

Ready for Rare?

Newborn Screening in the DoD and Dietary Treatment of Inherited Metabolic Diseases



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The views expressed in this presentation are those of the authors and do not reflect the official policy of the Department of the Army, Department of Defense, or U.S. Government.



Objectives

- Identify the components of a newborn screening program
- Recognize the challenges and benefits of a uniform, universal, comprehensive NBS program
- Understand how to find help for dealing with positive screens
- Be familiar with treatment for inherited metabolic disease

The traditional public health mission for newborn screening is as valid and important as ever.



The goal is to test all newborn infants, find those who will become ill, and change their environment so that they remain well.

Traditional Principles of Population Screening

- Disease is serious and the natural history well-understood
- Treatment is effective, available, and accepted
- Test is rapid, cheap, specific, and sensitive
- Follow-up and counseling are available
- Benefits outweigh costs
- Case-finding is continuous

WHO (1968), Wilson & Junger (1968), Frankenburg (1974), National Academy of Sciences (1975)

NBS History

- 1960s PKU
- 1970s Congenital Hypothyroidism
- 1980s Sickle Cell Disease
- 1990s Galactosemia, CAH, Biotinidase, Others
- 2000s Tandem Mass Spectrometry (MS/MS), Hearing, Cystic Fibrosis

Inherited Metabolic Disease

- Defects in the metabolism of the dietary constituents, protein, carbohydrate, fat, vitamins and minerals
- Caused by mutations in genes that code for specific enzymes or enzyme systems
- Can occur in the nuclear DNA or in mitochondrial DNA
- Usually autosomal recessive
- *They don't go away*

Inherited Metabolic Disease

- Range of severity
 - Lethal in untreated galactosemia and Maple Syrup Urine Disease
 - Exercise intolerance in the adolescent with glycogen storage disease type V
 - Clinically insignificant in pentosuria
- Treatment is primarily diet
- Great variation within diseases
- More adult onset being recognized

What does a “positive screen” mean?

- A positive diagnosis? No.
- A potential diagnosis? Yes.
- NBS identifies biochemical markers related to disorders, for example:
 - Cystic Fibrosis
 - immunoreactive trypsinogen is the protein marker
 - confirmatory testing is a sweat test and/or CFTR DNA analysis
 - PKU
 - phenylalanine is the marker
 - confirmatory testing determines whether it's classic PKU, a biopterin defect, or benign hyperphe

John Hancock



True or False?

- IMDs are rare, we'll never see them.
 - Individually rare but collectively not
 - **1/800 newborns** have potentially severe or lethal conditions for which screening and treatment are available
(HRSA/ACMG Rept of Uniform NBS Panel, March 05)

The Case of the College Scholarship



- Ten day old male presents with + NBS for PKU. He appears to be a healthy, thriving infant without any neurological, physical, or feeding issues.

Phenylketonuria

- One of the 1st treatable genetic disorders
- Mental retardation is preventable with dietary modification.
- Monogenetic disorder located on chromosome 12
- 1/10-15,000 live births in US
- Autosomal recessive
- >400 different mutations in the PAH gene with enormous genetic heterogeneity
- All States screen infants for PKU at birth

