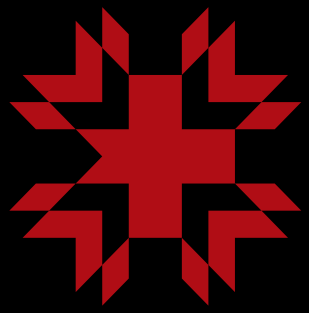


One Community's Effort to Control Genetic Disease

Kevin A. Strauss, M.D.*

*No Disclosures

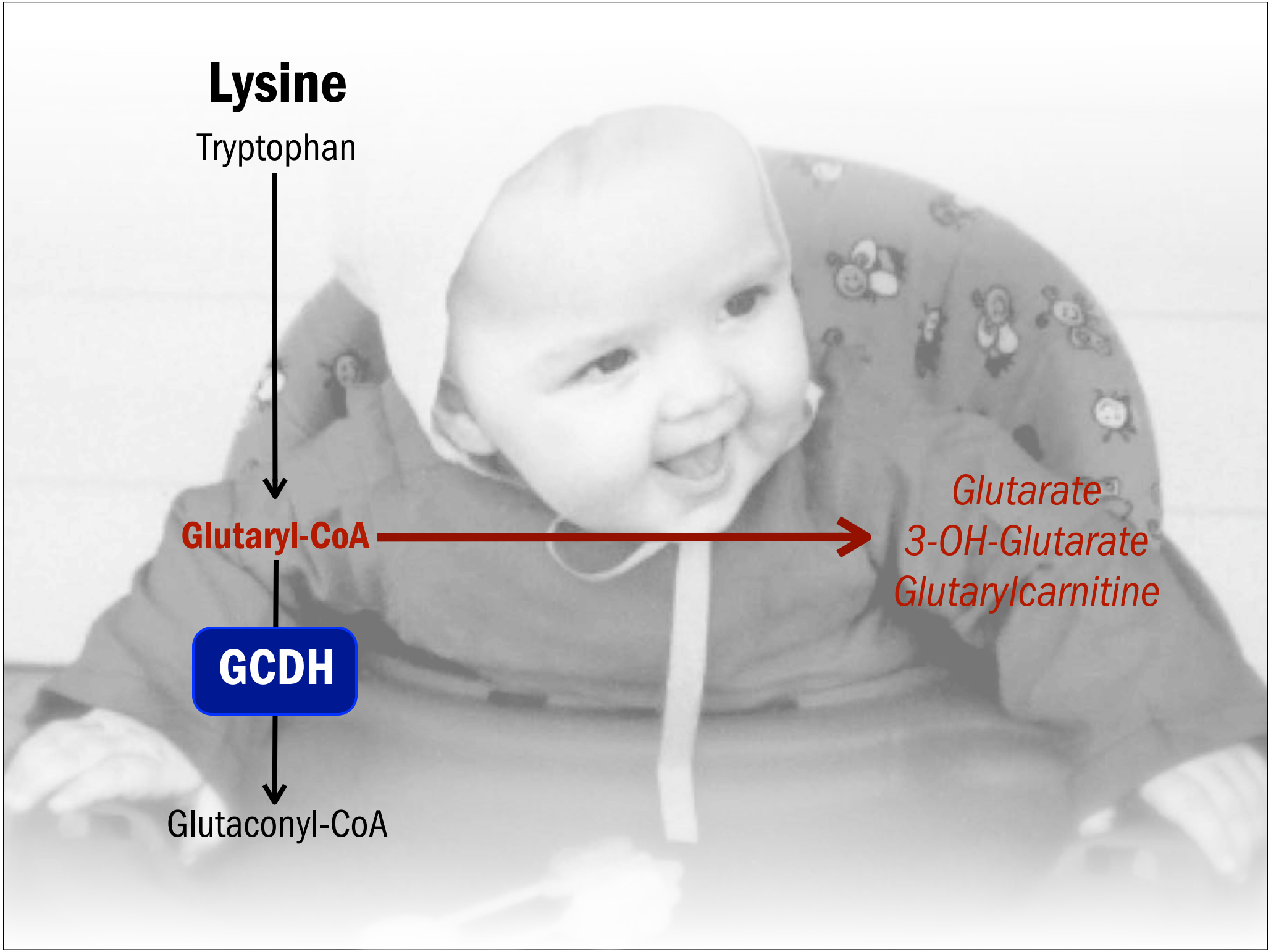
Photos and Videos used with parental permission

Start with a Healthy Child

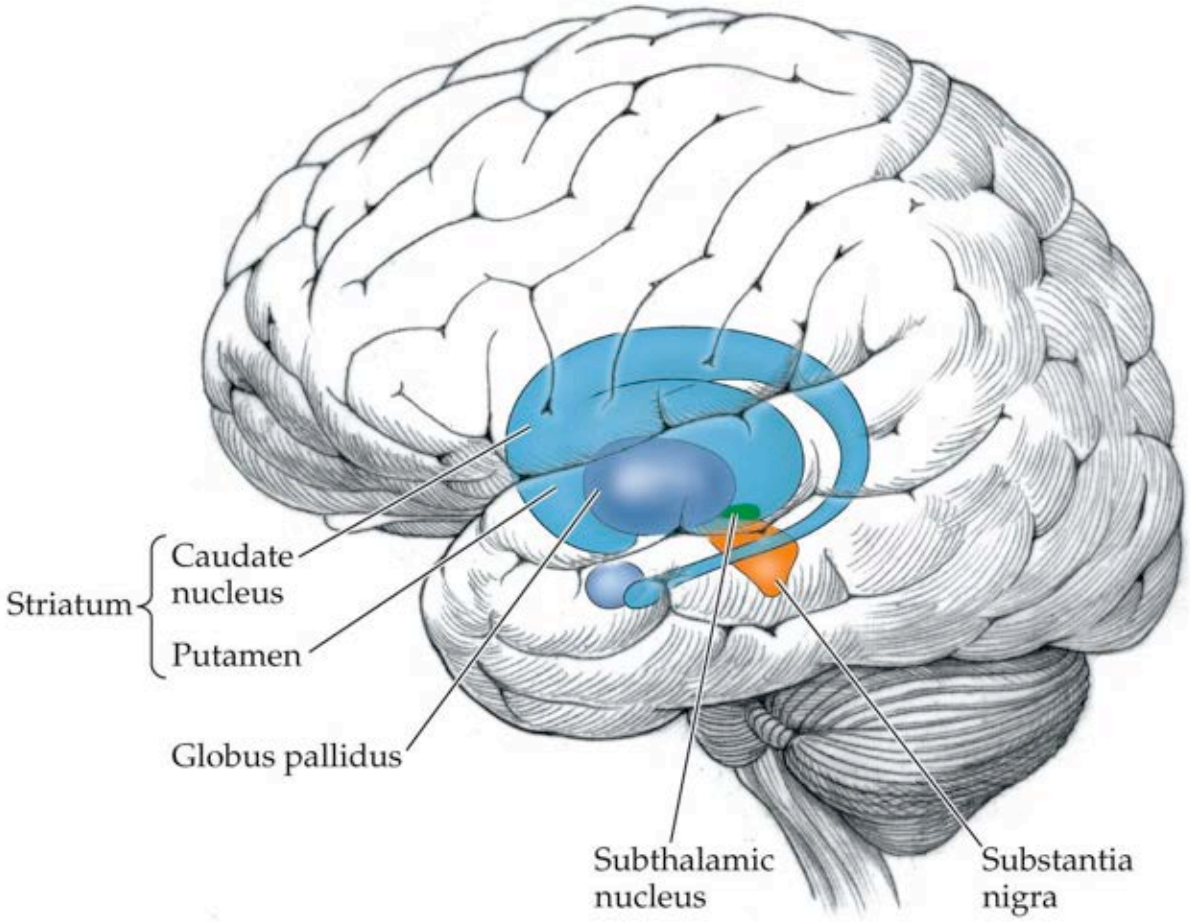
Build a Medical Home

Local, Accessible, Affordable Care

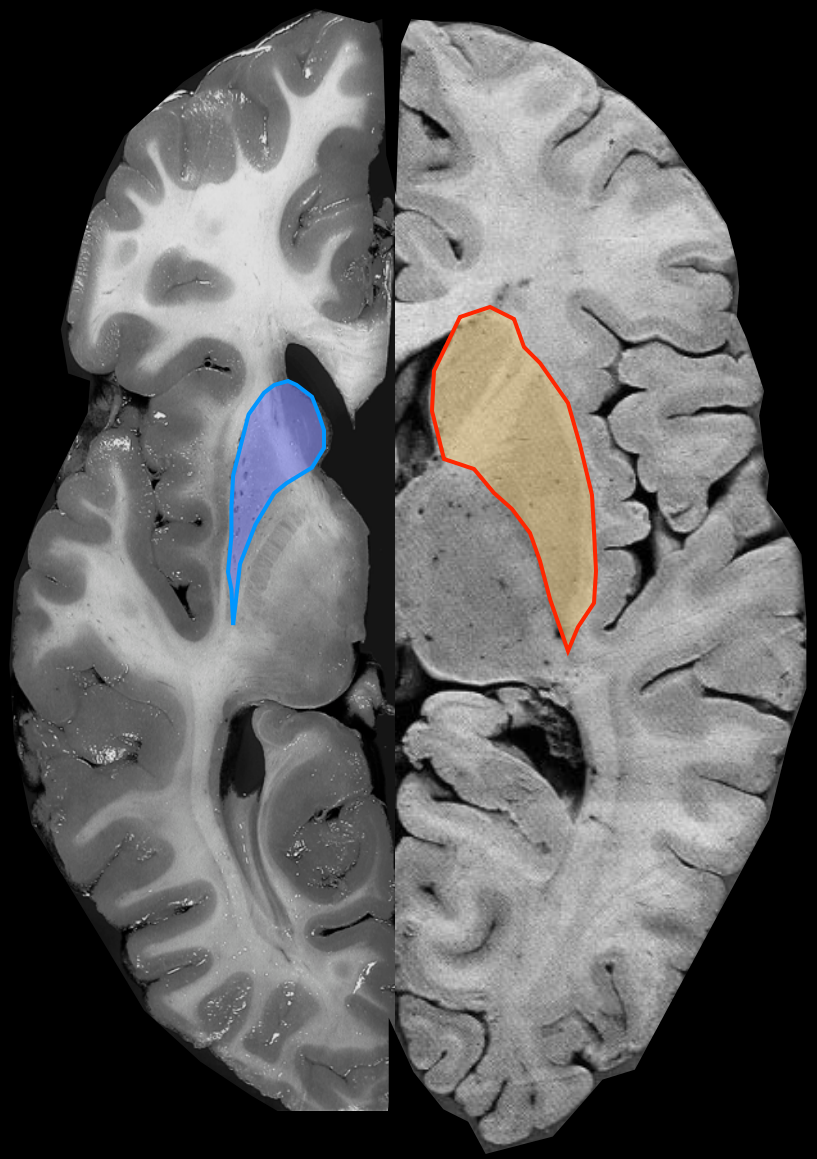
Identify Needs


Lysine
Tryptophan
Glutaryl-CoA
GCDH
Glutaconyl-CoA
Glutarate
3-OH-Glutarate
Glutarylcarnitine

