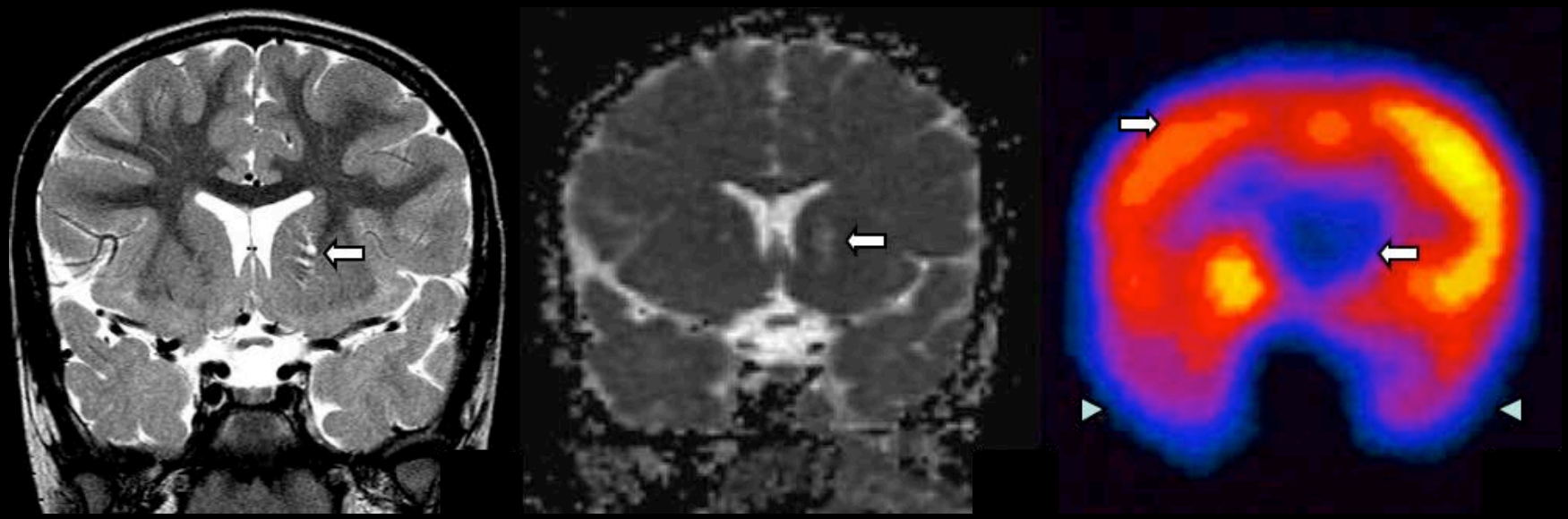

Hemimegalencephaly
Infantile Spasms

STRADA Deficiency

Complex Partial Symptomatic Epilepsy

CNTNAP2 Deficiency

Autism Spectrum Disorder




MTPAP Deficiency
Complicated Cerebellar Ataxia

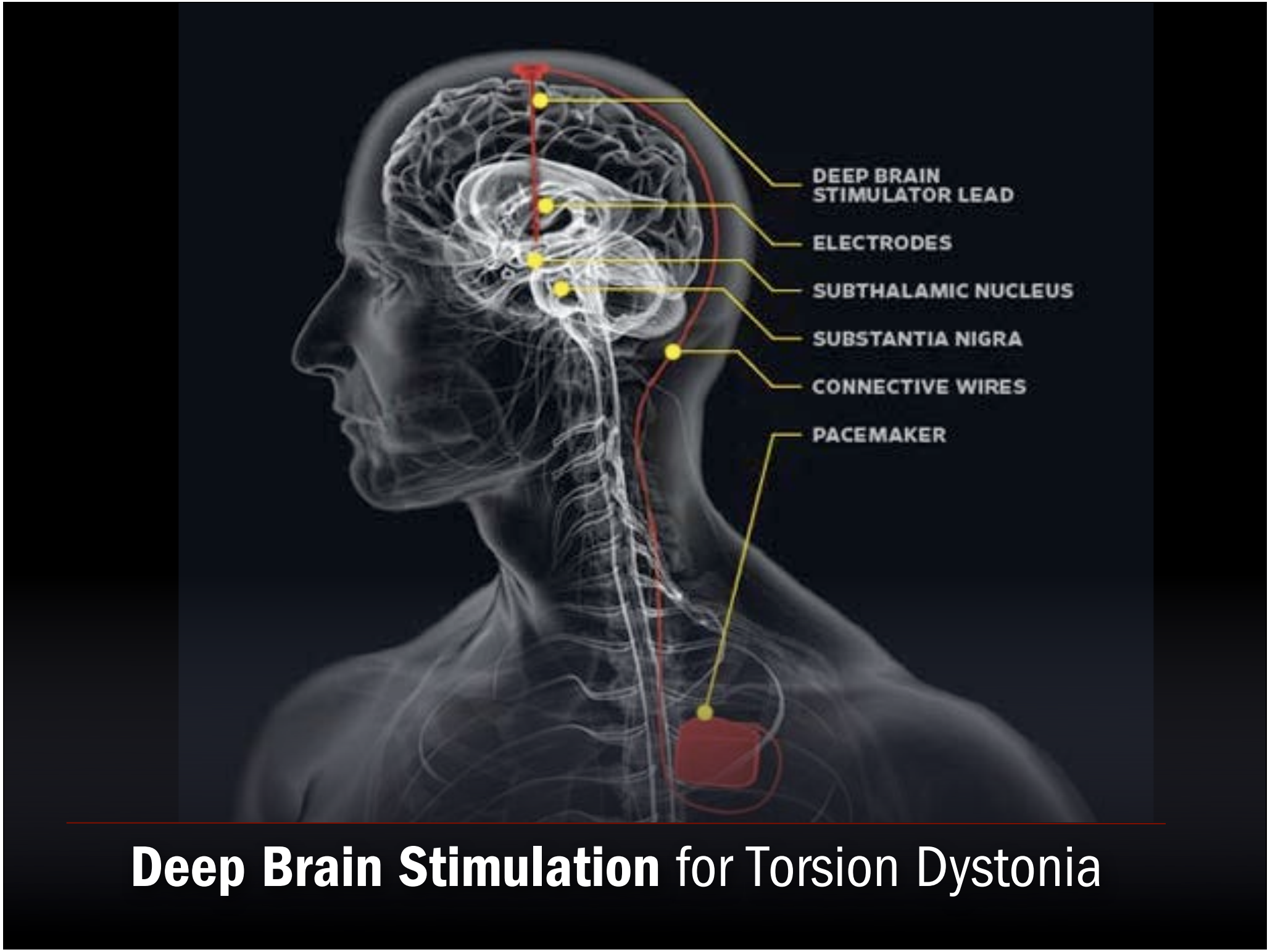
Glutaric Aciduria 1

Brain Injury


Glutaric Aciduria 1
Healthy

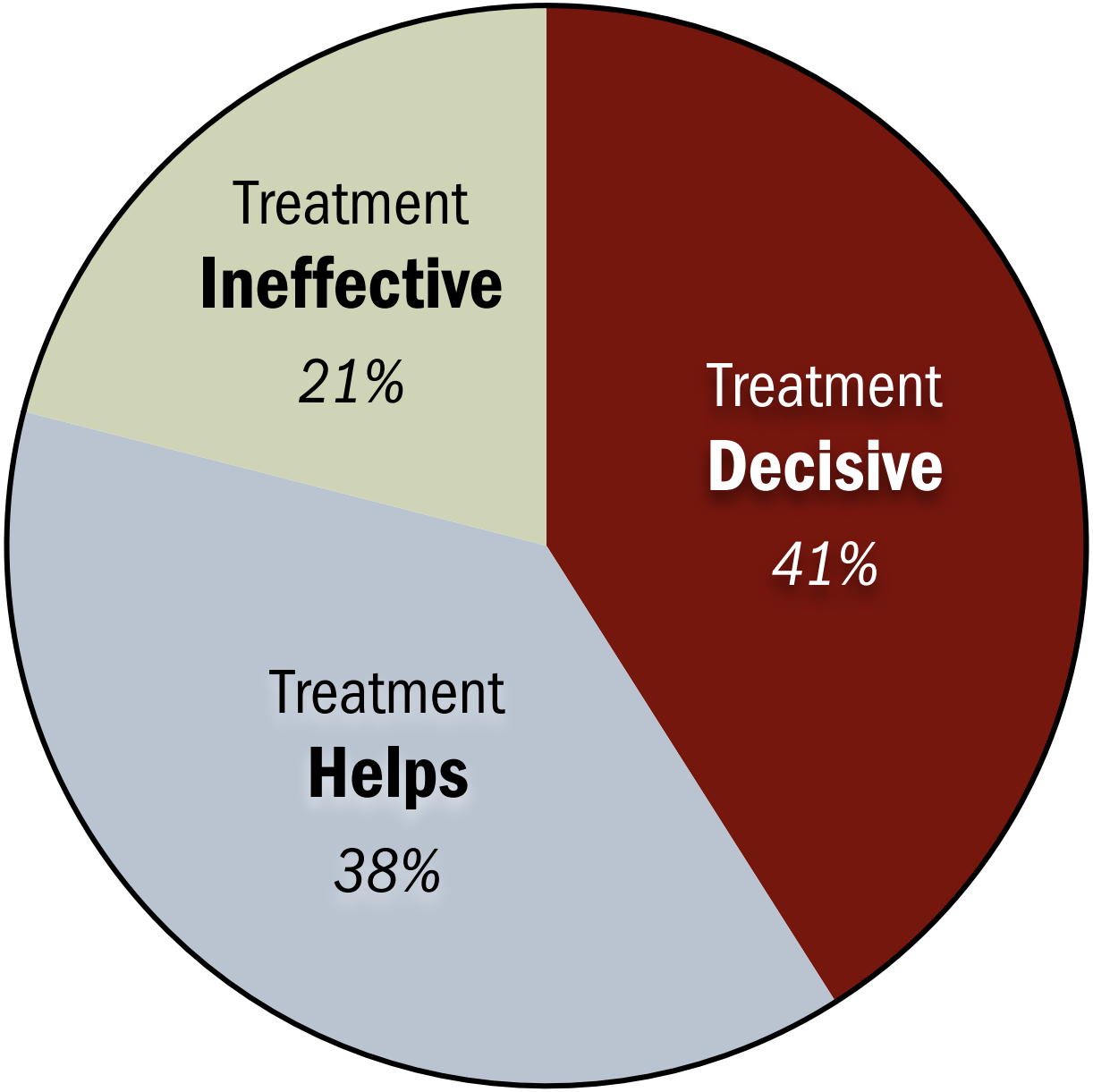
THAP1 (DYT6)