Child with PKU –
born before NBS

Full expression of
the disease

+ gene mutation

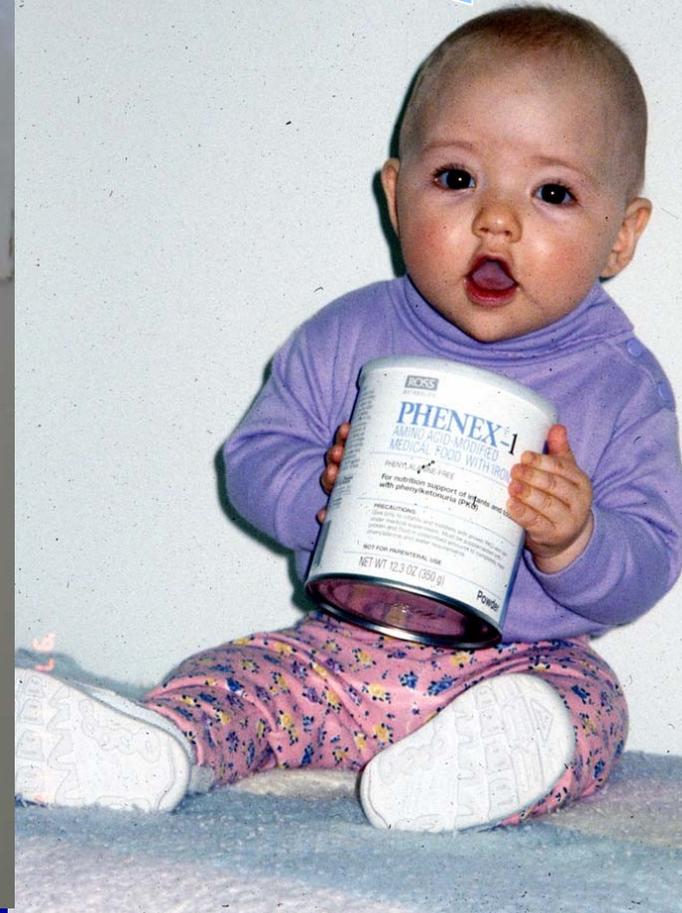
+ environmental
exposure



+ genetics
+ exposure

- genetics

+ genetics
- exposure



What Happens in PKU?