Understand Natural History

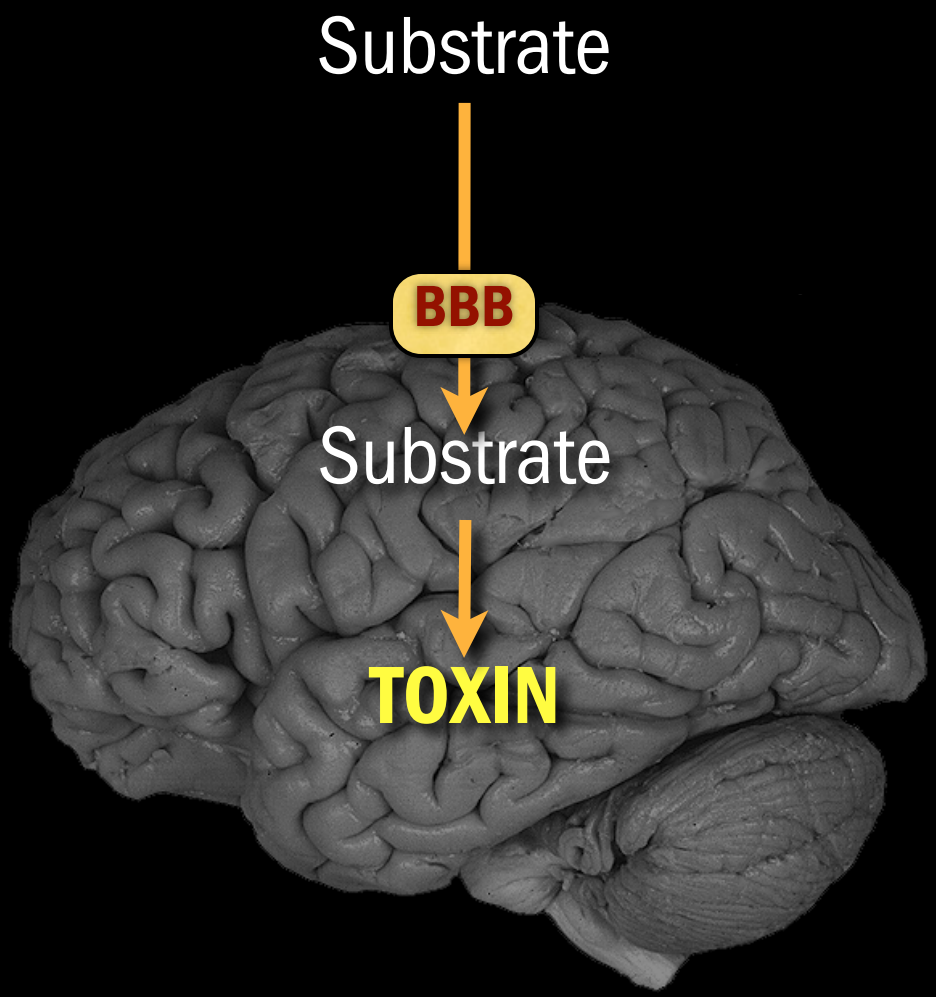


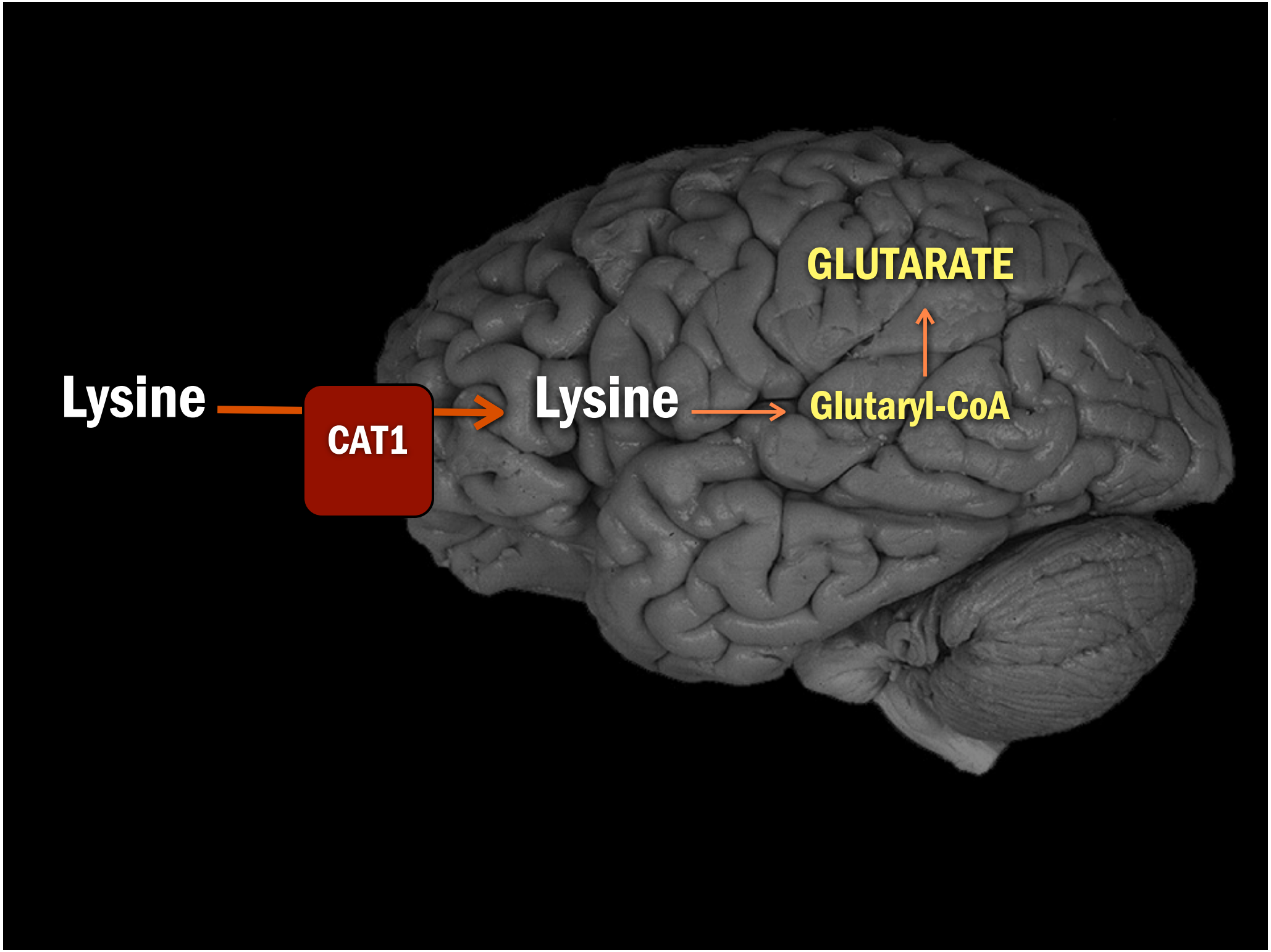
GA1

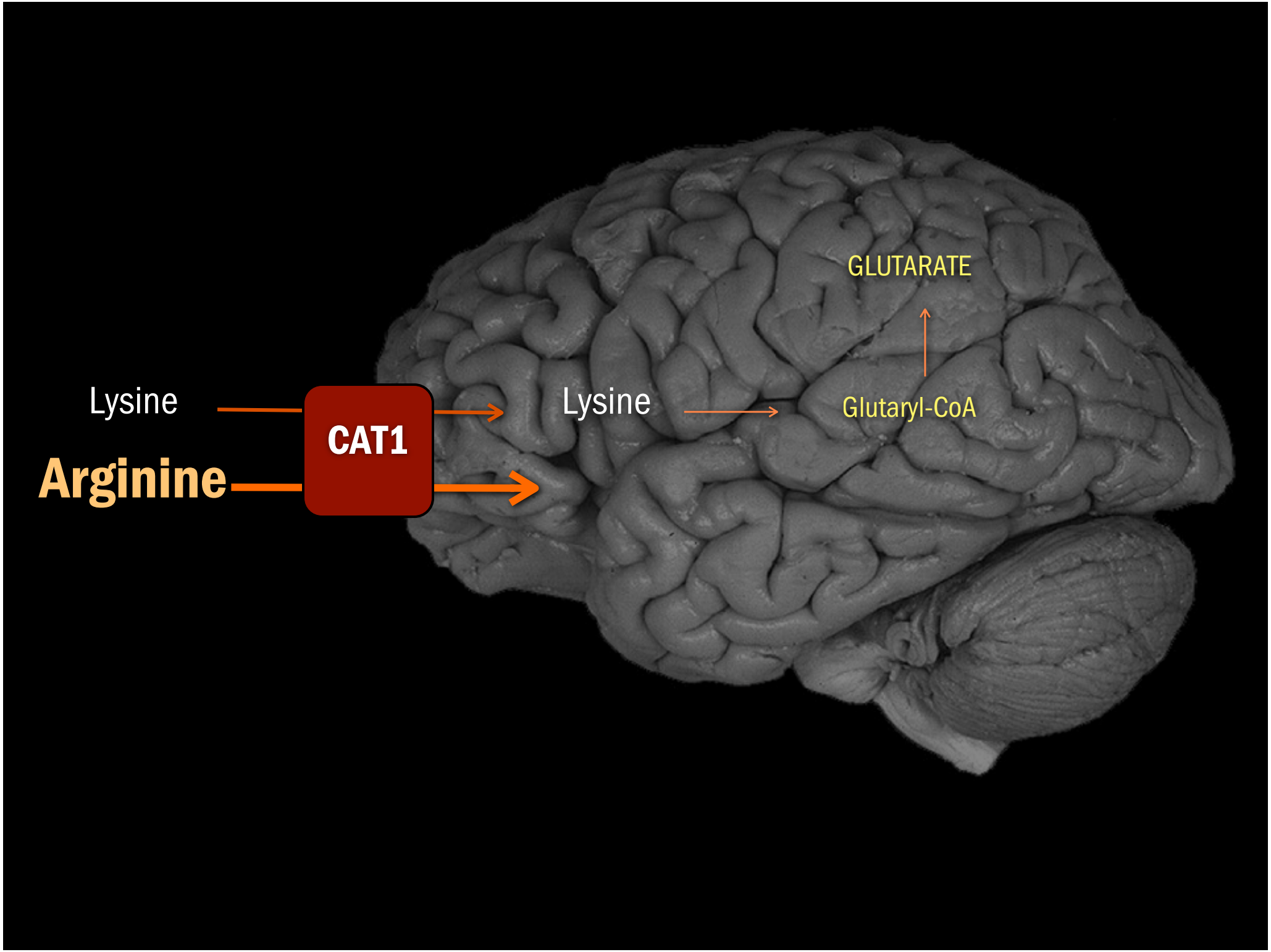


Normal

Study Disease Mechanisms

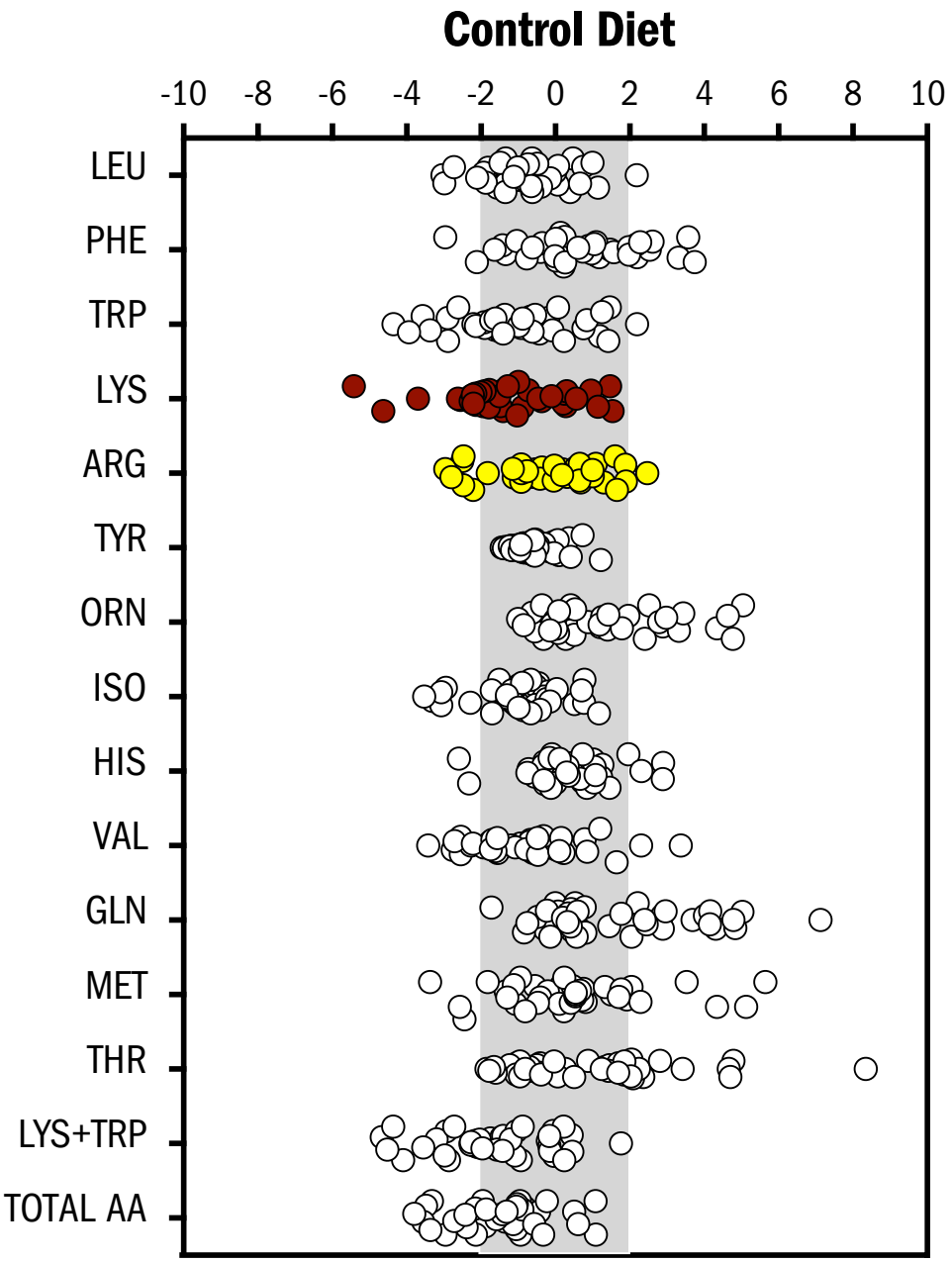

Substrate
BBB
Substrate
TOXIN


GLUTARATE
Lysine
CAT1
Lysine
Glutaryl-CoA

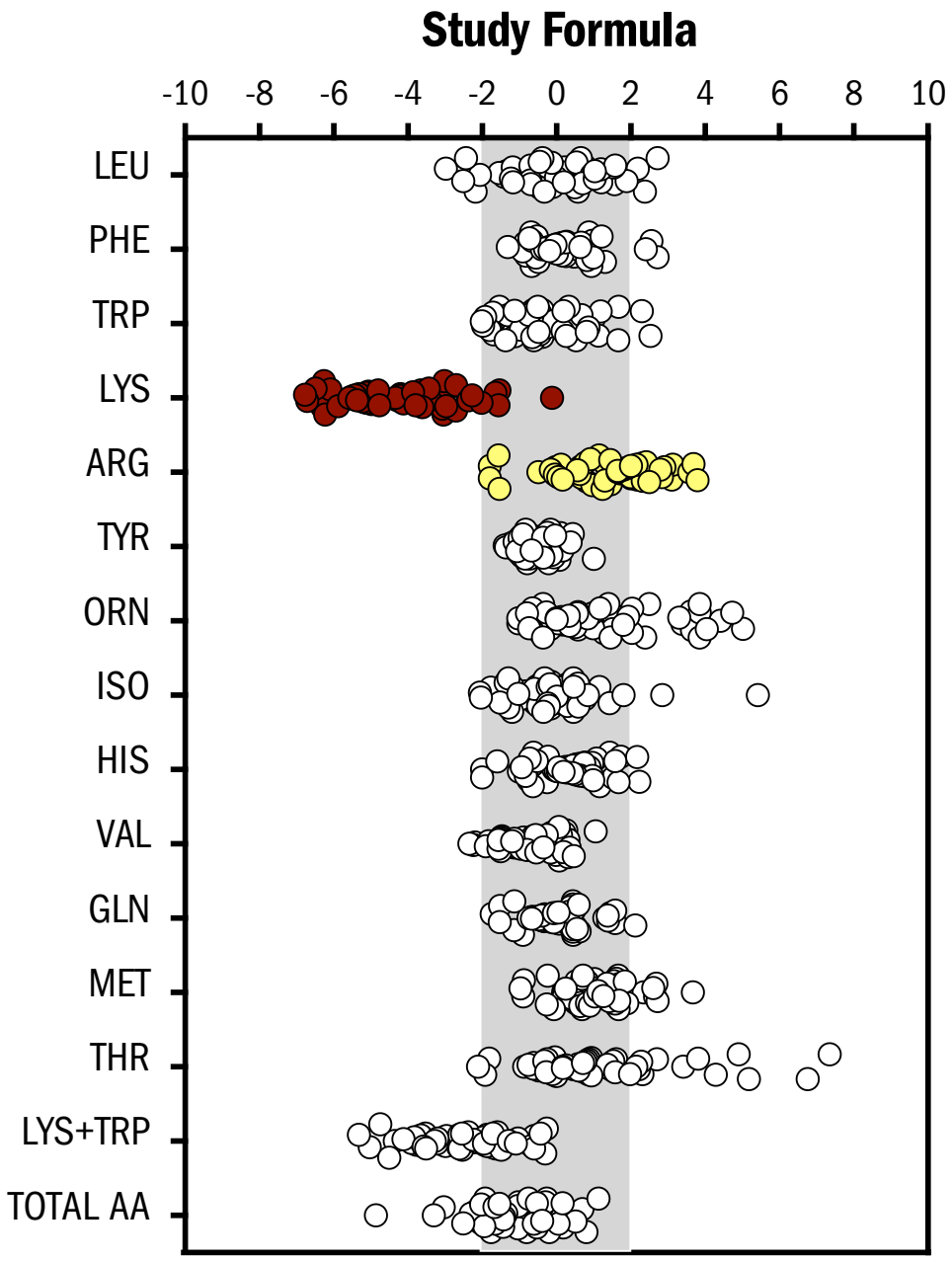

GLUTARATE
Lysine
CAT1
Arginine
Lysine
Glutaryl-CoA

Implement Solutions

Calculated Brain Amino Acid Influx (z-scores)