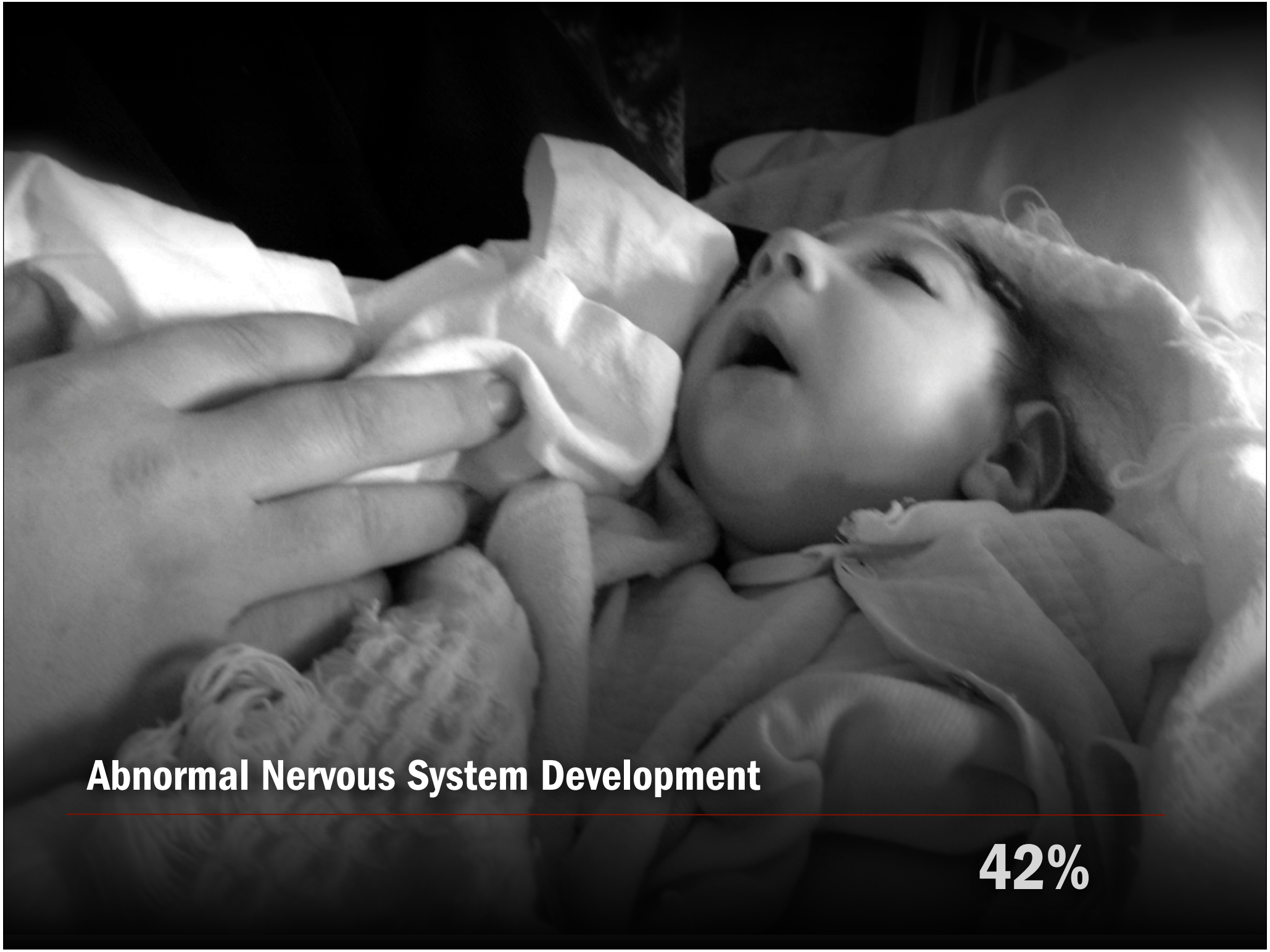
“Idiopathic” Torsion Dystonia



Deep Brain Stimulation for Torsion Dystonia

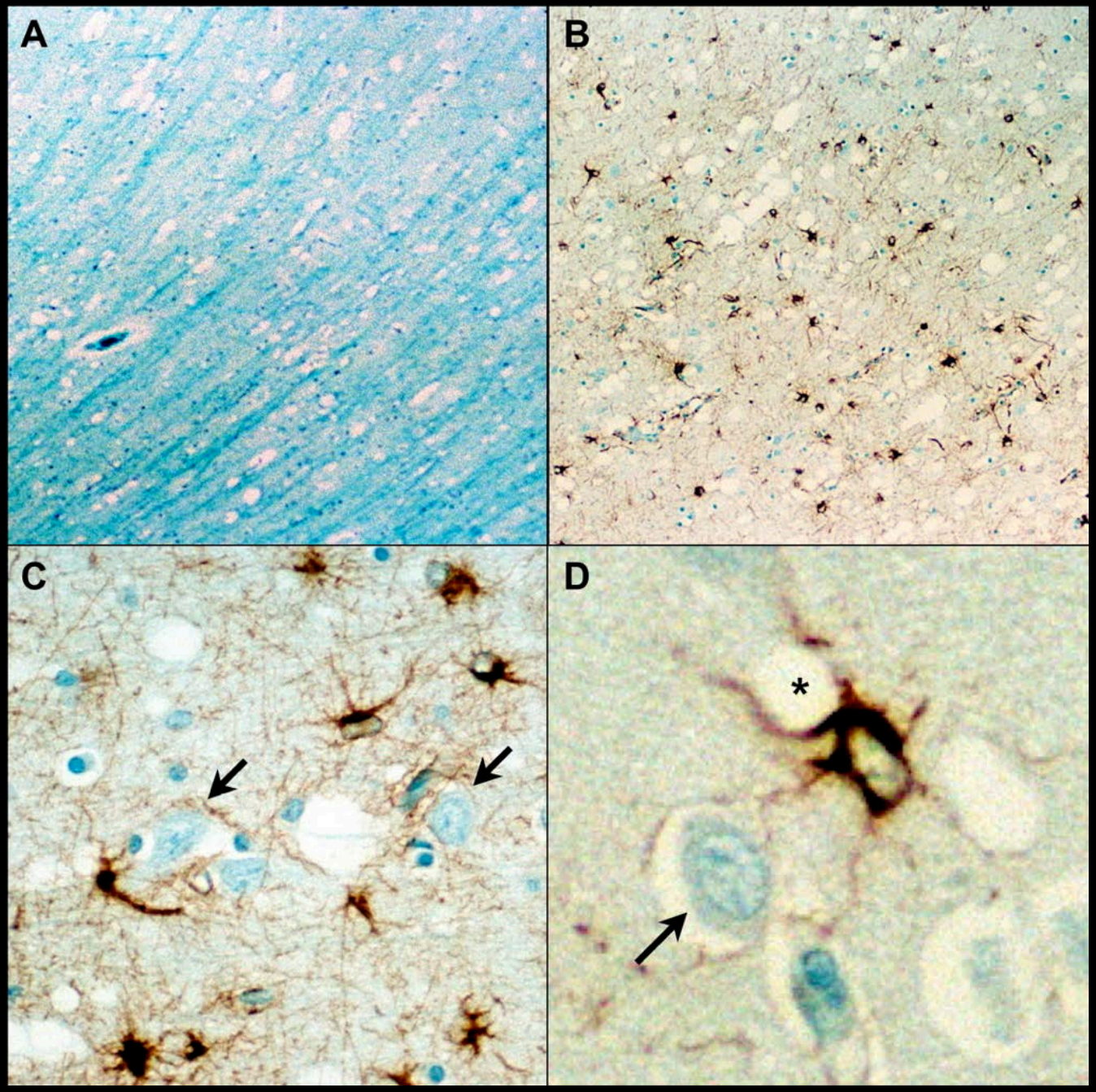

TOR1A (DYT1)
“Idiopathic” Torsion Dystonia


Treatment
Ineffective
21%
Treatment
Decisive
41%
Treatment
Helps
38%


Abnormal Nervous System Development
42%

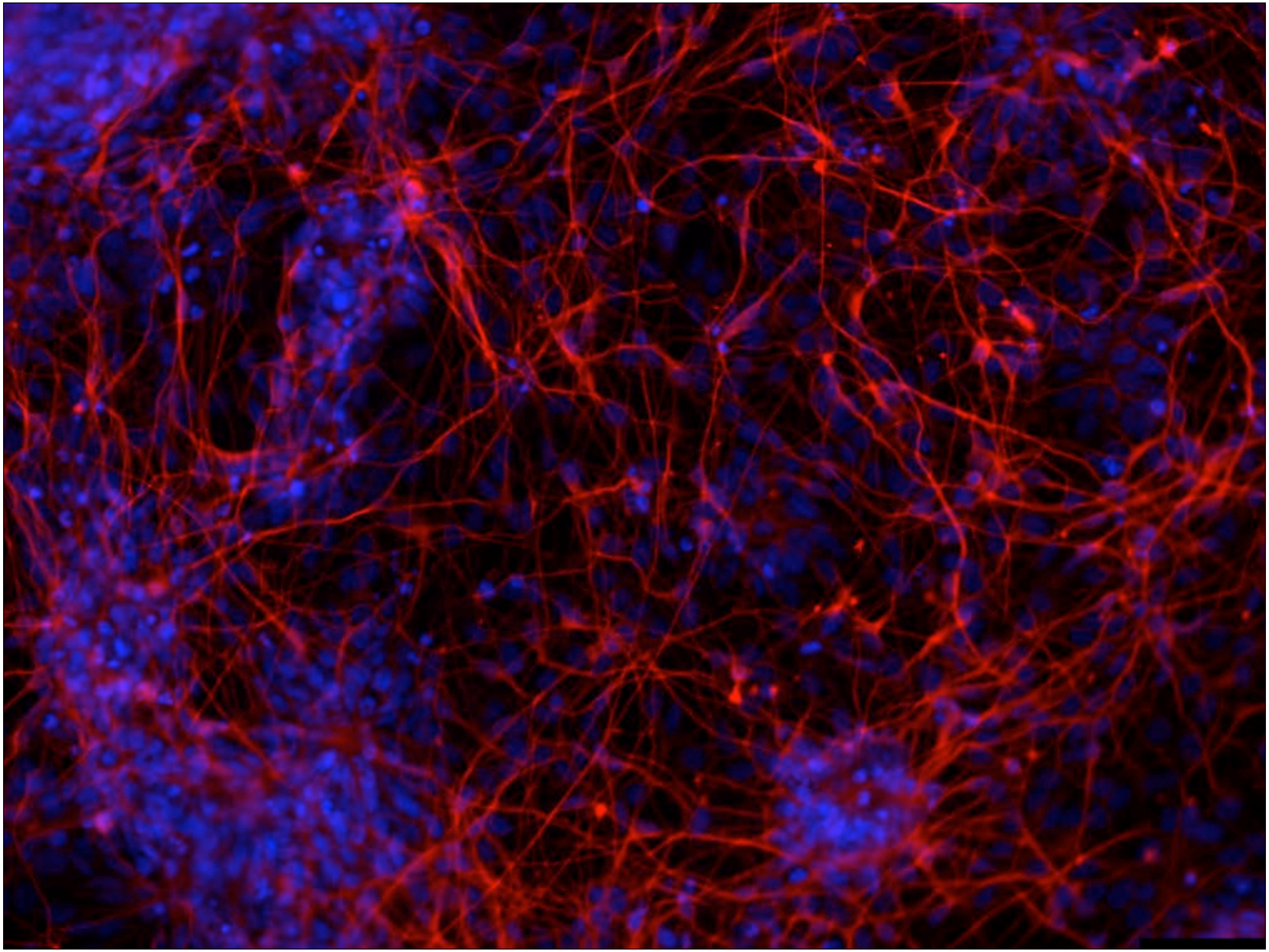
Translational Science

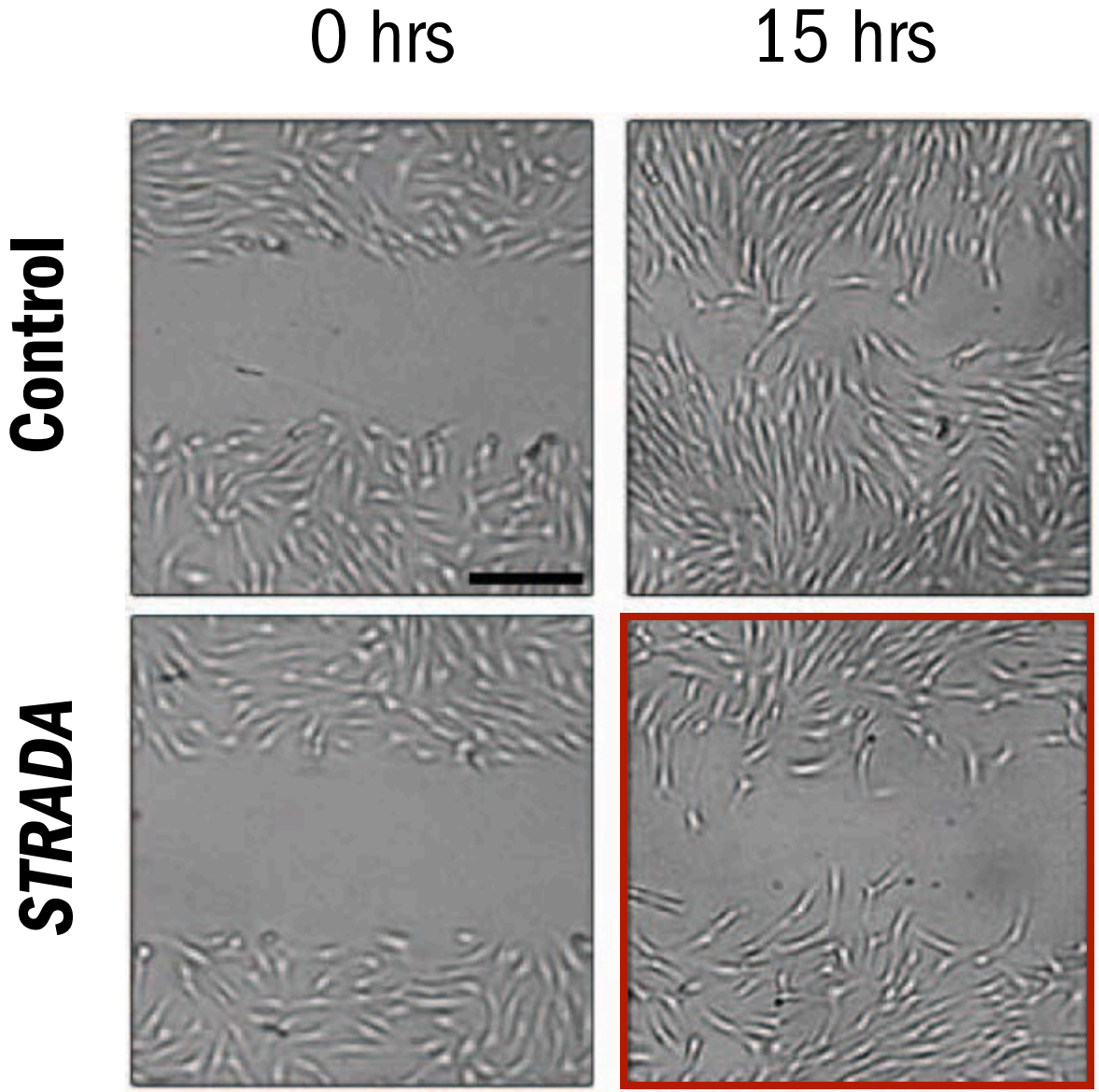
STRADA 7kb Deletion

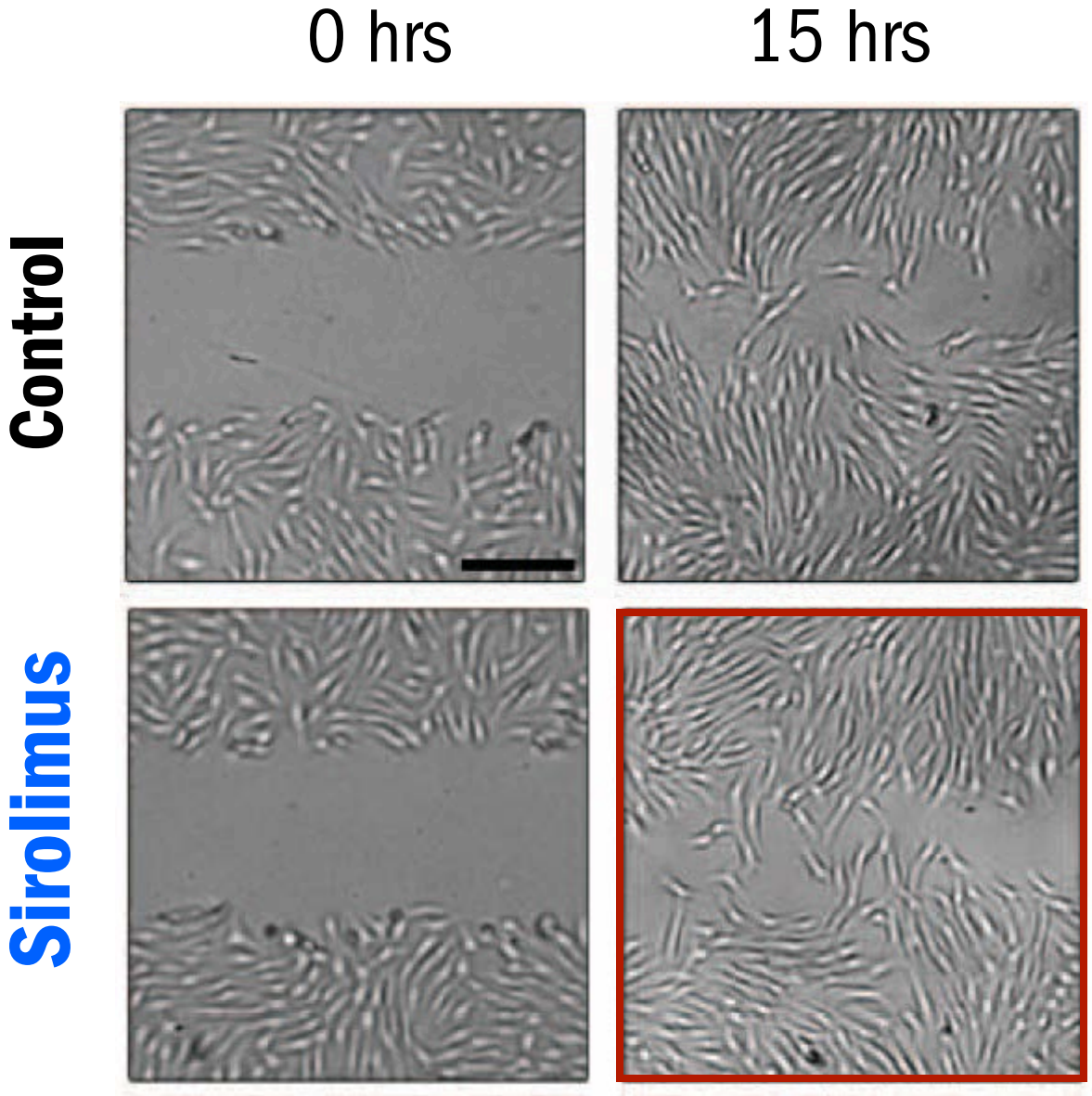

A
B
C
D
*

Collaboration