Food



Phenylalanine

Catabolized
tissue



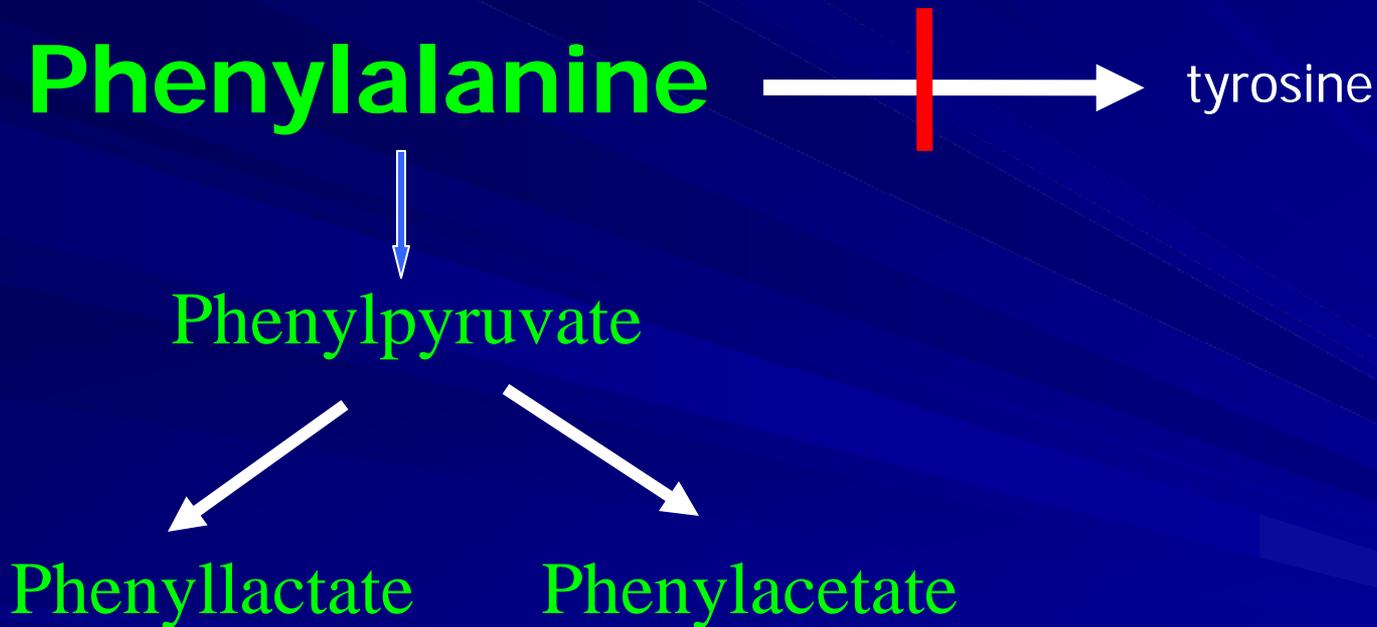
tyrosine



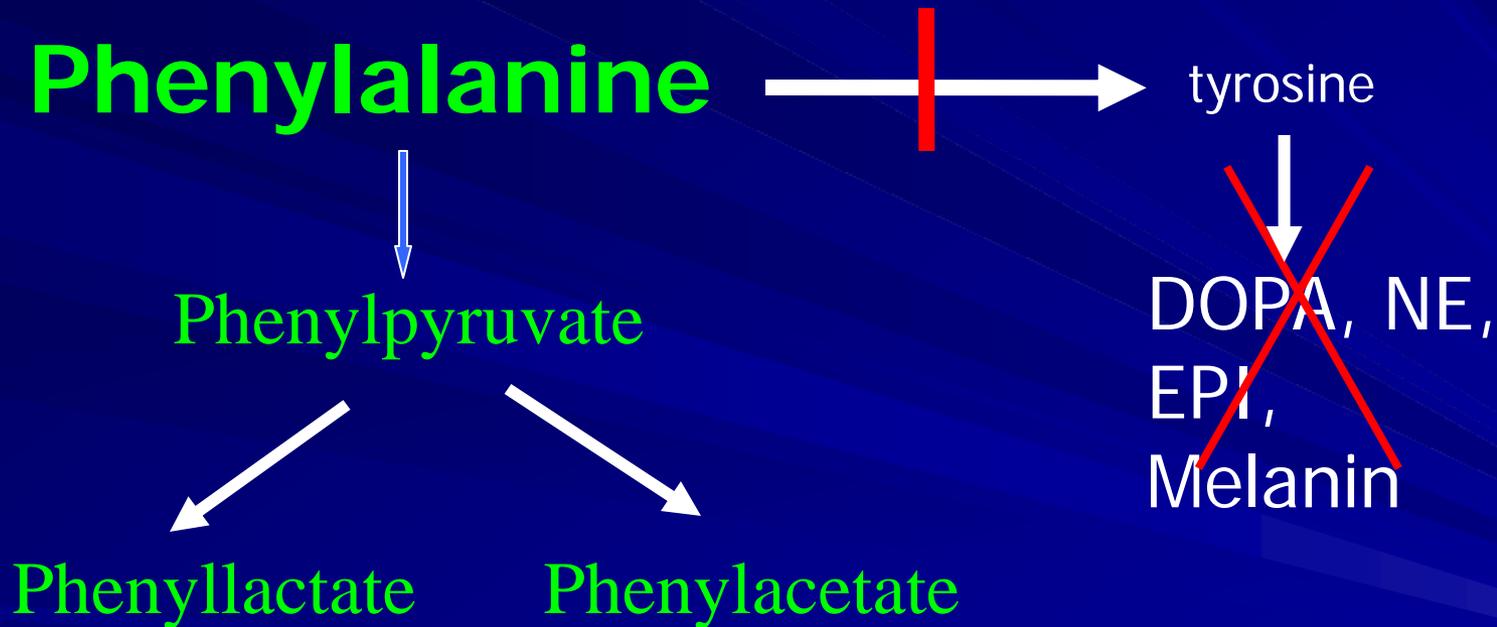
DOPA, NE,
EPI, Melanin

Absent
phenylalanine
hydroxylase

Increased PHE and Production of Alternate Products



Product of Blocked Reaction Is Not Made



Solution:

Phenylalanine → tyrosine



Restrict Precursor

Supply Product

Dietary Treatment

- Remained basically unchanged since it was developed in 1953 by Dr. Bickel
 - Phe-restricted diet supplemented with tyrosine, vitamins and minerals and CHO and fat enriched amino acid mixtures
 - 1960-1970's discontinuation in late childhood was recommended
 - Studies in the mid-1980s showed that discontinuation in childhood was associated with poorer outcome
 - Untreated maternal PKU results in death or severe mental retardation in offspring
 - Off-diet adults have increased neurological and psychosocial problems
 - Diet is now recommended for life.

The Case of the College Scholarship



- Ten day old male presents with + NBS for PKU. He appears to be a healthy, thriving infant without any neurological, physical, or feeding issues.
 - Plasma PHE: 24 mg/dL
 - Normal newborn PHE level < 2 mg/dL
 - Weight: 3.5 kg

Establish the Dietary Rx

	Per kg	Total
PHE:	25 mg	88 mg
TYR:	300 mg	1050 mg
Protein:	3-3.5 g	11-12 g
Kcal:	120	420
Fluid:	135-160 ml	473-560 ml