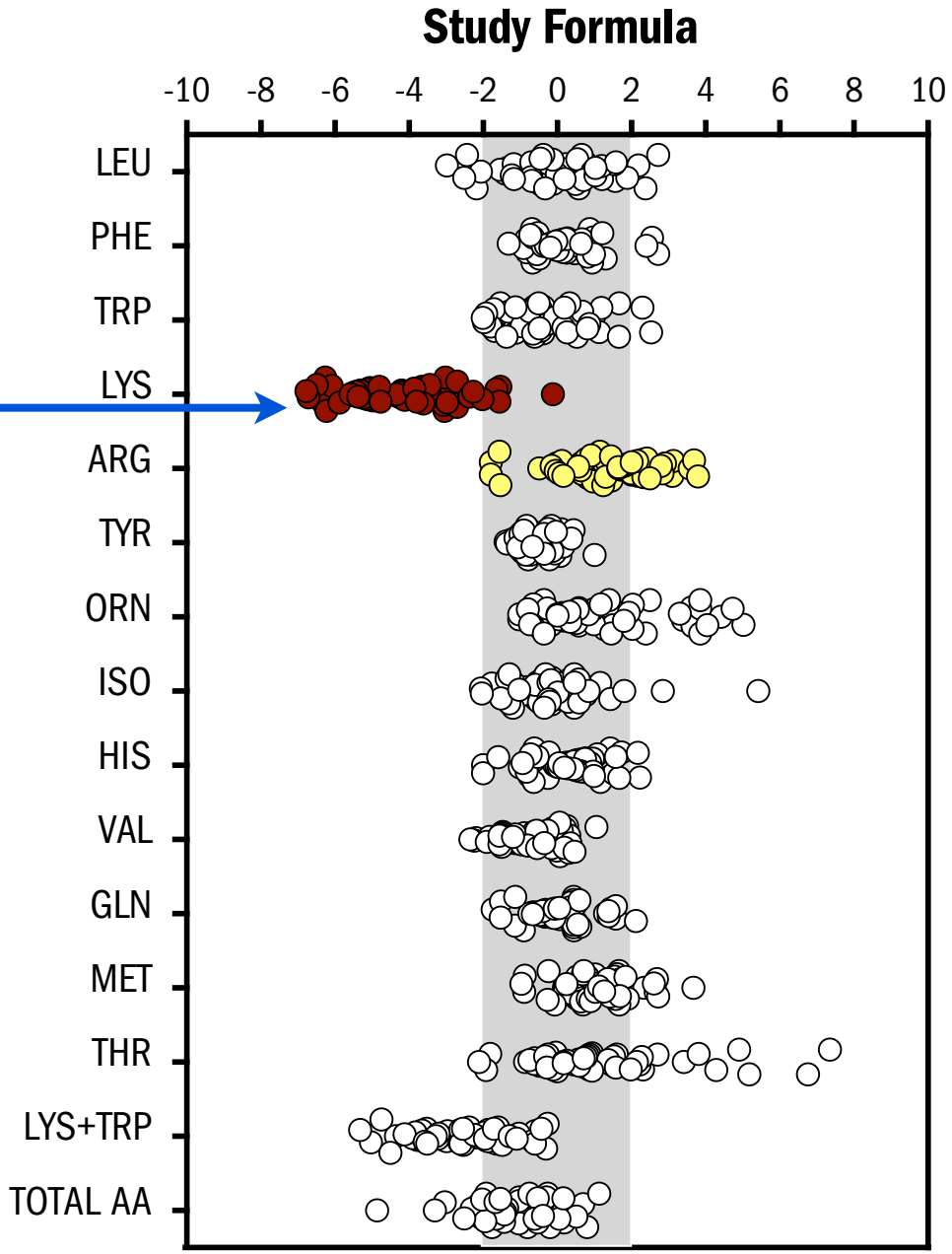


Calculated Brain Amino Acid Influx (z-scores)



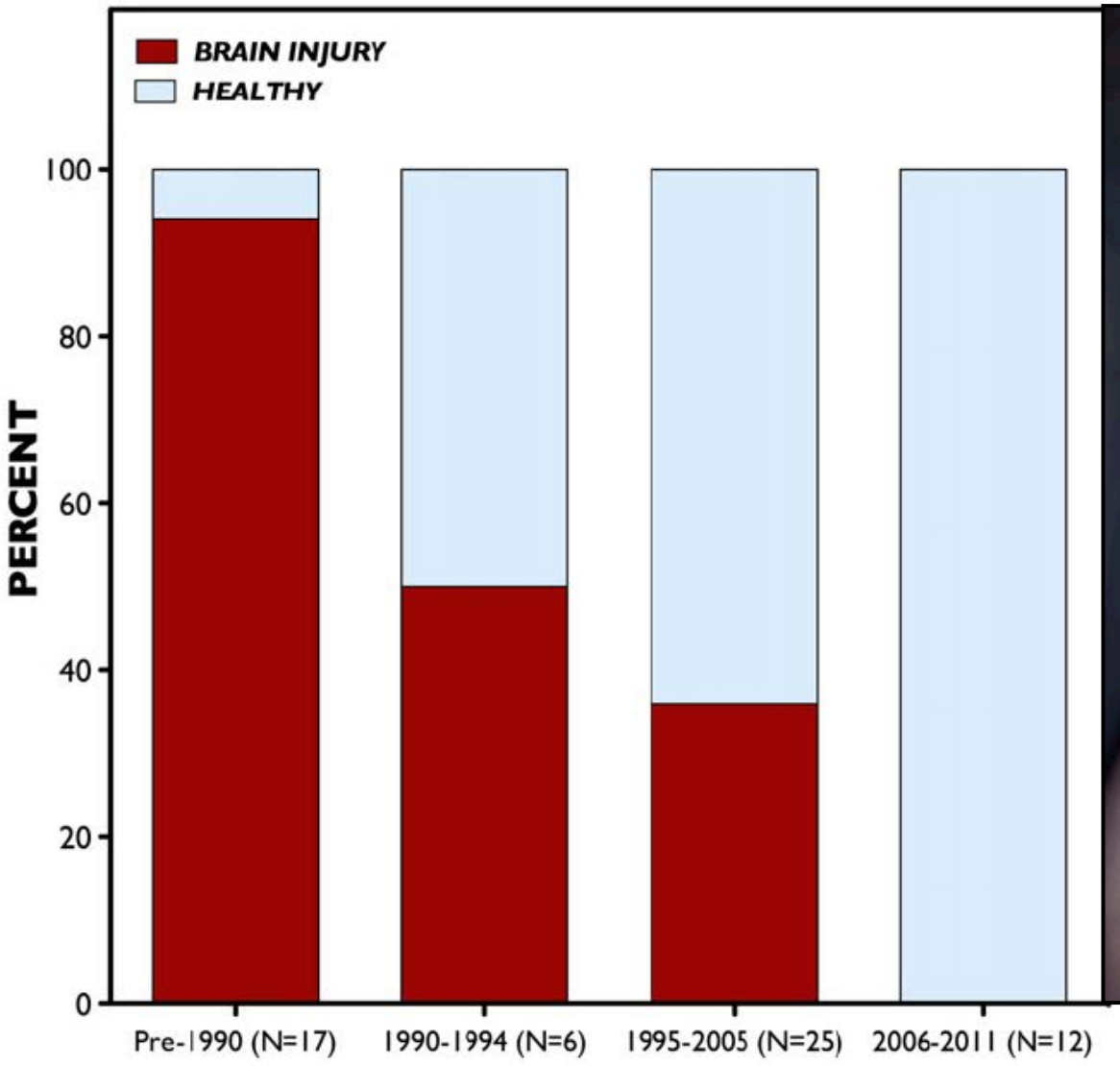
Calculated Brain Amino Acid Influx (z-scores)

50% Reduction in Brain Glutaryl-CoA Production



Measure Progress

Track Clinical Outcomes



Map the Causes of Childhood Illness

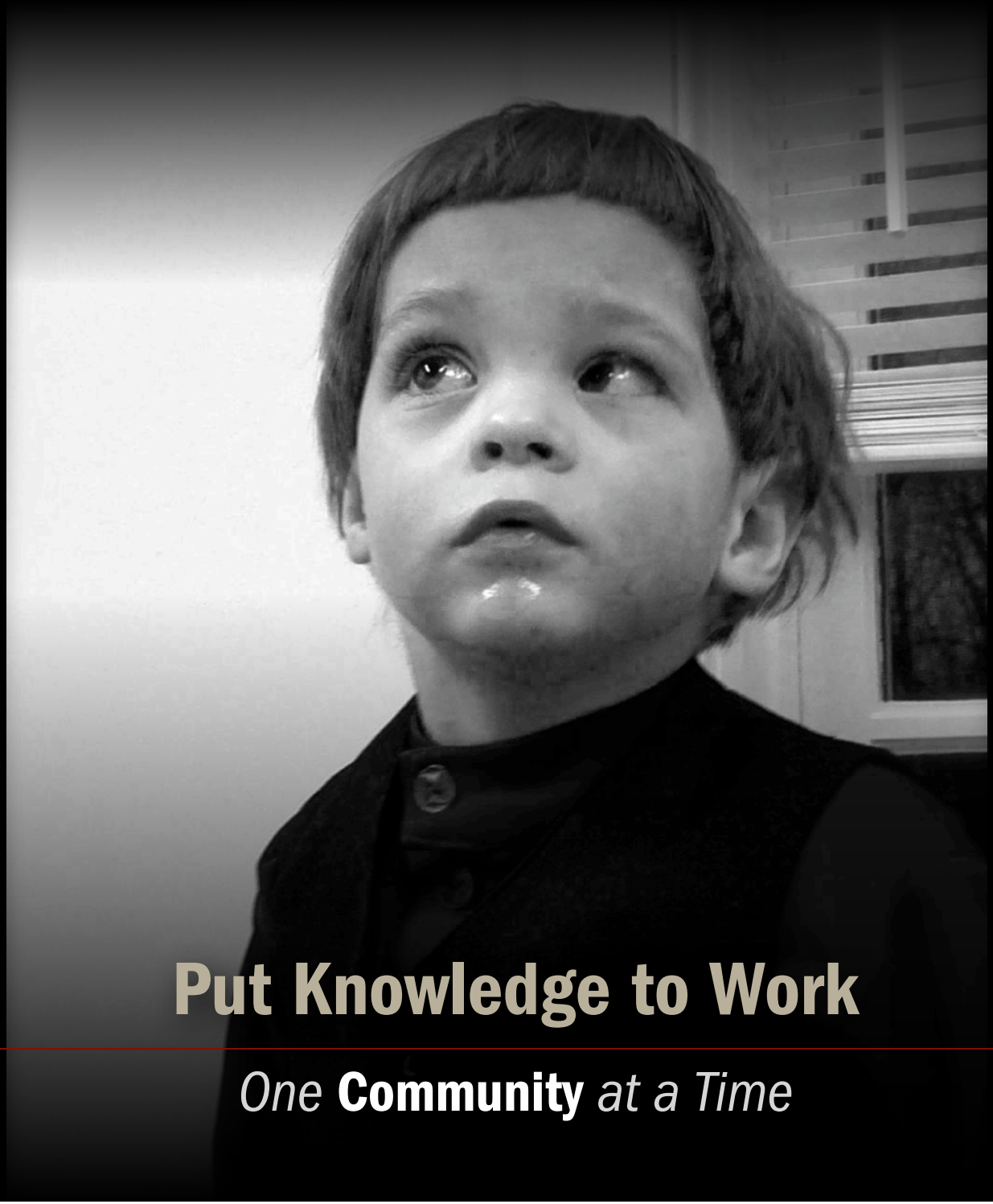
CLINICAL DIAGNOSIS	DISORDER	GENE
Cerebral palsy	Glutaric aciduria, type 1	*GCDH*
	Propionic acidemia	*PCCB*
	Gap junction deficiency	*GJA12*
	Crigler-Najjar syndrome	*UGT1A1*
	Hereditary spastic paraplegia	*SPG20*
	Segawa dystonia syndrome	*TH*
	Idiopathic dystonia	*DYT1*
Mental retardation	MTHFR deficiency	*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*