To Improve Patient Care




0 hrs
15 hrs
Control
STRADA


0 hrs
15 hrs
Control
Sirolimus

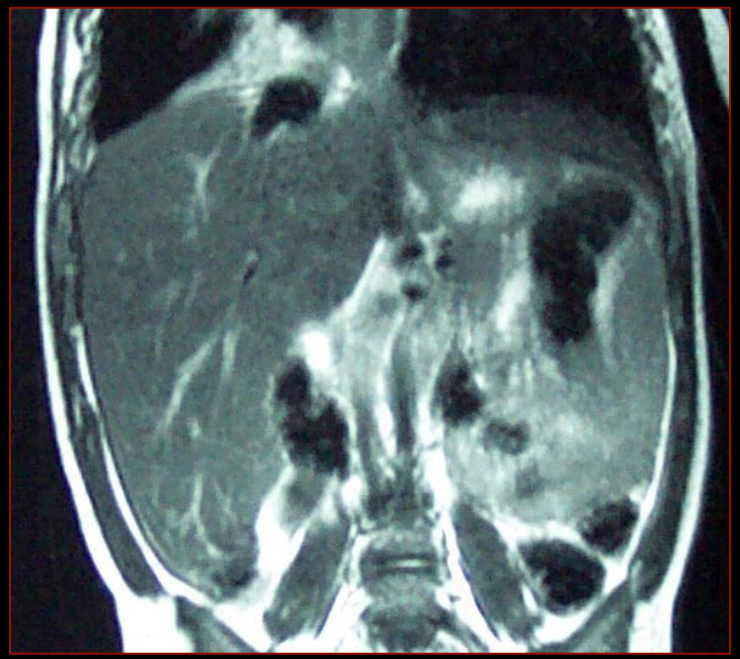
New Treatment Paradigms

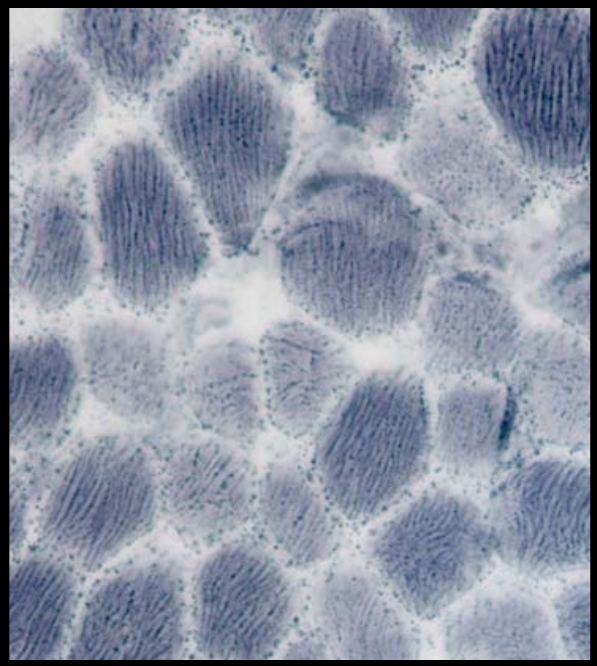
Sirolimus Clinical Trial, N=6

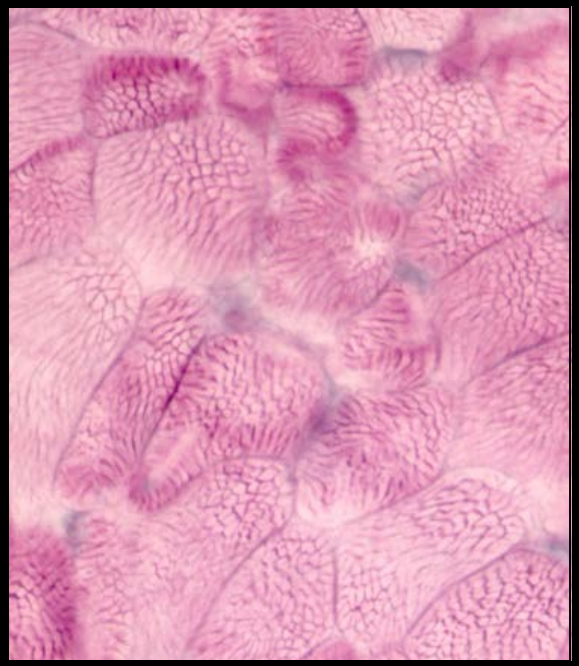
Patient	1	2	3	4	5	Average (SD)
Age	8 months	1 year 7 months	3 years 6 months	4 years 6 months	4 years 8 months	3 years 0 months (1 year 8 months)
BMI (kg/m^2)	15.0	16.2	14.4	13.3	15.0	14.8 (1.1)
Sirolimus start (month)	3	8	6	3	4	4.8 (2.2)
Current dose (mg/m^2)	1.0	1.8	1.1	3.9	4.9	2.5 (1.8)
Average sirolimus trough (ng/ml)	18.5	1.3	12.9	4.6	3.6	8.2 (7.2)
AEDs	OXC	OXC PB	LEV TOP	CBZ	OXC TOP	
GTC/SE	0	0	22	1	2	6 (11)
Worst no. of seizures/year	0	4	180	1	4	38 (80)
No. of seizures in the last 12 months	0	0	0	0	1	0.2 (0.4)
Gross motor	0.76	0.44	0.24	0.14	0.22	0.37 (0.22)
Adaptive	0.69	0.56	0.24	0.27	0.22	0.40 (0.21)
Expressive language	0.63	0.44	0.14	0.12	0.14	0.29 (0.23)
Receptive language	0.63	0.44	0.41	0.49	0.40	0.47 (0.10)
Social	0.69	0.60	0.33	0.33	0.27	0.44 (0.19)