Amount of
phe in 5 oz
of formula



Infant needs
>18oz to grow

Determine Quantities of the Formula Components

1. **Breast milk or infant formula** provides PHE Rx as a small amount of whole protein
2. **Metabolic formula** provides remaining protein needed as purified amino acids (plus CHO, fat, vitamins, minerals)
3. **Polycose** provides any remaining calories needed
4. **Water** provides fluid

Life After Formula

- Solid foods are added to the infant's diet in an age appropriate manner
- Begin with cereals and advance to vegetables then fruit
- Amounts are calculated using exchange lists and food composition tables
- Every bite of food must be weighed!
- Infant/child/adult continues to drink medical formula

Typical Day's Intake for a 8 year old with PKU--PHE Rx is 350 mg

		g pro	Kcal
Breakfast:	1 slice low pro bread	0.2	60
	8 oz medical formula	14	190
Lunch	1 rice cake w 1 t marg	0.8	70
	1/2 cup low pro soup	0.2	19
	5 saltine crackers	1.4	65
	8 oz medical formula	14	190
Snack:	2 c popcorn w 2 t marg	1.8	164
Dinner:	50 g low protein rice	0.3	176
	3 T tomato sauce	0.6	14
	8 oz medical formula	14	190
Snack:	3/4 oz potato chips	1.3	110
	12 oz fruit drink	0	160

Typical Day's Intake for a 8 year old with PKU--PHE Rx is 350 mg

		g pro	Kcal
Breakfast:	1 slice low pro bread	0.2	60
	8 oz medical formula	14	190
Lunch	1 rice cake w 1 t marg	0.8	70
	1/2 cup low pro soup	0.2	19
	5 s		5
Snack:	8 o		90
	2 c		64
	50		76
Dinner:	3 T		4
	8 oz medical formula	14	190
	3/4 oz potato chips	1.3	110
Snack:	12 oz fruit drink	0	160

Reality Check:

1 oz cheese = 355 mg

1 oz chicken = 345 mg

7 g protein
and 730
kcal from
food

44 g protein
and 570
kcal from
medical
formula



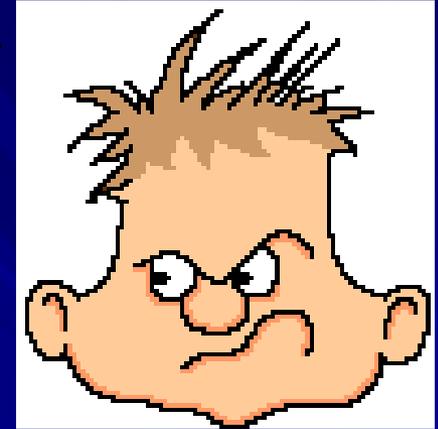


Cost Comparison of LP Products and Their Regular Counterparts

Food Item	Regular	Low Protein
Flour, 16 oz	\$0.27	\$5.00
Spaghetti, 16 oz	\$1.25	\$10.00
Crackers, 16 oz	\$0.79	\$15.00
Rice, 16 oz	\$0.55	\$10.00
Cream Cheese, 8 oz	\$1.99	\$5.60
Am Cheese, 10 oz	\$2.30	\$10.00
Tomato Sauce, 4 oz	\$0.25	\$4.00

Shipping and handling runs \$5.00 to \$25.00 per order

Practical Issues of Dietary Treatment



■ Compliance

- these diets are complicated!!
- harder to adhere to as the child ages

■ Cost

- \$\$\$\$ medical formula and low protein foods
- insurance coverage

■ Repeated blood draws and doctor's visits

Diet Alternatives

- Large Neutral Amino Acids (LNAA)
 - Compete with phenylalanine at the blood brain barrier
 - provide precursors to neurotransmitters
 - Still need some protein restriction
 - Being used successfully in the US for adolescent and adult males
- Tetrahydrobiopterin
 - Cofactor for phenylalanine hydroxylase
 - Works in patients with milder forms of PKU
 - In phase 3 trials in the US
 - Very expensive
- Phenylalanine Ammonia Lyase
 - Plant derived enzyme that works in the gut to break down phe before absorption
 - Technical issues
- Gene Therapy—on going research

The Good News Is....

- Adherence to diet and maintenance of therapeutic blood phe levels results in normal cognition



The Case of the Sleepy Boy



- DOL3 ↓ desire to feed, poor latch/suck-- begun on Similac; taken to the ER but told that his behavior was normal.
- DOL 7, became difficult to waken for feeds, consuming 5-6 oz/d; again taken to the ER and subsequently transferred to WRAMC.
- Blood and urine were obtained.