Map the Causes of Childhood Illness

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

"Stunning scientific and technological advances in genetics will mean little **if they do not benefit people.**"

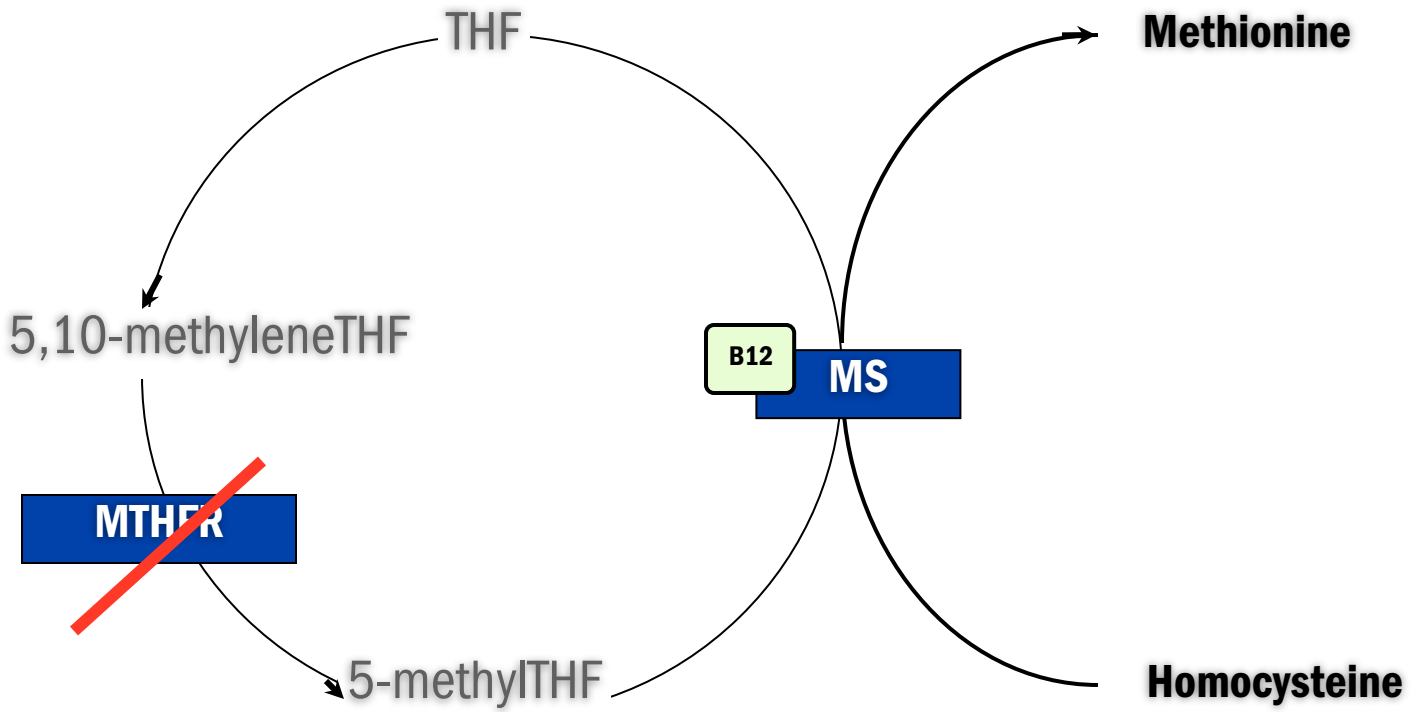
A. Guttmacher et al., 2012

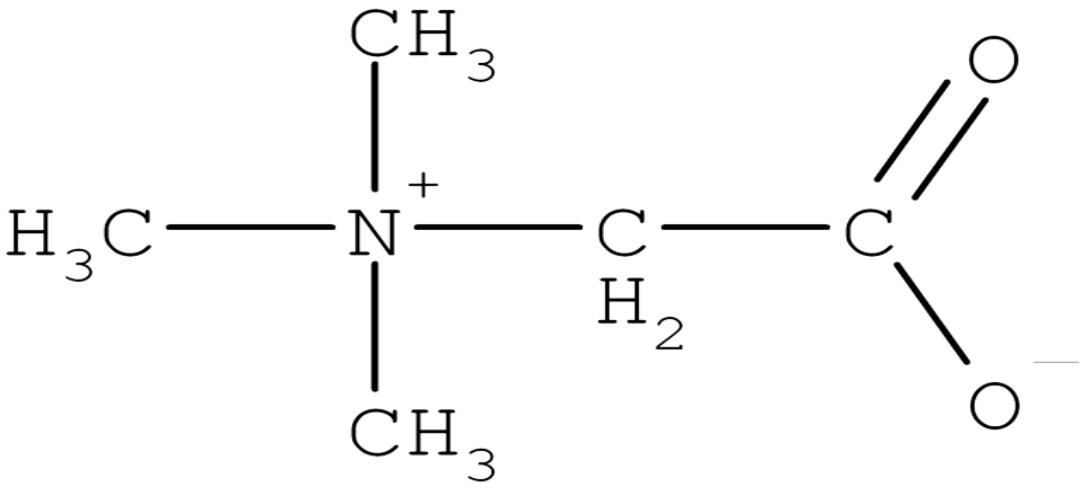


Put Knowledge to Work

One **Community** *at a Time*

5,10-Methylenetetrahydrofolate Reductase (**MTHFR**) Deficiency




CH3
O
+
H3C
N
C
C
H2
O
CH3

Johnny Walks

Population Screening

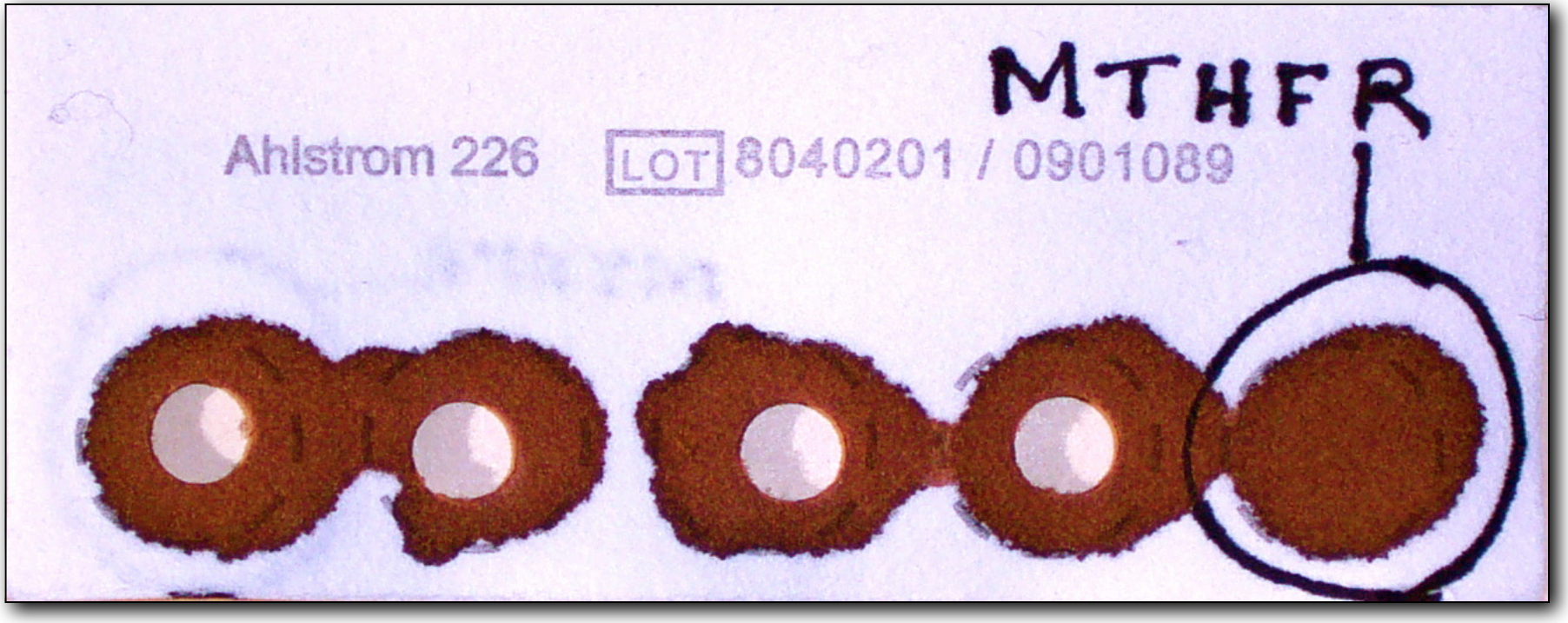
Quantify Risk

LightScanner 32

by Idaho Technologies

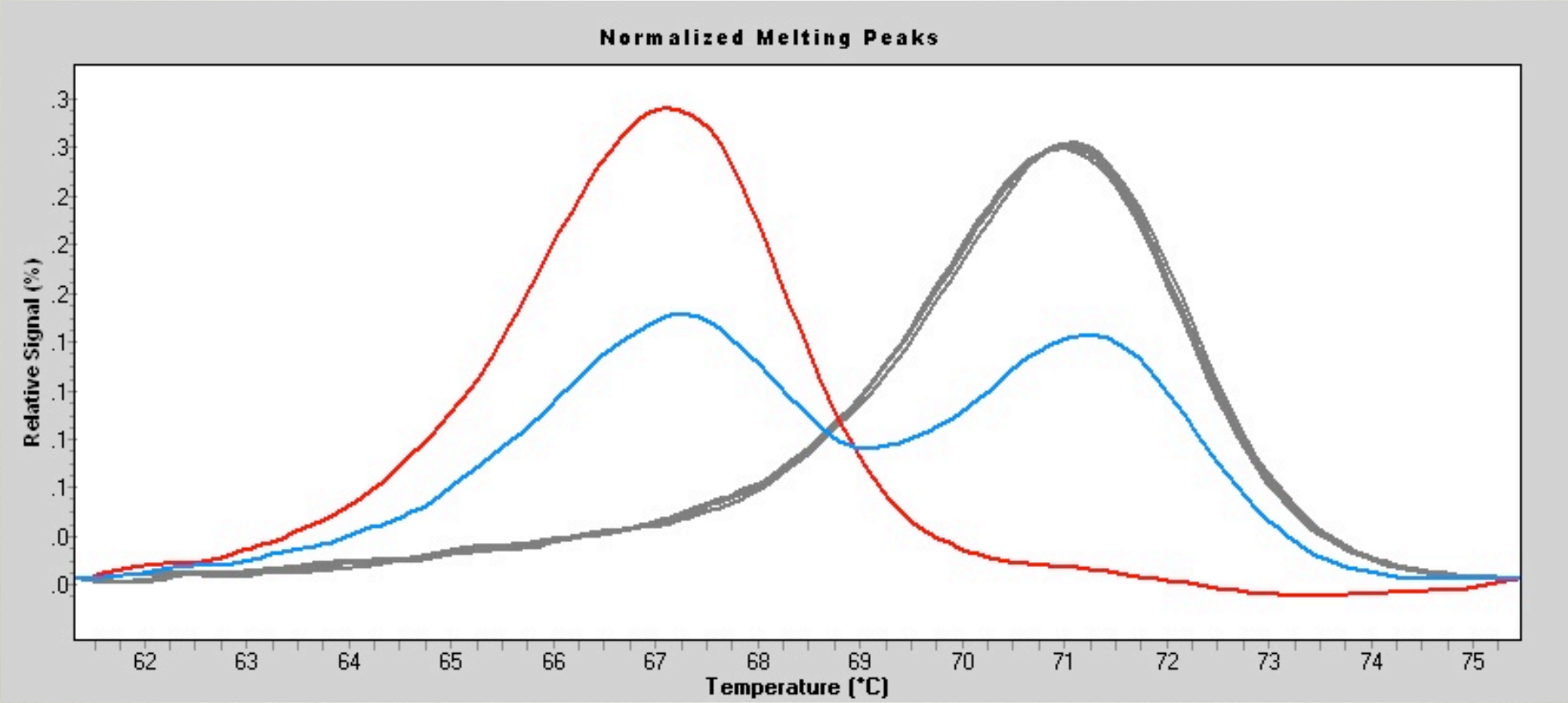
Population Screening

Implement Solutions



Population Screening

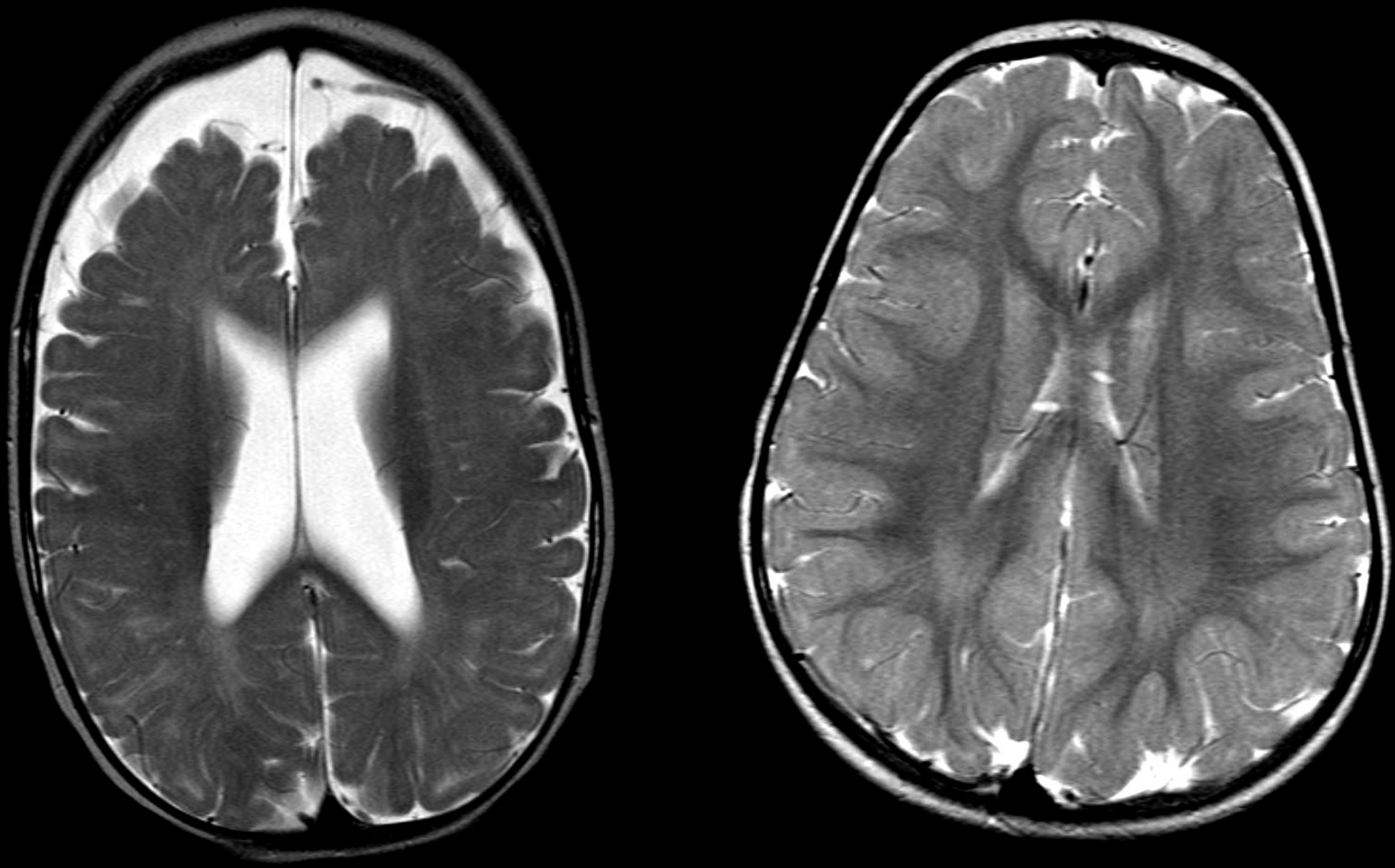
Implement Solutions



MTHFR c.1129C>T LunaProbe assay

Measure Outcomes

Measure Outcomes

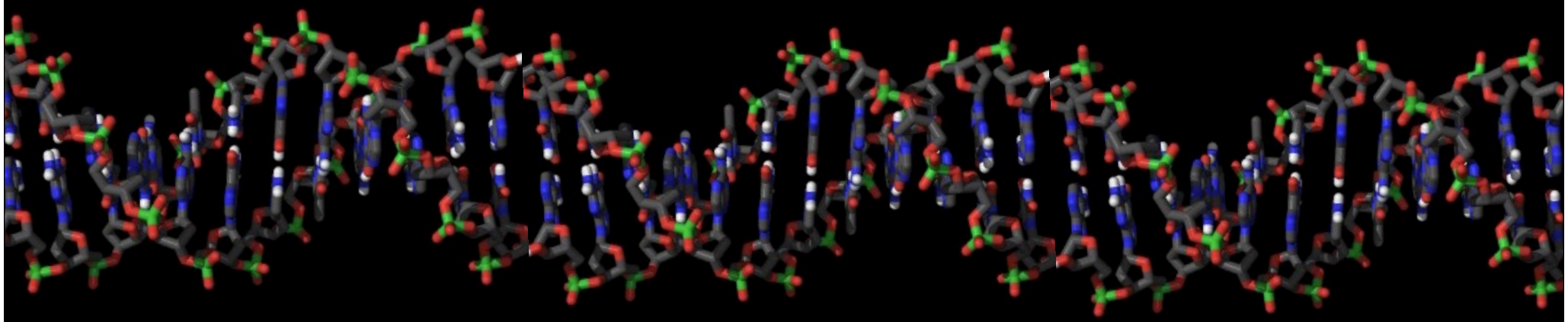


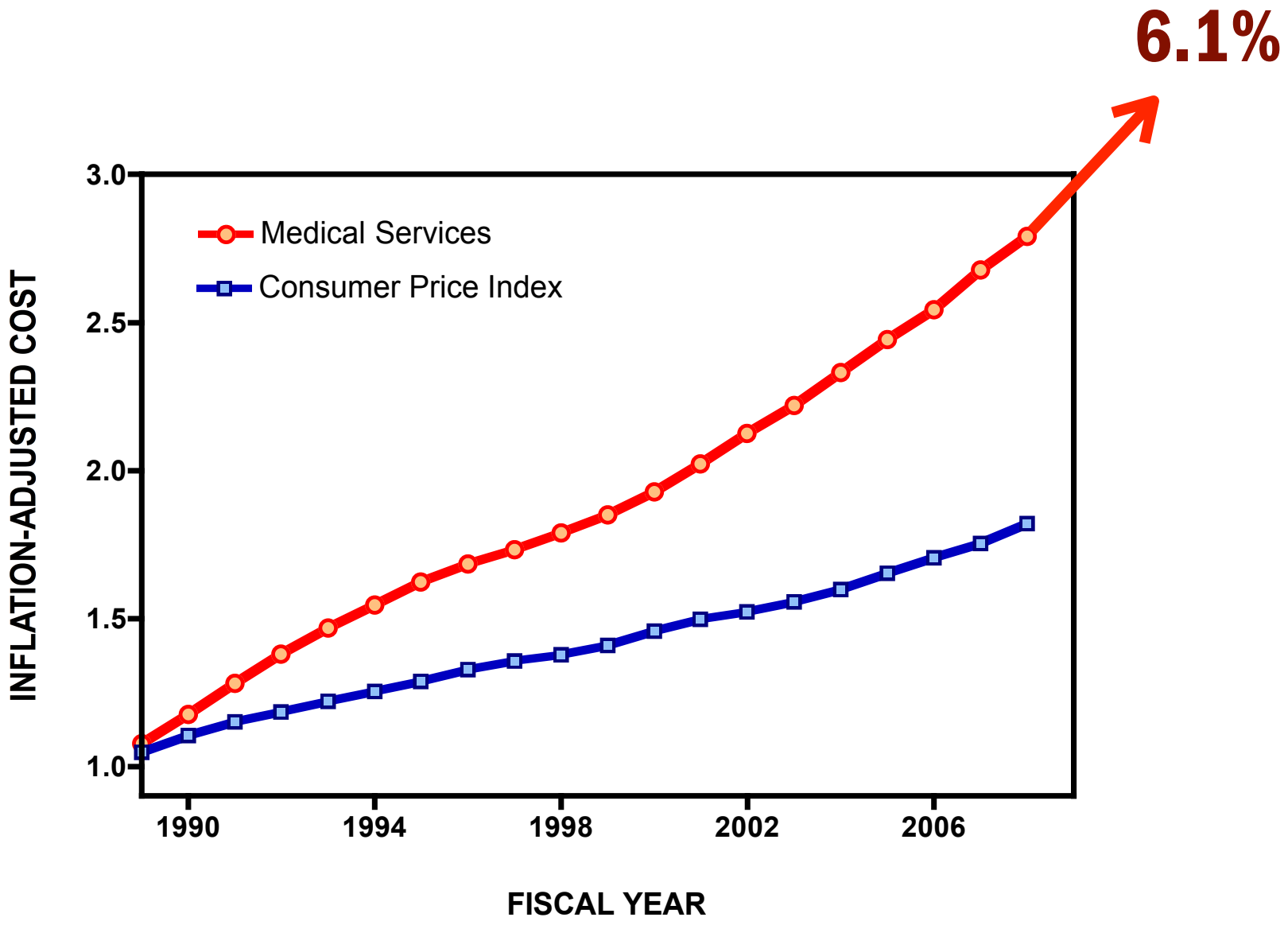
Untreated

Treated

The Economics of Prevention

Genes, Money, and Public Health




6.1%
3.0
2.5
2.0
1.5
1.0
Medical Services
Consumer Price Index
INFLATION-ADJUSTED COST
1990
1994
1998
2002
2006
FISCAL YEAR

Measuring Community Savings

Diagnostic Efficiency

Hospitalization Rates

Hospital Discounts

Disability Prevention

4% of Pediatric Patients

40% of Medical Costs

	Cost per patient*	New Cases/year†	Annual Cost Savings
Troponin myopathy (*TNNT1*)	$35,000	4.5	$157,500
Amish microcephaly (*SLC25A9*)	$27,000	4.4	$118,800
CDFE syndrome (CNTNAP2)	$21,500	3.0	$64,500
Yoder dystonia	$27,000	2.3	$62,100
GM3 synthase deficiency	$27,000	2.0	$54,000
Spinal muscular atrophy	$35,000	2.0	$70,000
SIDDTsyndrome (*TSPYL*)	$27,000	1.3	$35,100
Pretzel syndrome (*STRADA*)	$27,000	0.8	$21,600
Symptomatic epilepsy and skull dysplasia (*SNIP1*)	$21,500	0.6	$12,900