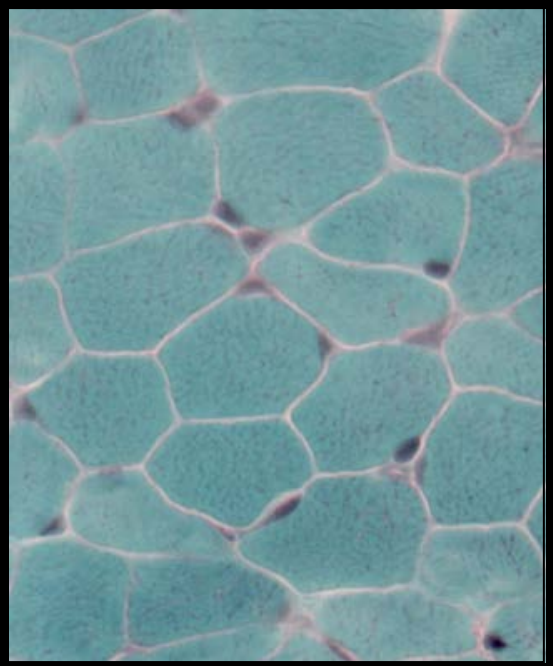
Parker et al., Sci Transl Med 2013

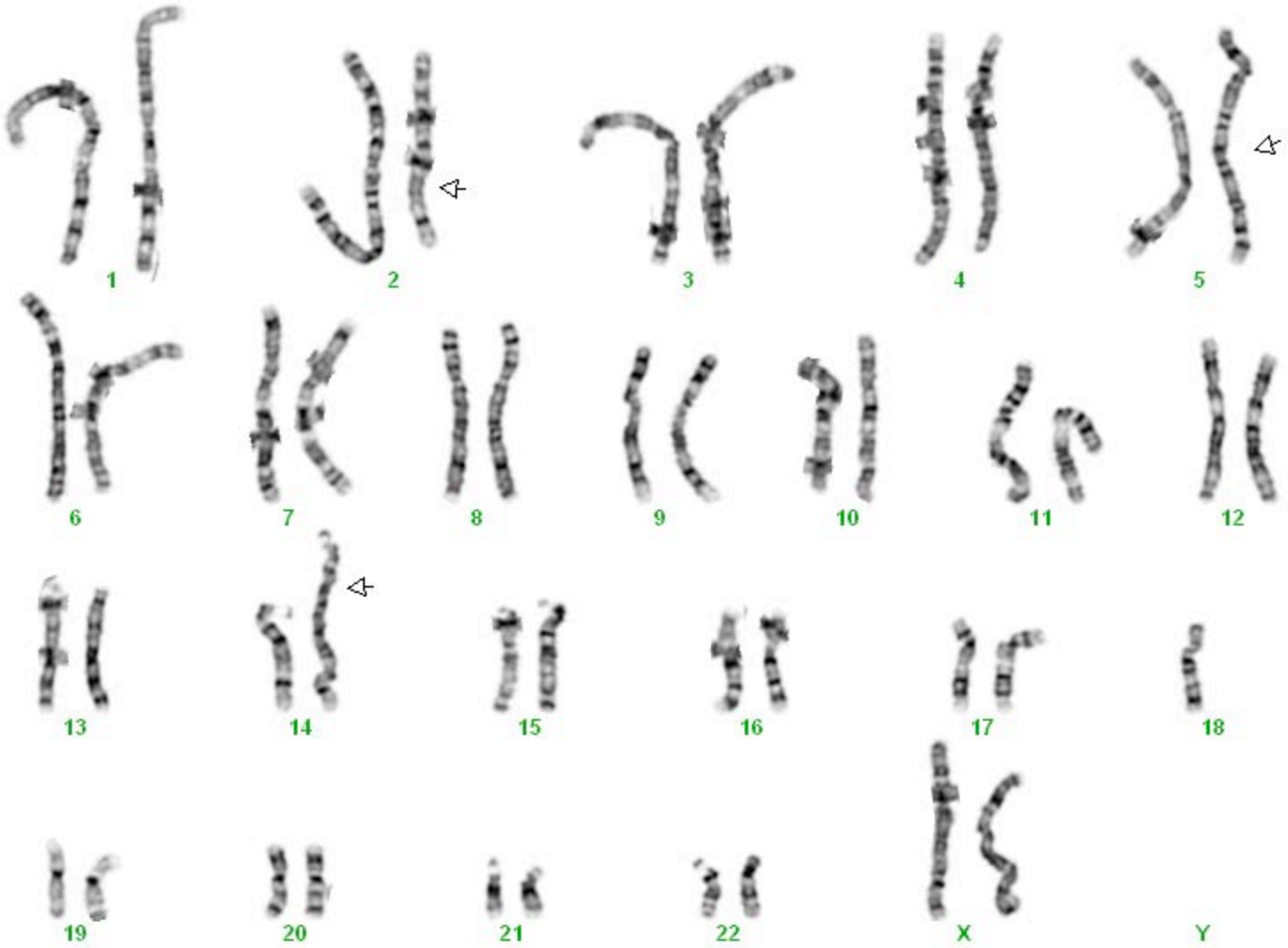
New Diagnostic Paradigms



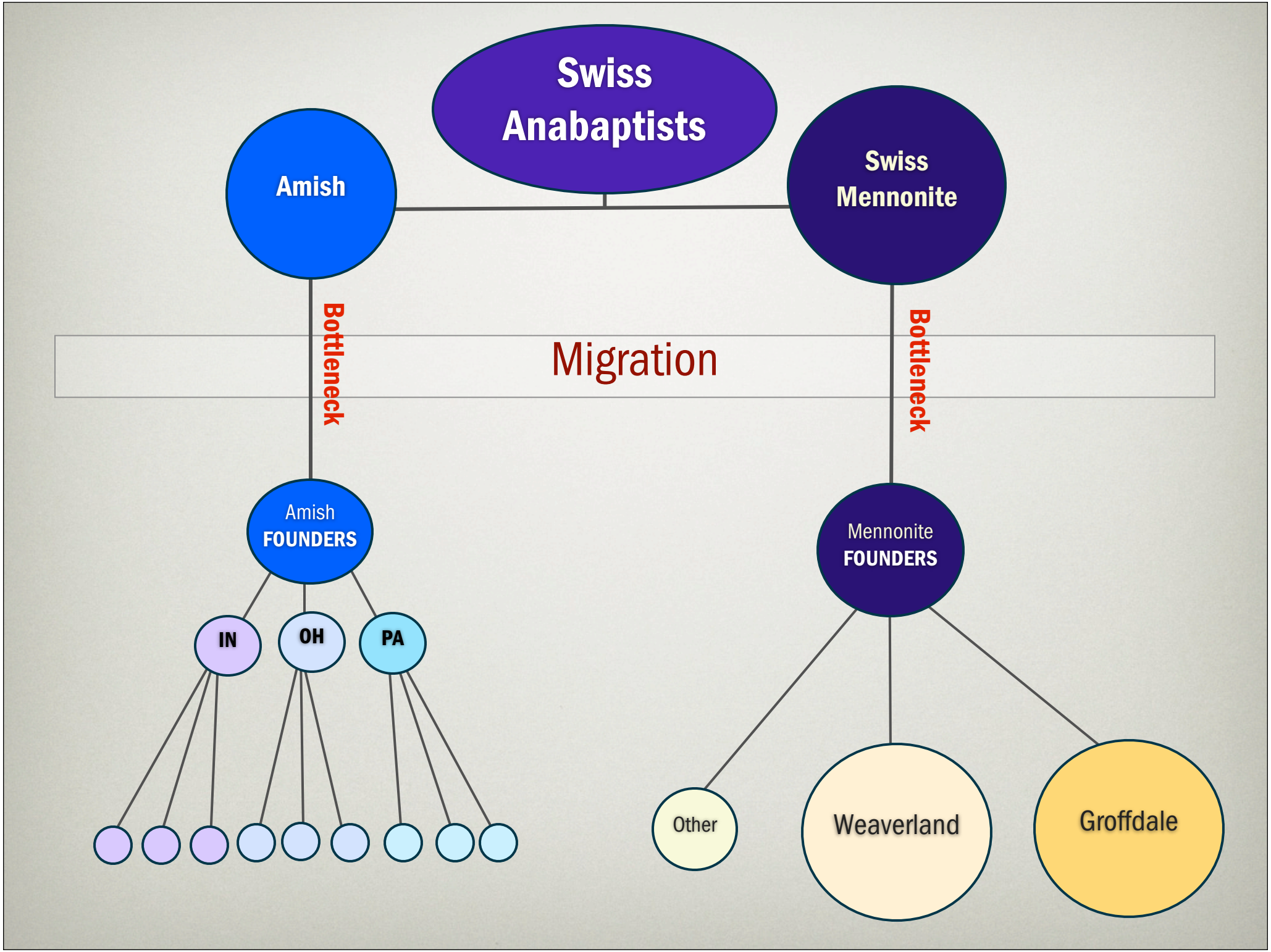



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y