- The State metabolic lab was called re NBS and provider told that it was normal.
- Diseases screened:
 - Biotinidase
 - Galactosemia
 - MCAD
 - Homocystinemia
 - MSUD
 - PKU
 - CAH
 - Hemoglobinopathies

- HR 150, temp 96.8, BP 60/38
- Pale, difficult to arouse, with signs of dystonia
- Labs obtained in the ER
 - UA
 - Sp gv 1.010
 - Ketones 150 mg/dL
 - CBC
 - 52.4/18
 - Heel stick BMP
 - Na 136, K 7.0, CL 98, CO2 19, glucose 65, Ca 10
 - Anion gap = 19

What Makes This Suspicious for Metabolic Disease??

- Normal newborn with clinical symptoms developing in the first few days of life
 - “Intoxication” disorders where products of intermediary metabolism build up
 - Protein, fat, carbohydrate
- Rapid deterioration
- Lab findings
 - Ketonuria, low glucose, increased anion gap acidosis

Disorders of “Intoxication”

- Present after a period of normalcy in the first days of life.
- Triggered by
 - exogenous intake of a specific dietary component or
 - endogenous breakdown of fat or protein during catabolism
 - Results in a buildup of toxic by-products due to faulty metabolism
- Includes: Urea cycle disorders, Organic acidemias, Amino acidemias, Fatty acid oxidation disorders, Galactosemia, Hereditary fructose intolerance

Hospital Course

- The infant was admitted to the ward where IV dextrose was started.
- IMD was high on the differential so urine and plasma were hand carried to a nearby metabolic center for rapid turnaround
- Urine began to have a characteristic smell

ODOR!

Glutaric acidemia (type II)	Sweaty feet
Hawkinsinuria	Swimming pool
Isovaleric acidemia	Sweaty feet
Maple Syrup Urine Disease	Maple Syrup
Methionine malabsorption	Cabbage
Multiple Carboxylase Deficiency	Tomcat Urine
Oasthouse Urine Disease	Hops-like
Phenylketonuria	Mousy or musty
Trimethylaminuria	Rotting Fish
Tyrosinemia	Rancid, fishy, or cabbage like

Adapted from Nelson's Pediatrics, 15th edition, 1996
(Sorry that HTML does not yet include olfactory links)

■ Plasma amino acids (umol/L)

	value	normals
– Leucine	2,322	50-185
– Isoleucine	468	50-105
– Valine	513	130-318