TMCO1 syndrome	$27,000	0.6	$16,200
Amish lethal rigidity/seizures	$27,000	0.5	$13,500
OPPG syndrome	$27,000	0.5	$13,500
Cardiomyopathy and lactic acidosis (*SLC25A4*)	$35,000	0.3	$10,500
MTHFR deficiency	$27,000	0.3	$8,100
Non-syndromic mental retardation (*CRADD*)	$27,000	0.3	$8,100
Usher-like syndrome (*HARS*)	$27,000	0.3	$8,100
AXPC1 syndrome *(FLVCR1)*	$27,000	0.2	$5,400
Bardet-Biedel	$27,000	0.2	$5,400
Cockayne	$27,000	0.2	$5,400
Hereditary spastic paraplegia	$35,000	0.2	$7,000
Hypomyelinating leukodystrophy (*GJC2*)	$27,000	0.2	$5,400
Infantile Parkinsonism-dystonia (*SLC6A3*)	$27,000	0.1	$2,700
Thanatophoric dysplasia (*FGFR3*)	$27,000	0.1	$2,700
Totals	-	**25**	**$708,500**

	Cost per patient*	New Cases/year†	Annual Cost Savings
Troponin myopathy (*TNNT1*)	$35,000	4.5	$157,500
Amish microcephaly (*SLC25A9*)	$27,000	4.4	$118,800
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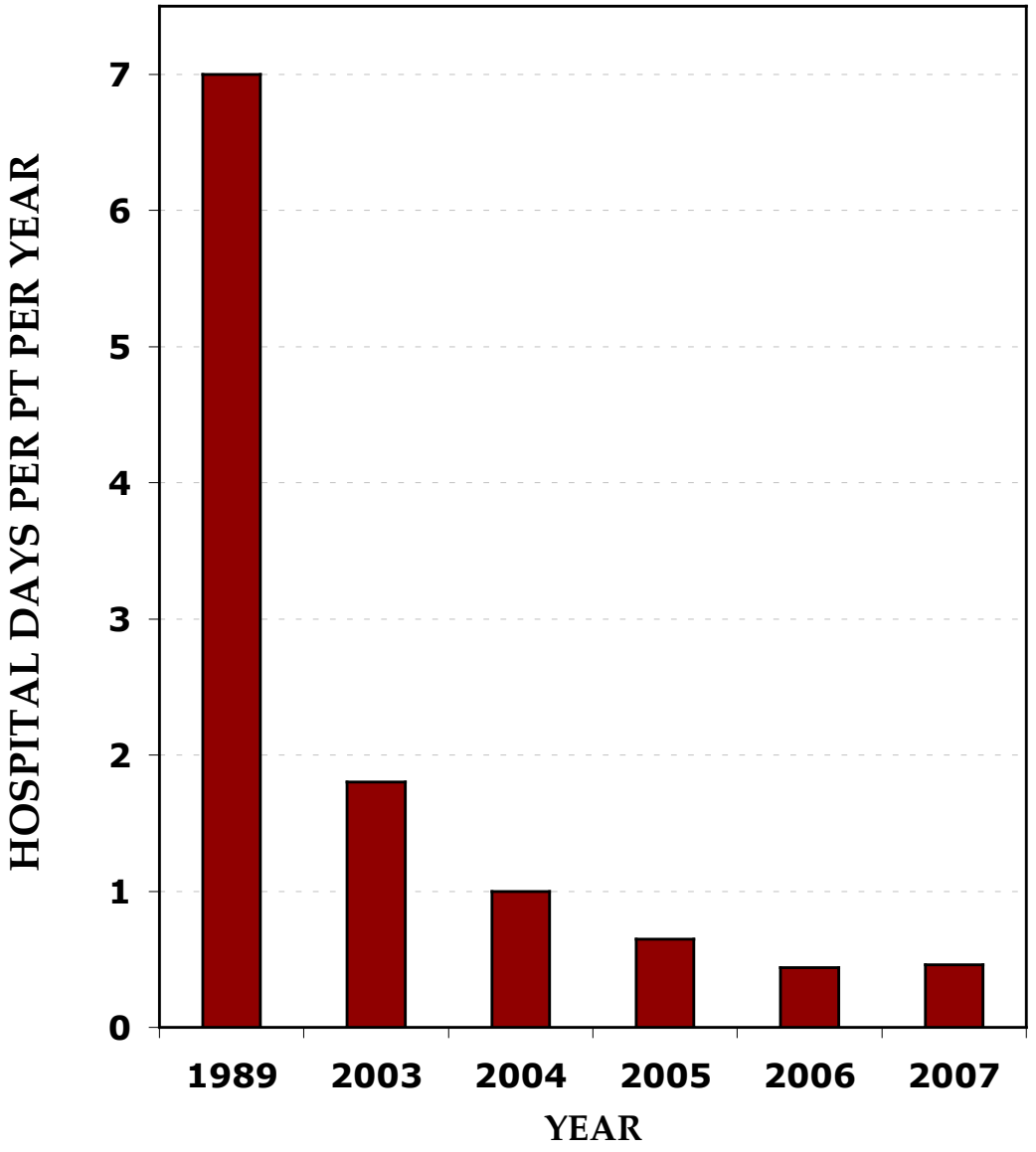
SIDDTsyndrome (*TSPYL*)	$27,000	1.3	$35,100
Pretzel syndrome (*STRADA*)	$27,000	0.8	$21,600
Symptomatic epilepsy and skull		0.	$12,900
TMCO1 syndrome	$27,000	0.6	$16,200
Amish lethal rigidity/seizures	$27,000	0.5	$13,500
OPPG syndrome	$2		$13,500
Cardiomyopathy and lactic acidosis (*SLC25A4*)	$35,000	0.3	$10,500
MTHFR deficiency	$27,000	0.3	$8,100
Non-syndromic mental retardation (*CRADD*)	$27,000	0.3	$8,100
Usher-like syndrome (*HARS*)	$27,000	0.3	$8,100
AXPC1 syndrome *(FLVCR1)*	$27,000	0.2	$5,400
Bardet-Biedel	$27,000	0.2	$5,400
Cockayne	$27,000	0.2	$5,400
Hereditary spastic paraplegia	$35,000	0.2	$7,000
Hypomyelinating leukodystrophy (*GJC2*)	$27,000	0.2	$5,400
Infantile Parkinsonism-dystonia (*SLC6A3*)	$27,000	0.1	$2,700
Thanatophoric dysplasia (*FGFR3*)	$27,000	0.1	$2,700
Totals	-	**25**	**$708,500**