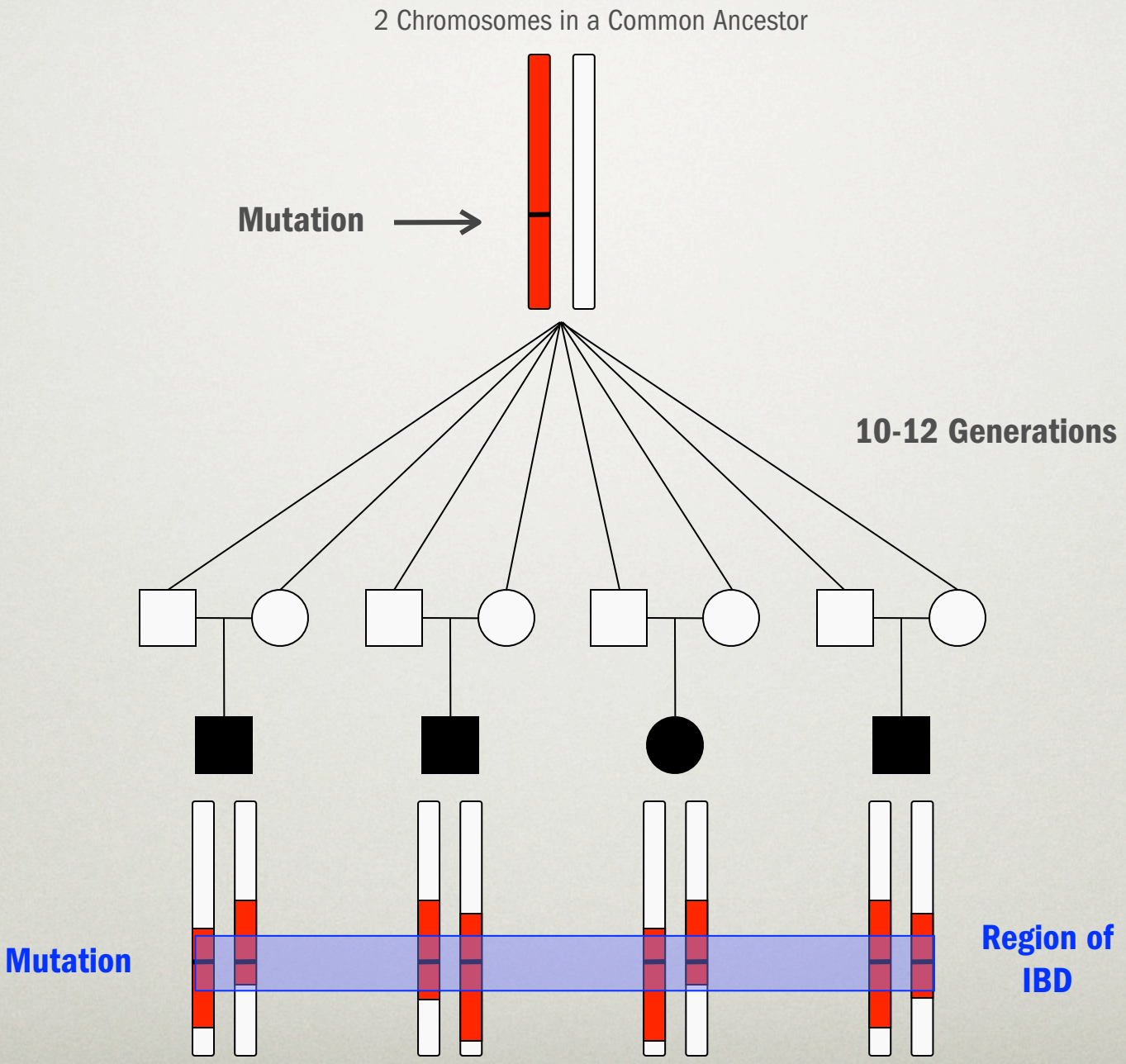
	Average Inpatient Workup Cost
Hyptonia/Neuromuscular Disease	$35,000
Syndromic Developmental Delay	$27,000
Symptomatic Epilepsy	$21,500

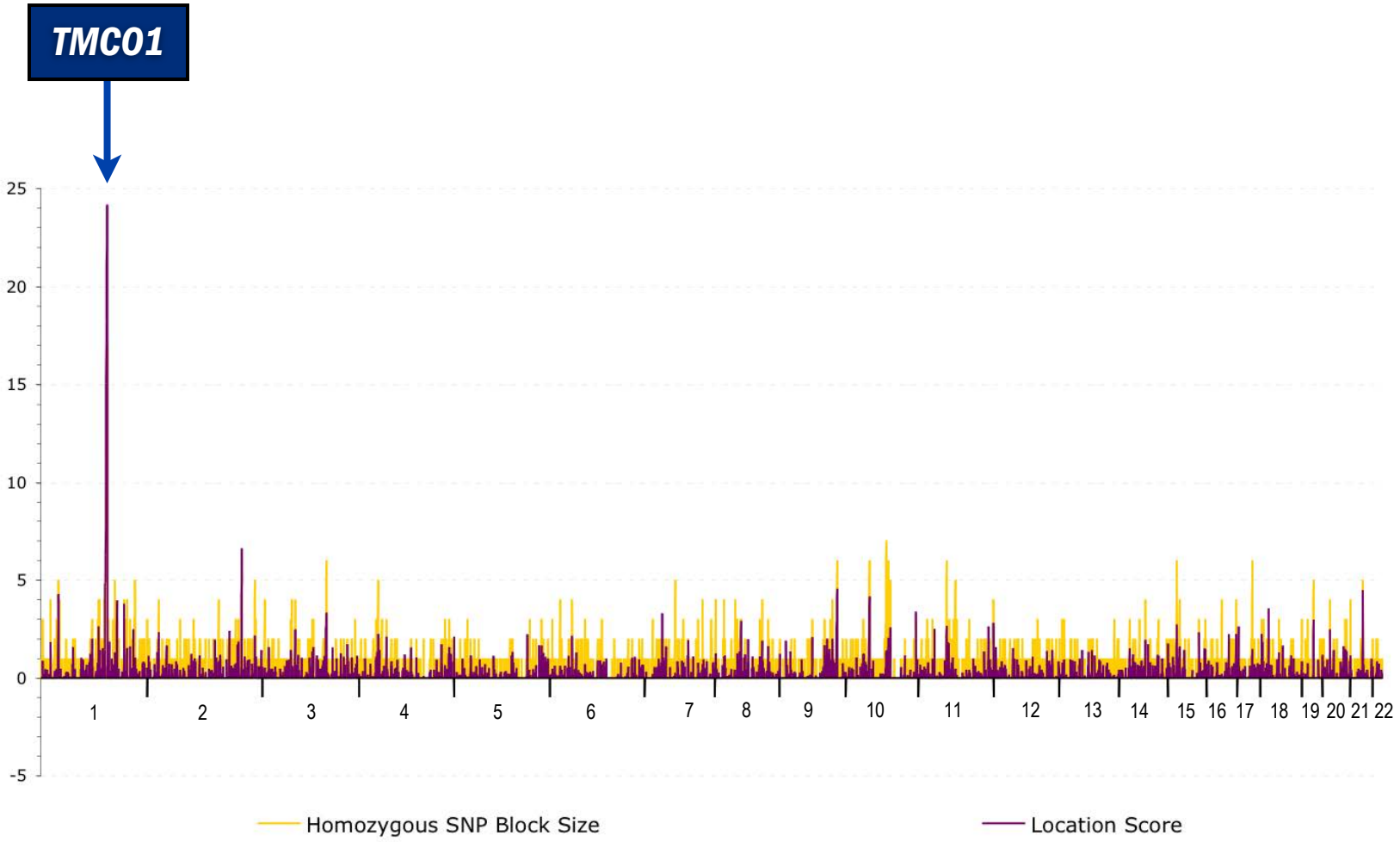
“We haven’t the money, so we’ve got to think.”