■ Urine organic acids

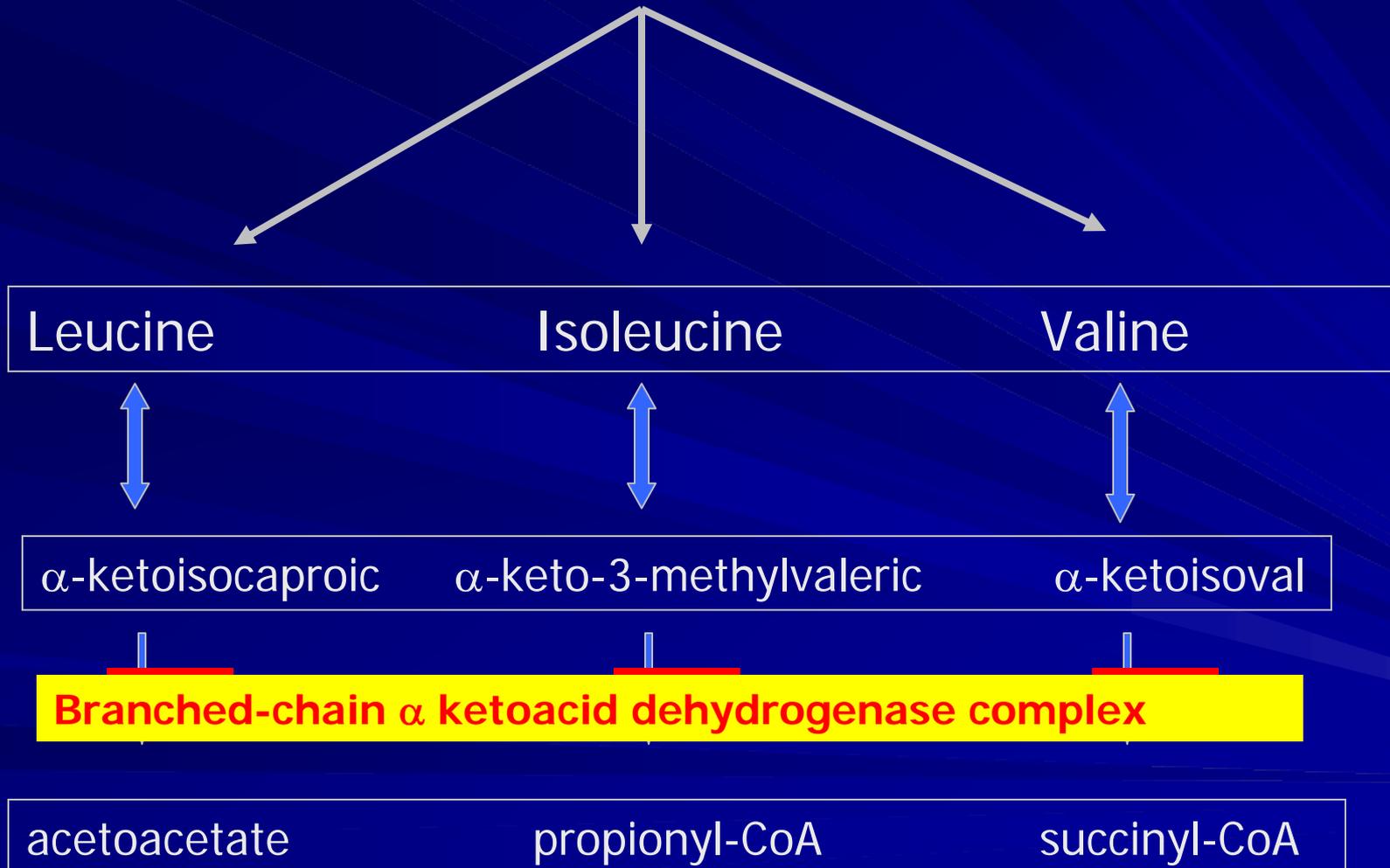
- ↑ 2-OH-isovaleric acid and 2-oxoisocaproic acid

Maple Syrup Urine Disease

- Autosomal recessive inheritance
 - 1/225,000
 - 1/200-350 in old world Mennonites
- Infants are normal at birth
- Seizures, apnea, and death can occur within 10 days of birth
- Branched-chain α -ketoacid dehydrogenase complex (BCKAD) deficiency

Dietary Protein

Tissue protein catabolism



Acute Management

- ABC's
- Stop protein-containing nutrition to prevent further buildup of toxic metabolites
 - max 24-48 hrs
- Hydrate—promote renal excretion of toxic metabolites
- Treat biochemical derangements
 - Bicarb for acidosis—IV drip
 - IV Glucose (D12 peripherally, more if central)
 - Carnitine—PO or IV; 50-200 mg/kg/day



Acute Management, cont

- Remove toxic metabolites
 - Hydration
 - Dialysis (only at presentation in a comatose patient with MMA)
 - Carnitine and other drugs depending on disease
- Prevent catabolism
 - Dextrose (>10%)
 - Insulin if needed
- Prevent increased ICP in MSUD—use zofran for nausea

Initiate Nutrition Support Immediately!

- High energy feeds
 - 120-150 kcal/kg infants
 - 80-100 kcal/kg children
- If the gut works, use it
- PO, n/g, g-tube
 - metabolic formula without added whole protein (initially restrict offending amino acids)
- Source of whole protein will need to be added within 24-48 hours to prevent muscle breakdown
- Get Help!!
 - Endocrine, genetics, biochemical genetics, neurologist, intensivist, outside resources

Acute Management, cont:

- If gut cannot be used or if sufficient formula cannot be delivered enterally:
- IV via *central line* *peripheral line*
 - hypertonic dextrose 12% dex
 - lipids lipids
 - replace electrolytes incl 4-6 mEq sodium
- Can use a combination, e.g:
 - drip feeds of formula to supply non-offending amino acids + IV dextrose and lipids

Lessons Learned?