Savings from the Core Lab:

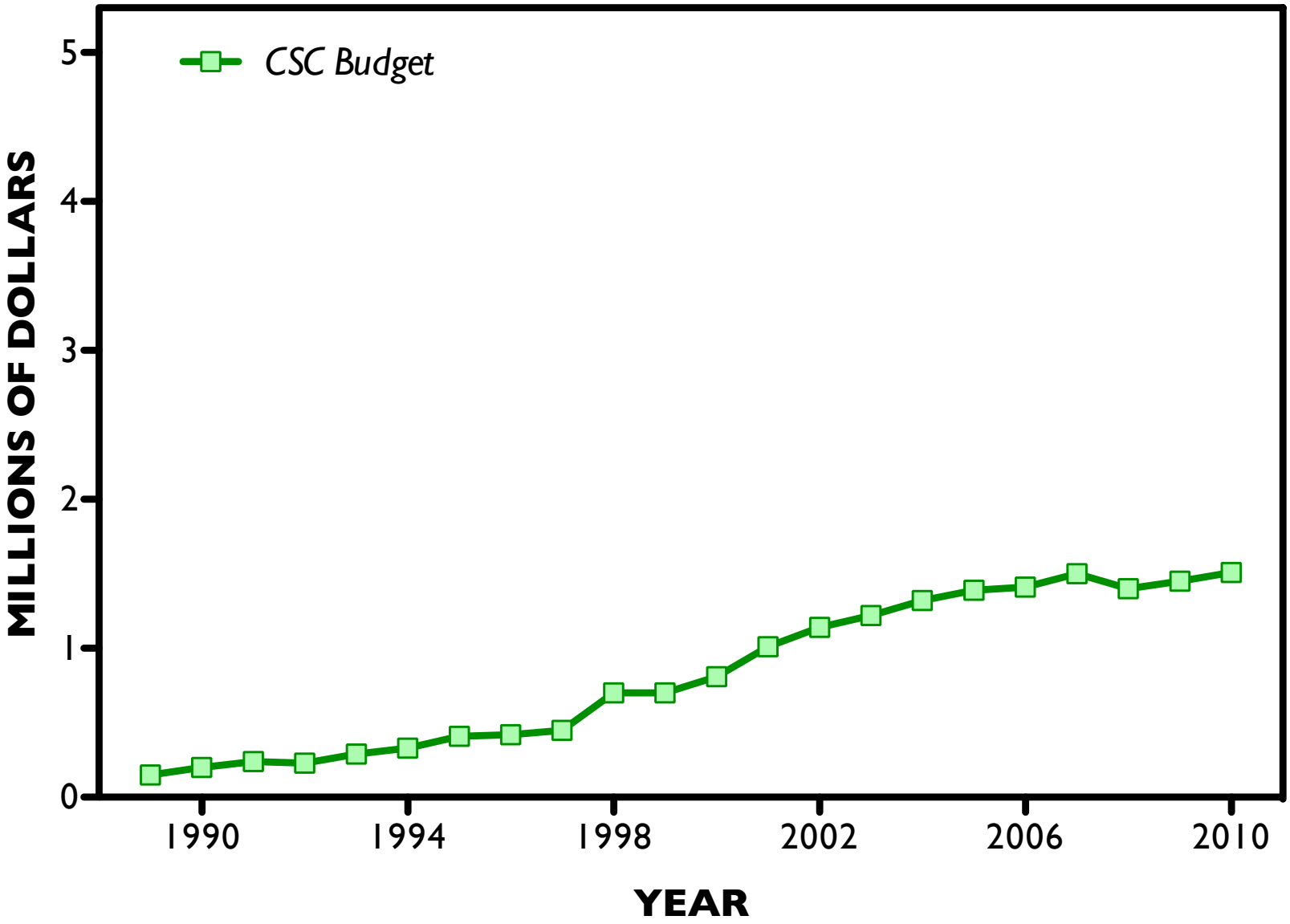
1 - 2 million dollars per year

Hospitalization

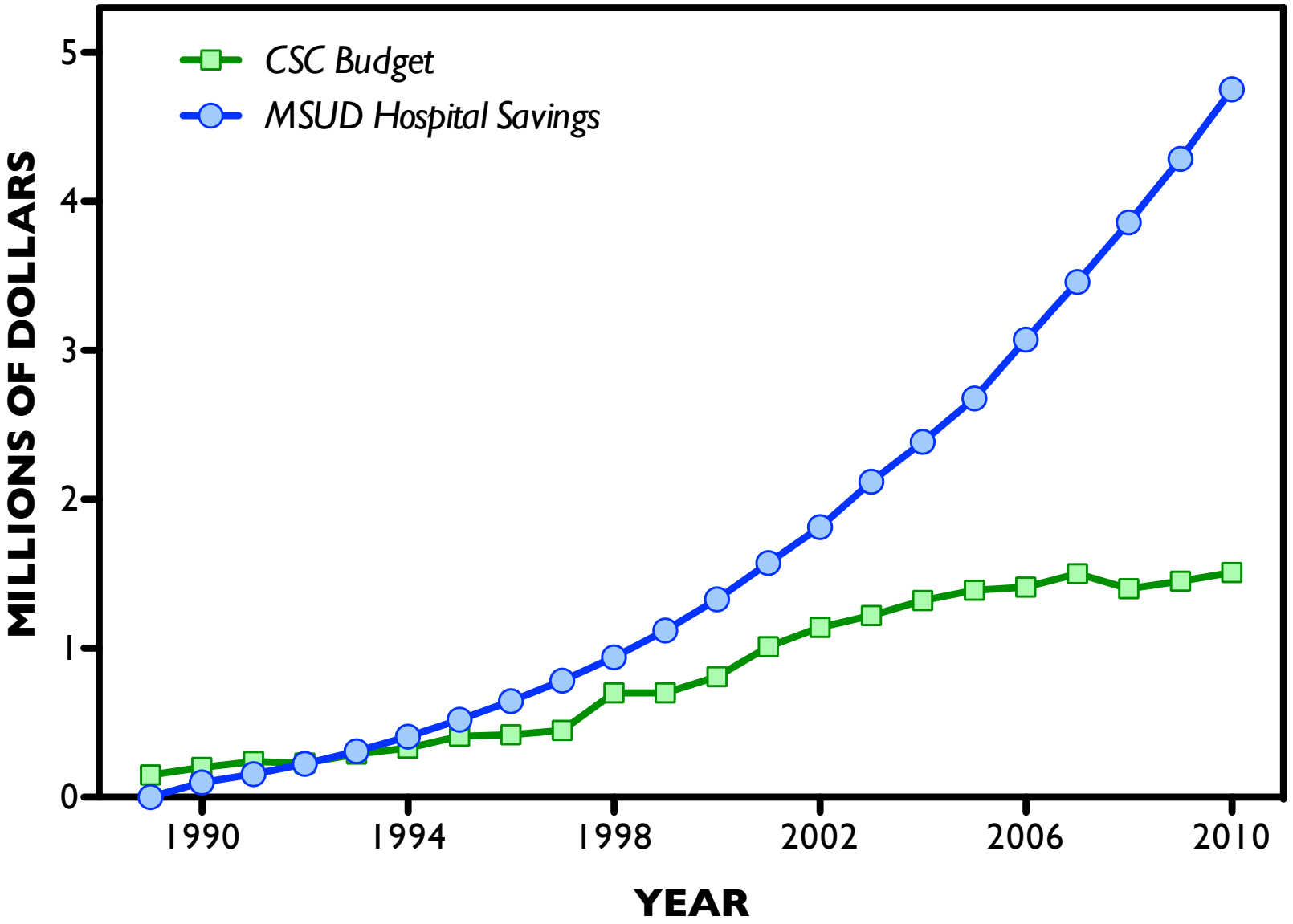
MSUD Hospitalization Rates, *2003-2007*



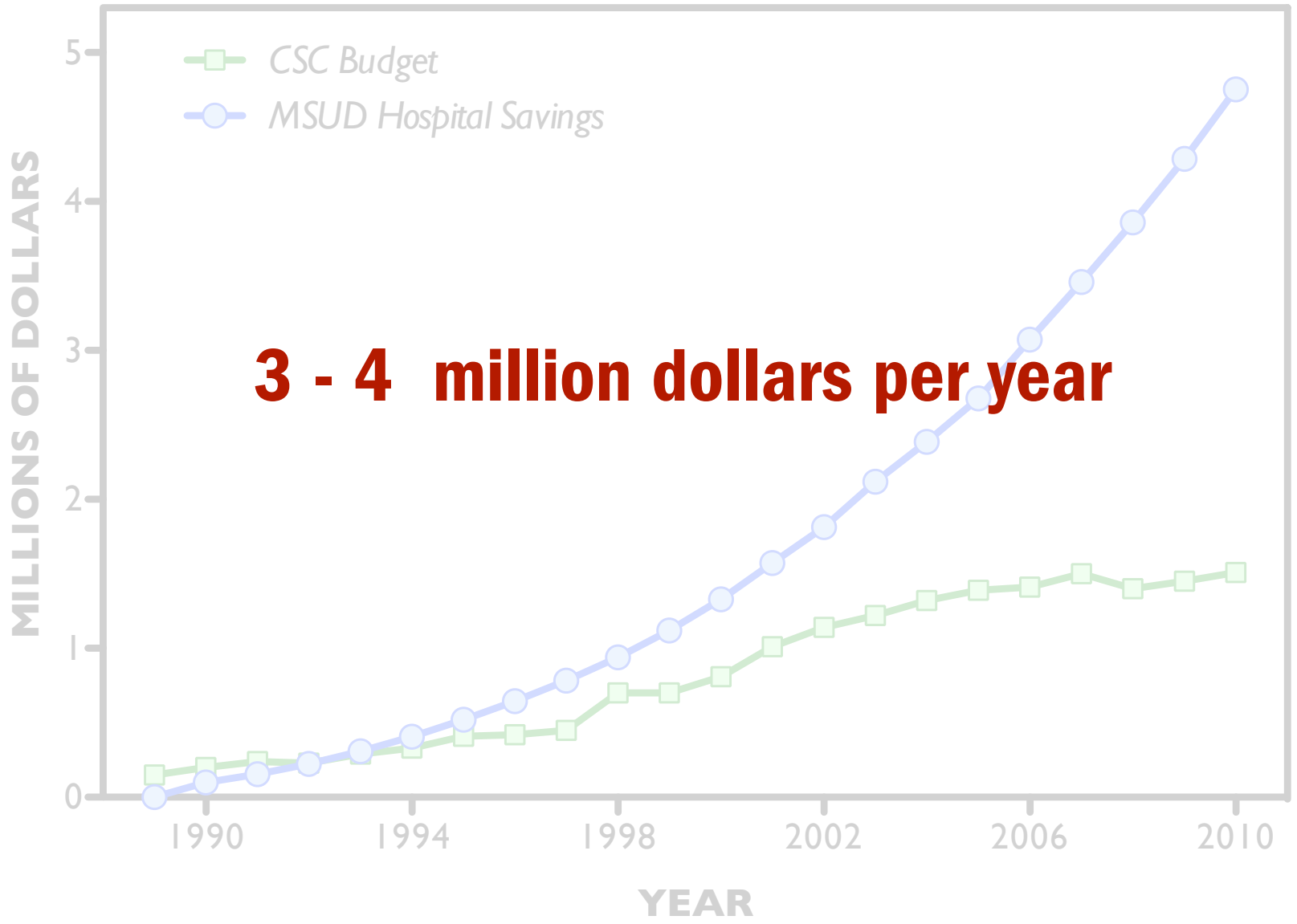
Hospitalizations: MSUD



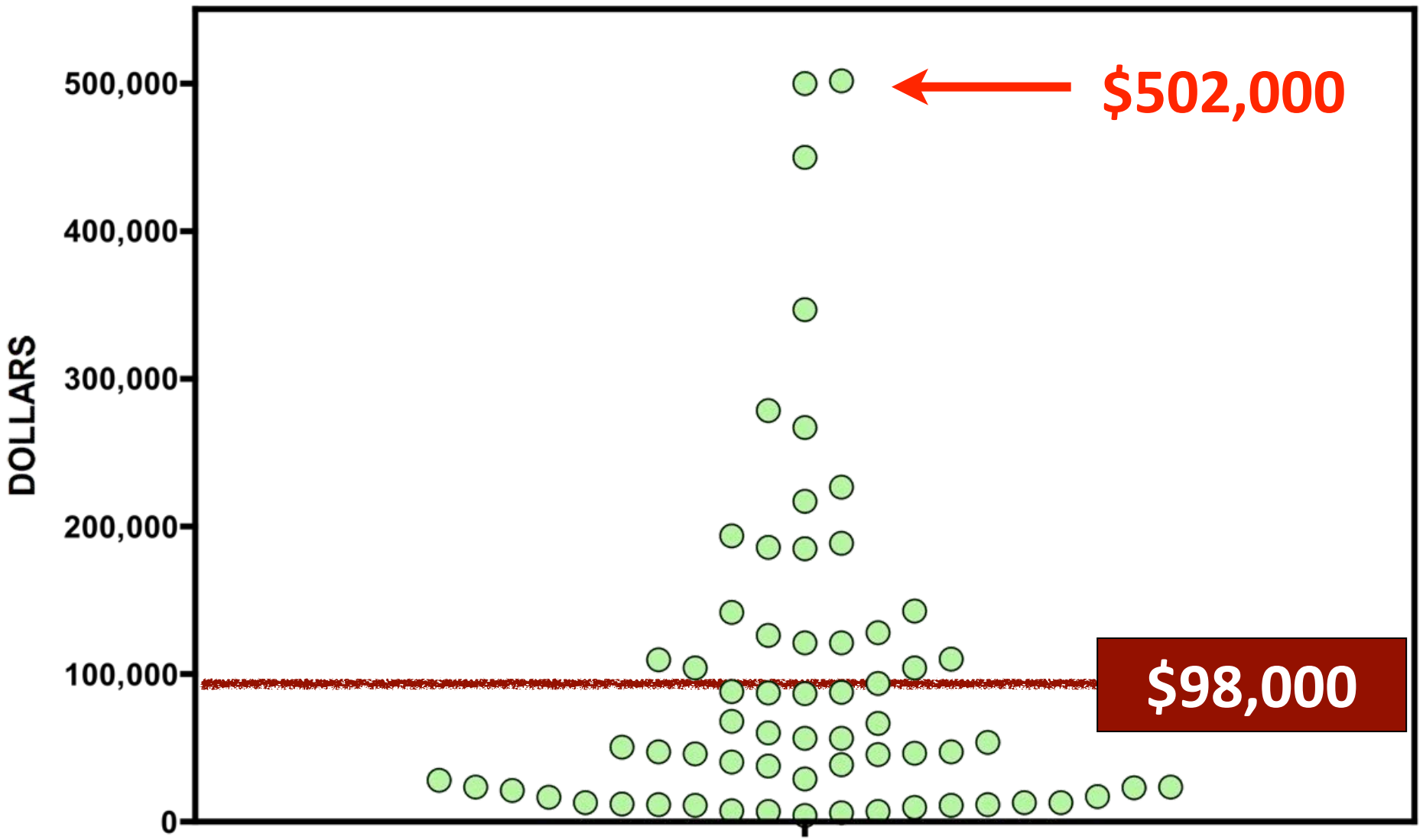
Hospitalizations: MSUD



Hospitalizations: MSUD



Hospital Charges



Hospital Charges

Hospital Charges

Savings from Hospital Discounts:

6 - 8 million dollars per year

Palliative Care

9%

The Cost of Inaction

Disability Prevention

Economic Implications

Table: Lifetime Direct and Indirect Medical Costs		
	2003 Dollars	**2010 Dollars**
MENTAL RETARDATION	$1,014,000	**$1,534,778**
CEREBRAL PALSY	$921,000	**$1,394,015**
HEARING LOSS	$417,000	**$631,166**
VISUAL IMPAIRMENT	$566,000	**$856,691**

Sources: MMWR 2004;53:57-59; www.cms.hhs.gov/NationalHealthExpendData