Lord Ernest Rutherford


Swiss Anabaptists
Amish
Swiss Mennonite
Bottleneck
Migration
Bottleneck
Amish FOUNDERS
Mennonite FOUNDERS
IN
OH
PA
Other
Weaverland
Groffdale

Identity-by-Descent

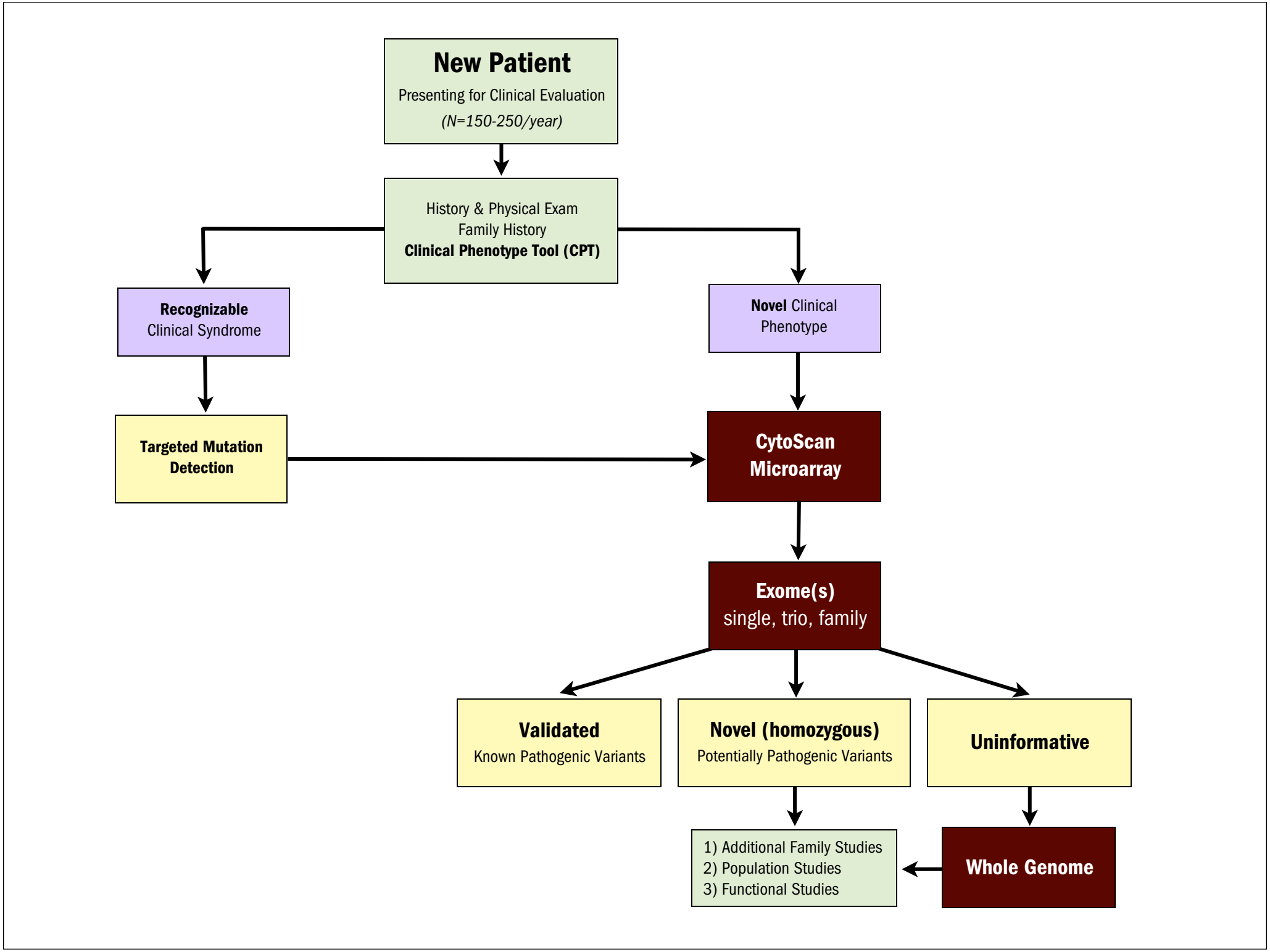


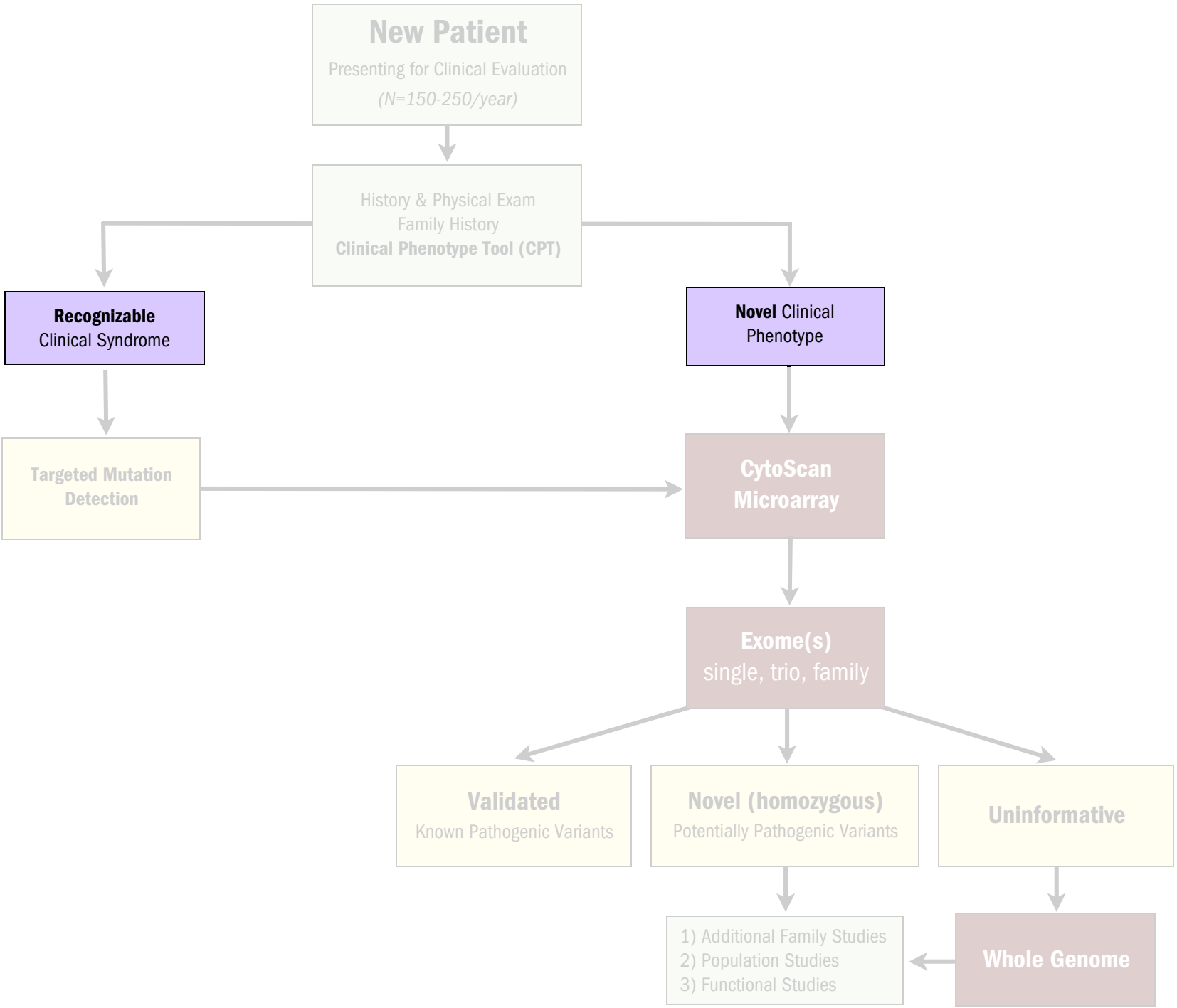

TMC01
25
20
15
10
5
0
-5
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
Homozygous SNP Block Size
Location Score