- A reportedly “normal” NBS on a sick baby does not rule out the possibility of a metabolic disease
- Acute onset of symptoms in an otherwise normal baby are suggestive of IMD
- Significant ketosis demands respect
- Parents are good observers

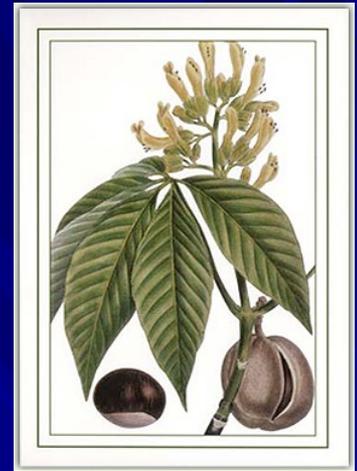
The Case of the Buckeye Babe



- Boy born in Texas on December 21
- January 6-- Fax from the State
 - “CAH Abnormal. Rescreen”
 - Infant had been seen that morning; was sent to the lab for a second NBS (routine in TX), but failed to go
 - Instead, they left for Ohio to visit family

Buckeye

- Called mom on cell phone and was told they would arrive at their destination the next day
- January 8--contacted mom again. Also called a pediatrician, a hospital lab in Ohio, and OH Department of Health to arrange for OH NBS (28 disorders)



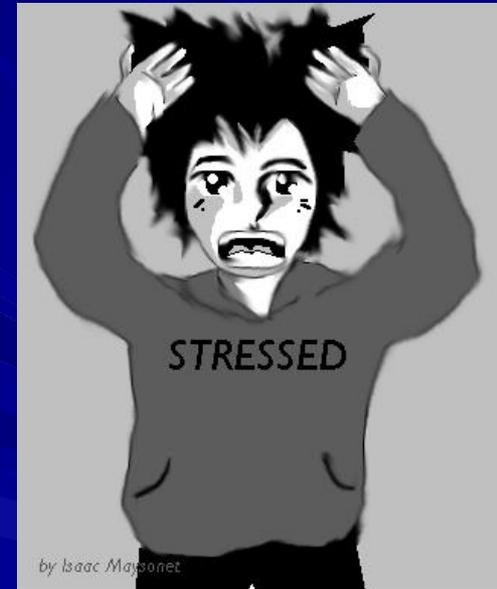
Buckeye



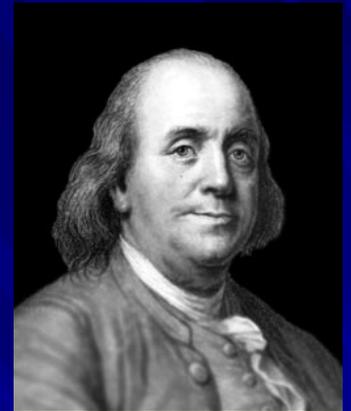
- Verbal OH NBS Report
 - CAH normal
 - Everything else normal, too
- January 10 → Fax : Arginine increased
 - Recommends diagnostic test to rule out argininemia
 - Called lab director, who told me there was a new normal range for arginine that was not yet official and that they would run the sample again when the new range becomes official
- 20 January – Arginine normal

Lessons Learned:

- Every element in the NBS system is a potentially weak link
- False positives mean work
- False positives make parents worry
 - 1/3 parents remain concerned, more stressed, more dysfunctional, and infants are hospitalized twice as frequently as other normal children

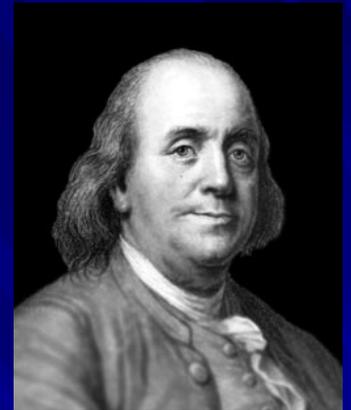


Philadelphia Story



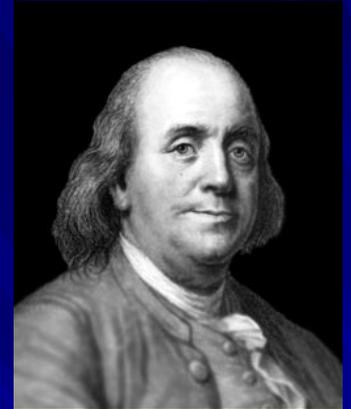
- Newborn girl has expanded NBS
 - Elevated C5-OH
 - Referred to Biochemical Genetics at CHOP who note normal exam at 2 weeks
 - Urine and blood tests confirm 3-methylcrotonyl-CoA carboxylase deficiency (3-MCCD)
 - Protein restricted diet plus carnitine
 - Genetic counseling (autosomal recessive)
 - “Sick Day” precautions and letter
 - Follow up arranged

Philly



- Time passes, baby is well
- Parents stop the diet and the carnitine
- 19 months → runny nose and fever
 - admitted with hypoglycemia, lethargy, acidosis, low carnitine
 - Rx D10 ½ NS, IV carnitine, bicarbonate
 - d/c well, and compliant. Excellent prognosis this time

Who was luckiest?