Disability Prevention

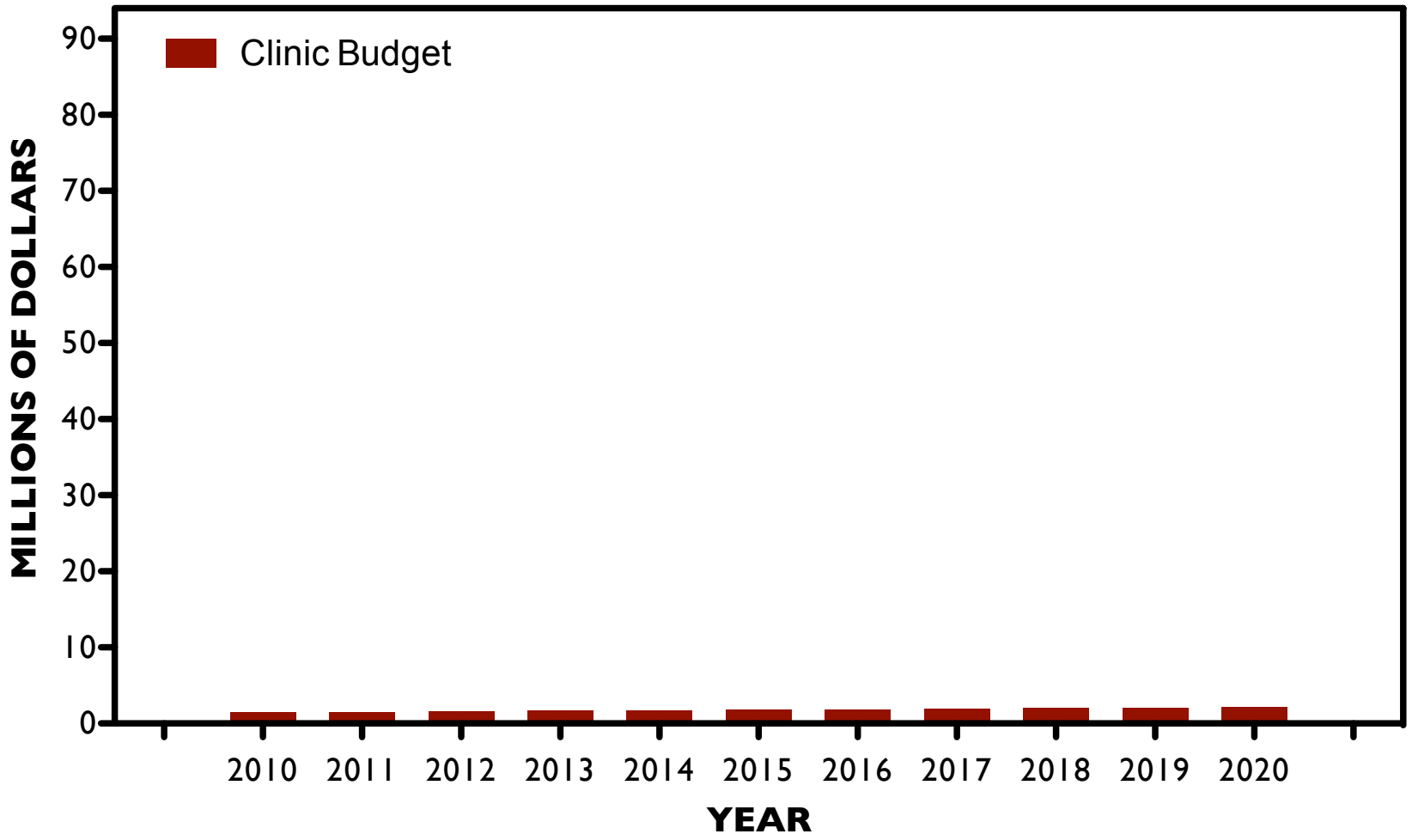
Eleven Selected Inborn Errors

	Lifetime cost/person	N persons	Medical Costs Saved	Annual Savings
Maple syrup urine disease	$1,274,294	64	**$81,554,816**	$4,077,741
Glutaric aciduria type 1	$1,157,421	25	**$28,935,525**	$1,446,776
Crigler-Najjar syndrome	$1,157,421	21	**$21,758,625**	$1,087,931
Familial hypercholanemia	$1,157,421	12	**$13,889,052**	$694,453
Medium-chain acyl dehydrogenase	$1,157,421	8	**$9,259,368**	$462,968
Propionic acidemia	$1,157,421	6	**$6,944,526**	$347,226
MTHFR deficiency	$1,274,294	4	**$5,097,176**	$254,859
Biotinidase deficiency	$1,274,294	4	**$5,097,176**	$254,859
Amnionless-B12 deficiency	$1,157,421	3	**$3,472,263**	$173,613
Tyrosine hydroxylase deficiency	$1,157,421	2	**$2,314,842**	$115,742
Classical galactosemia	$1,274,294	2	**$2,548,588**	$127,429
TOTALS	--	**151**	**$180,871,957**	**$9,043,598**