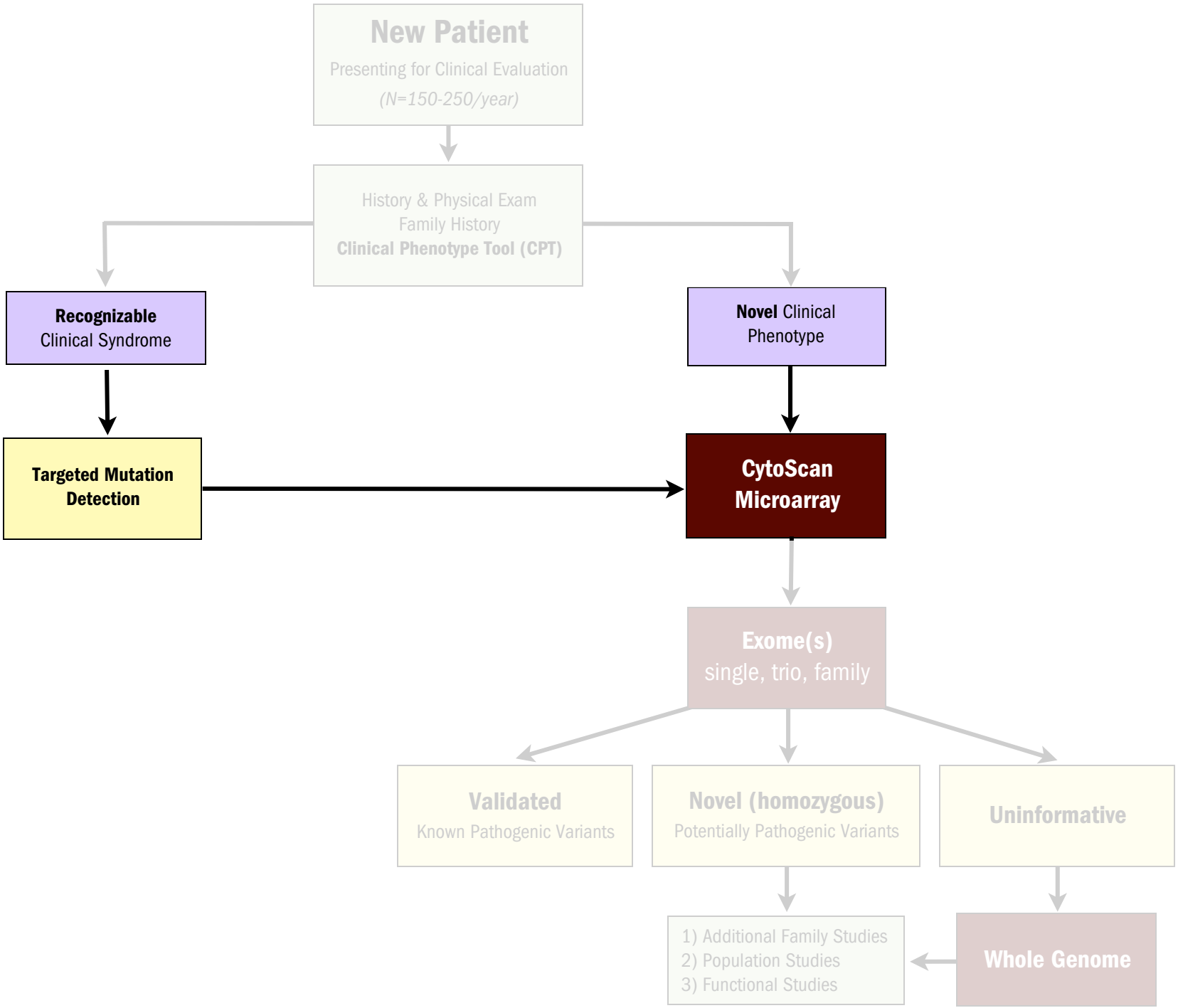
Can the Methods Be

Generalized?

Developmental Delay and **Next-Generation Technology**


New Patient
Presenting for Clinical Evaluation
(N=150-250/year)
History & Physical Exam
Family History
Clinical Phenotype Tool (CPT)
Recognizable
Clinical Syndrome
Novel Clinical
Phenotype
Targeted Mutation
Detection
CytoScan
Microarray
Exome(s)
single, trio, family
Validated
Known Pathogenic Variants
Novel (homozygous)
Potentially Pathogenic Variants
Uninformative
1) Additional Family Studies
2) Population Studies
3) Functional Studies
Whole Genome


New Patient
Presenting for Clinical Evaluation
(N=150-250/year)
History & Physical Exam
Family History
Clinical Phenotype Tool (CPT)
Recognizable
Clinical Syndrome
Novel Clinical
Phenotype
Targeted Mutation
Detection
CytoScan
Microarray
Exome(s)
single, trio, family
Validated
Known Pathogenic Variants
Novel (homozygous)
Potentially Pathogenic Variants
Uninformative
1) Additional Family Studies
2) Population Studies
3) Functional Studies
Whole Genome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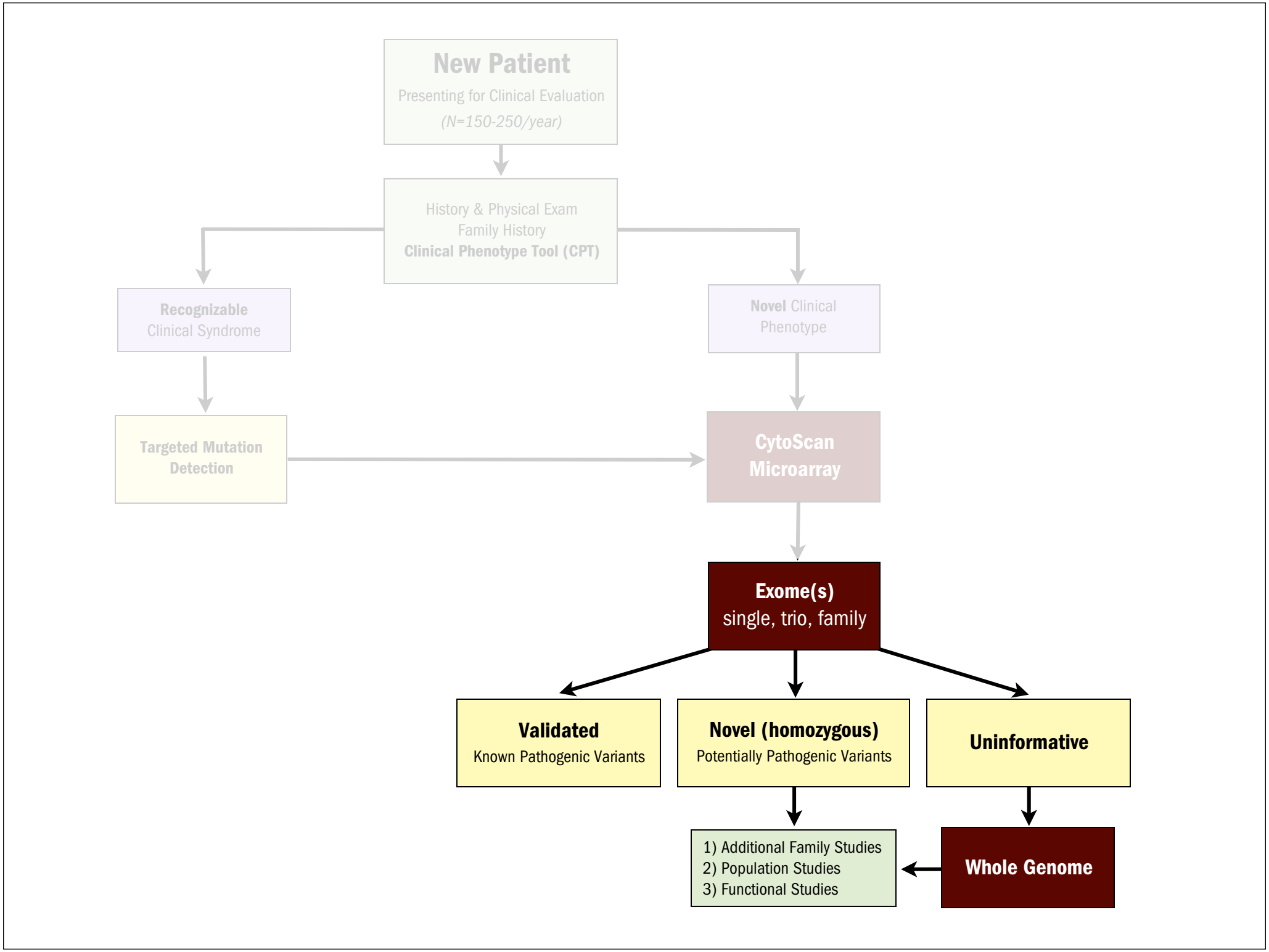
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Mitochondrial Disorder?

Or . . . .

Mowat-Wilson Syndrome

ZEB2 c.572_573insCCAA

Mowat-Wilson Syndrome

ZEB2 c.572_573insCCAA

Thank You!

- D. Holmes Morton
  Caroline Morton
  Erik G. Puffenberger
  Donna Robinson
  Christine Hendrickson
  Adam Heaps

- *Our Many Scientific and Clinical Collaborators*

- **The Community we Serve**