Total Clinic operational costs, 1989-2008: **$15,309,00**

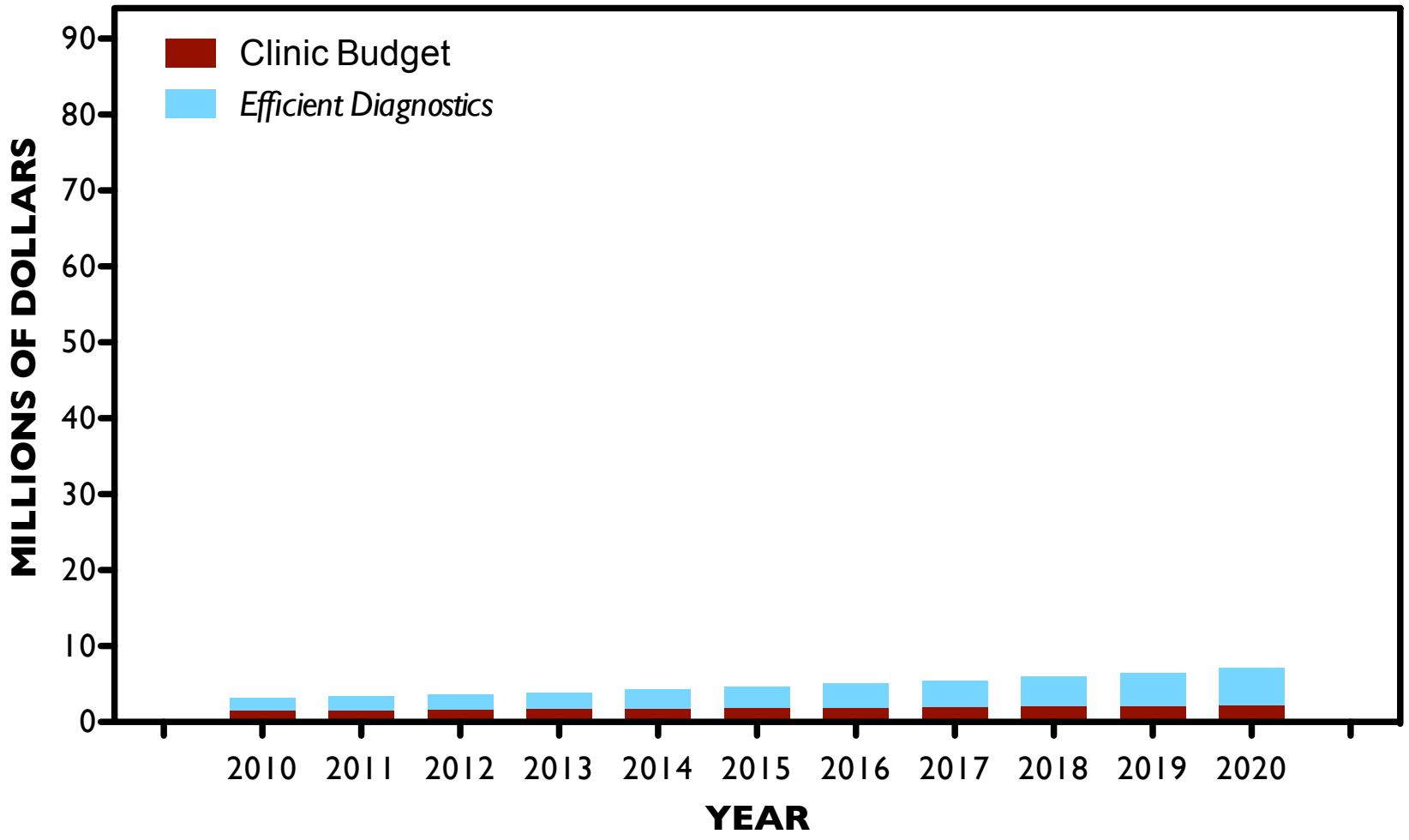
The Economics of Prevention

Clinic Budget



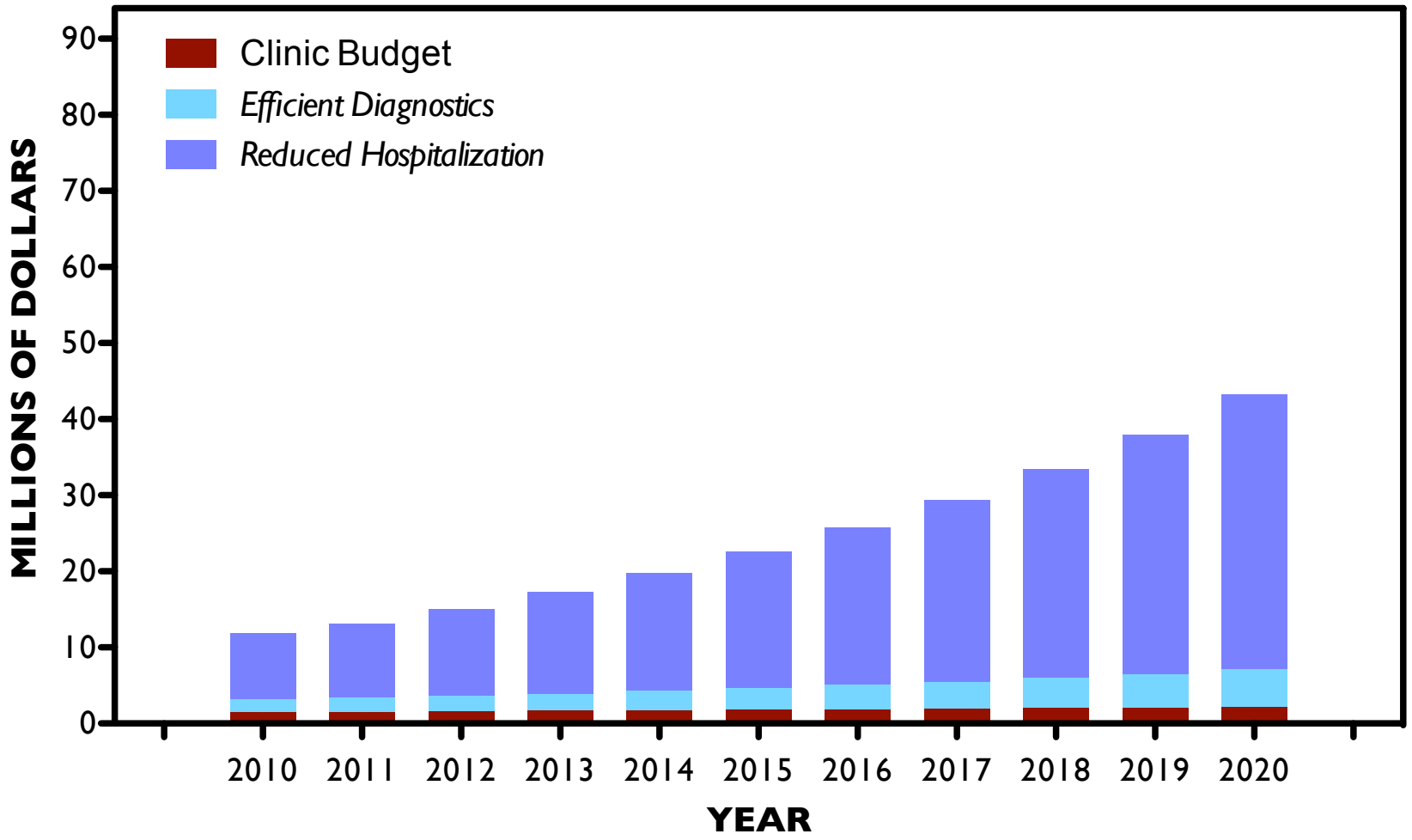
The Economics of Prevention

Diagnostic Savings



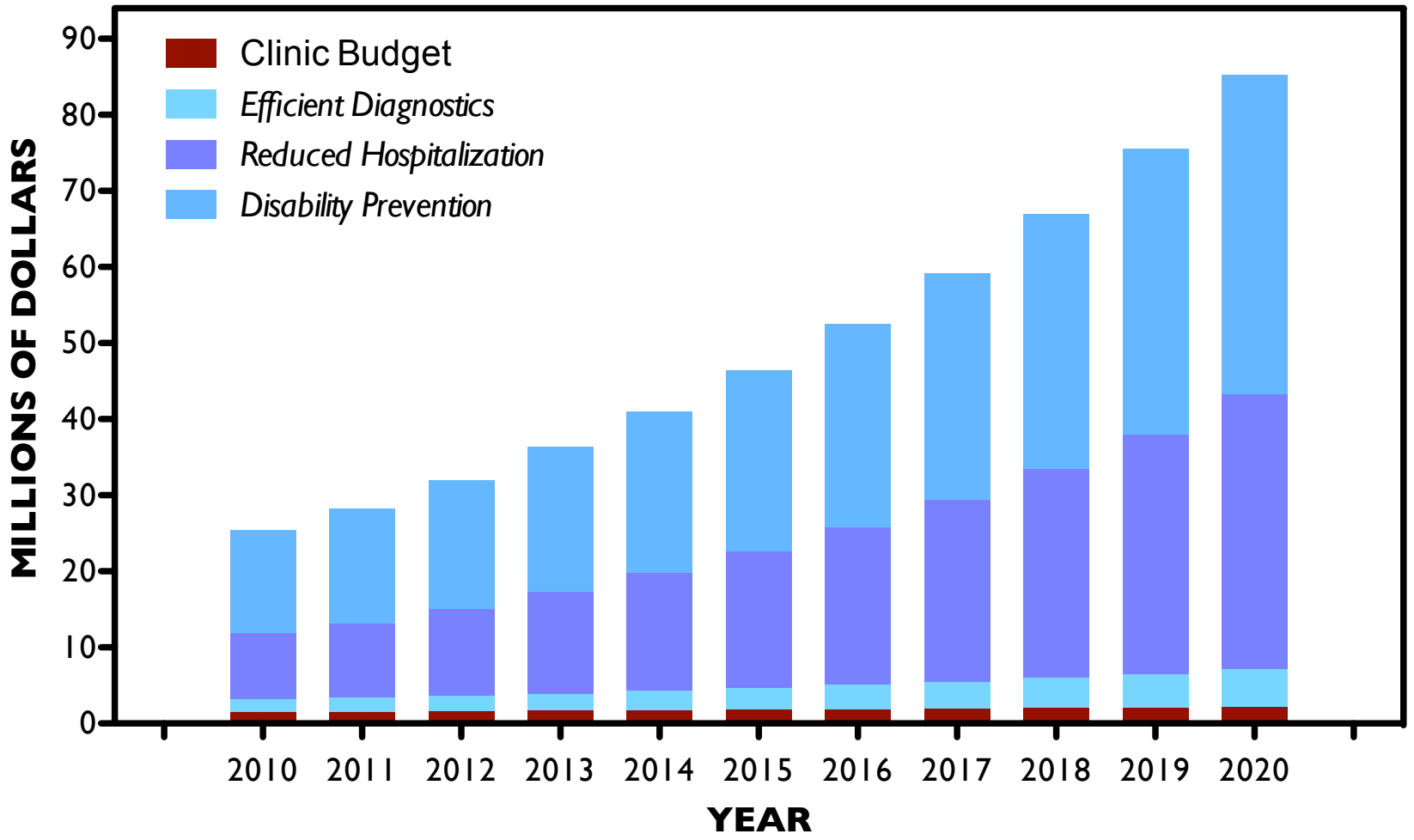
The Economics of Prevention

Reduced Hospitalization



The Economics of Prevention

Disability Prevention

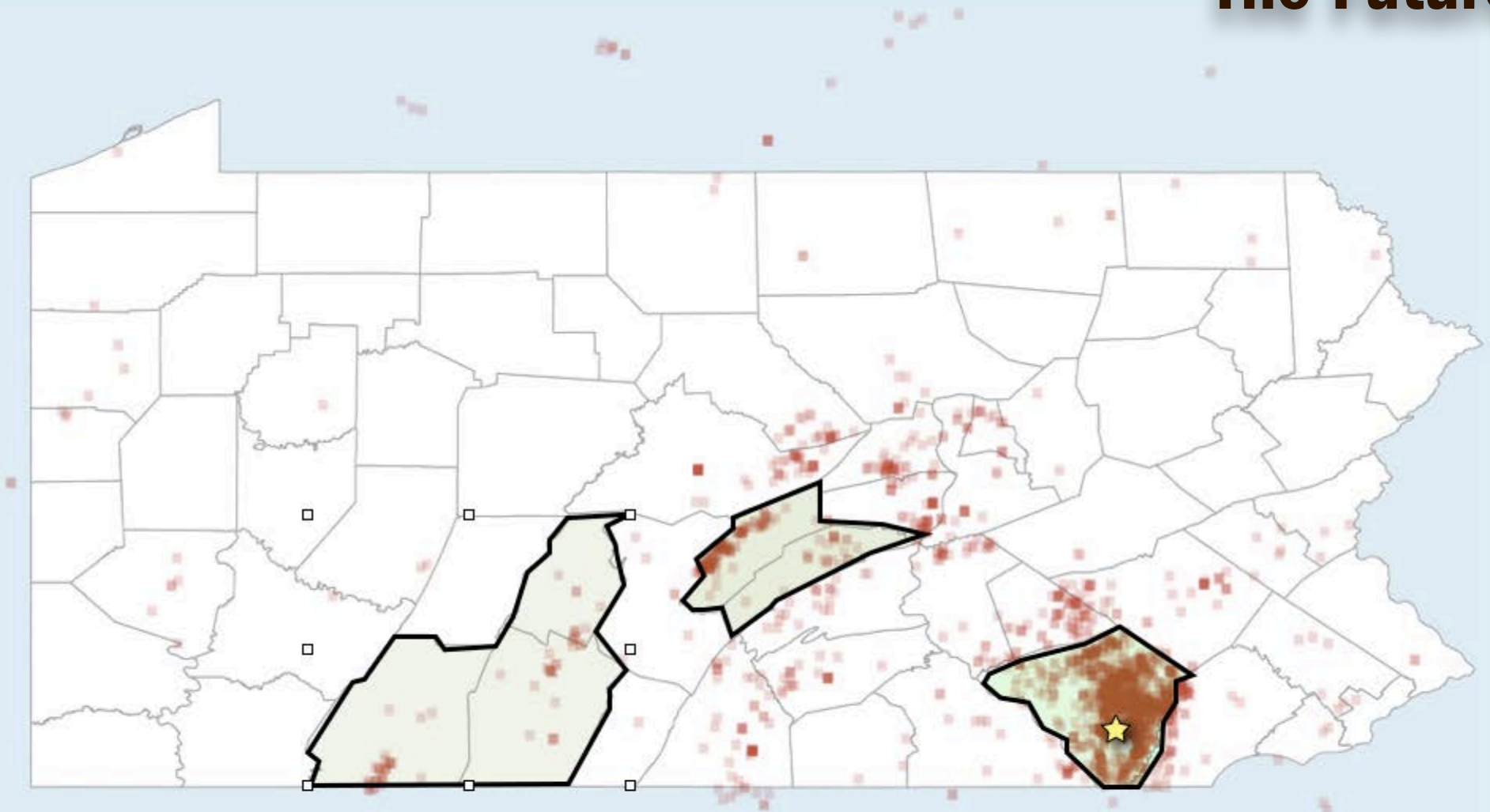


Budget: 2.1 million

Savings: 83 million

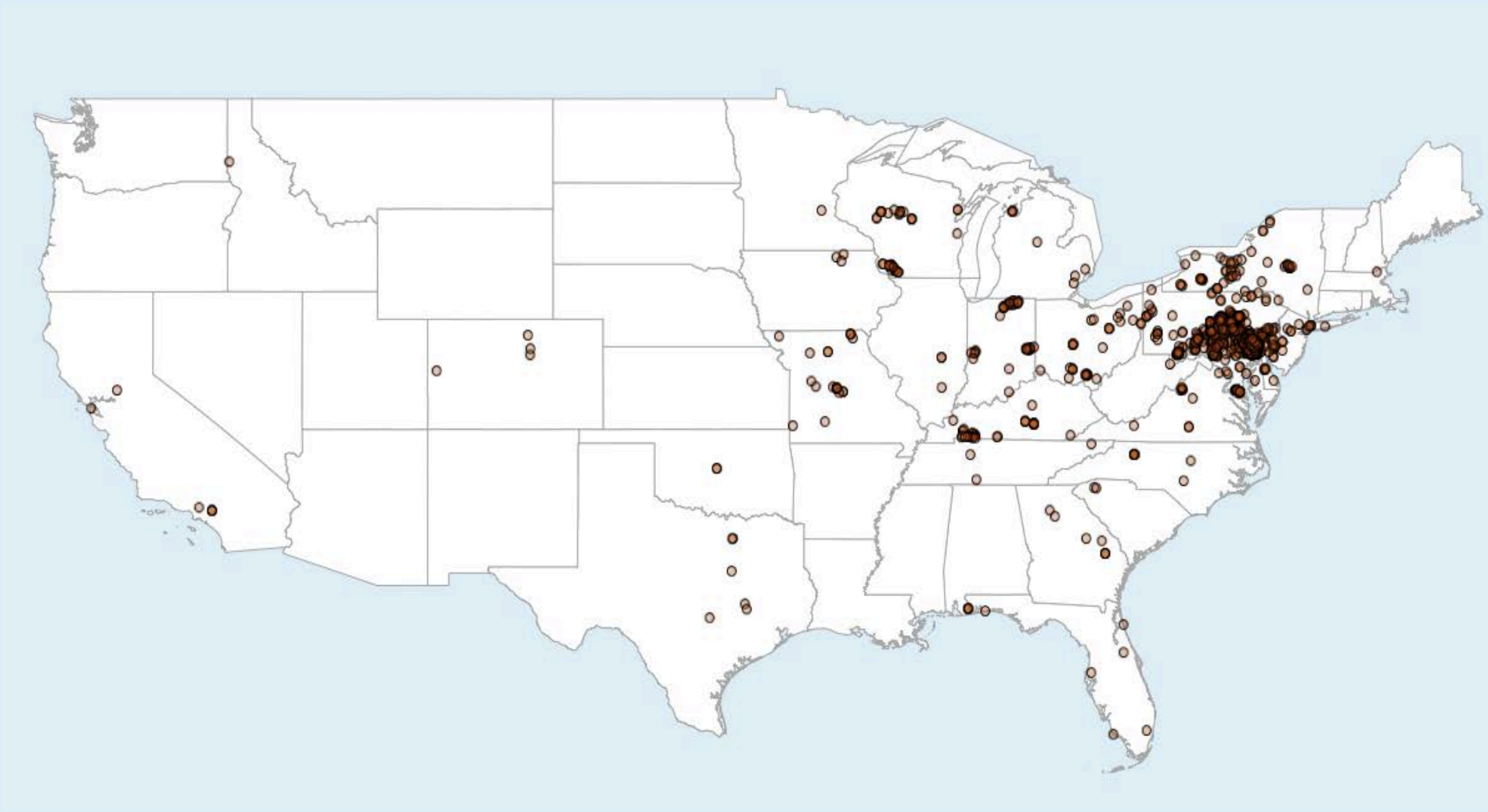

The Future

The Future



Regional *Medical Homes*

The Future



Regional *Medical Homes*

The Future

The Future

Think Globally, Act Locally

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**