- The child
- The insurance company
- The parents
- The taxpayers
- The metabolic specialists
- The department of health
- The pediatrician

A Case of Stridor

- 15 month old boy with admitted with stridor, responds to racemic epinephrine and steroids
- Readmit one week later with more stridor, lethargy → PICU
 - Apnea, mild hypotonia, dysmetria
 - Cultures and IF negative
 - ABG pH 7.44, pCO₂ 18, anion gap 20, lactate 12.9
 - MRI abnormal T2 hyperintensity in white matter

Stridor

■ PMH

- Previously well, normal growth and development, normal diet
- Unsteady gait began 2 weeks before 1st admission
- Thinning scalp hair x 2 months

■ FH

- Pakistani
- Sibling died with seizures, developmental delay, rash

Stridor

- Diagnosis clinically suspected, biochemically confirmed
 - Biotinidase deficiency
- Oral biotin 10 mg daily
 - Rapid clinical improvement
 - Severe hearing loss
 - Psychomotor retardation

Stridor

- Newborn screening had been done on DOL 2
- Biotinidase activity absent!
 - DNA testing confirmed homozygous mutation
- Letter sent requesting follow-up testing
 - Reason not stated
 - English not the family's primary language
- Private Lab – no follow-up system in place, not part of a public health program

The Components of the Newborn Screening System must fit together to form a seamless system.



Components of the Newborn Screening System

Management:

- Treatment
- Long-term follow-up
- Specimen storage

Screening:

- Sample collection
- Sample submission
- Laboratory testing

Evaluation:

- Quality assurance
- Outcome evaluation
- Cost effectiveness

Diagnosis:

- Subspecialist Assessment
- Results shared with family
- Counseling if necessary

Follow-up:

- Obtain test results
- Get results to family
- Repeat test(s) if needed
- Ensure diagnostic testing

Components of the Newborn Screening System

Management:

- Treatment
- Long-term follow-up
- S

Screening:

- Sample collection
- Sample submission
- ng

Education

- Subspecialist Assessment
- Results shared with family
- Counseling if necessary

- Obtain test results
- Get results to family
- Repeat test(s) if needed
- Ensure diagnostic testing

Sepsis in Syracuse



- 2 year old girl, previously well, presents to Ft Drum ER in 2001 with fever, hypotension, delirium
- Transferred to Syracuse University PICU where sepsis caused by *Streptococcus pneumoniae* is diagnosed.
- She dies





Syracuse

- Anemia is noted





Syracuse

- Pediatric hematologist wonders why this condition was not previously diagnosed, requests an explanation from the military health care system
- Record review – normal newborn screen documented
- Born in England at a National Health Service facility
 - Not until 2004 were hemoglobinopathies universally screening by the NHS



Newborn Screening in the DoD

- Infants born to military personnel
 - Screened in the State system in which the MTF is located
 - Or, MTF may contract with a private lab
 - OCONUS goes to several states
- Over 100,000 births per year in DoD
 - estimated 125 affected infants annually



Military Issues

- Frequent military family PCS travel – true positives lost to follow-up
- Widely dispersed population – many different screens, lack of uniformity
- Clinics/labs often have inexperienced supervisors and short institutional memories
- OCONUS arrangements foster delays in testing and intervention

American Academy of Pediatrics Newborn Screening Task Force

- Recommended that HRSA develop nationally recognized NBS standards
- HRSA contracts ACHG to produce this report

PEDIATRICS

August 2000
Volume 106
Number 2
Part 2 of 3

American Academy of Pediatrics



Vol. 106, Aug. 2000, Suppl.

S U P P L E M E N T T O P E D I A T R I C S

Serving the Family From Birth to the Medical Home

*A Report From the Newborn Screening Task Force
Convened in Washington DC, May 10–11, 1999*

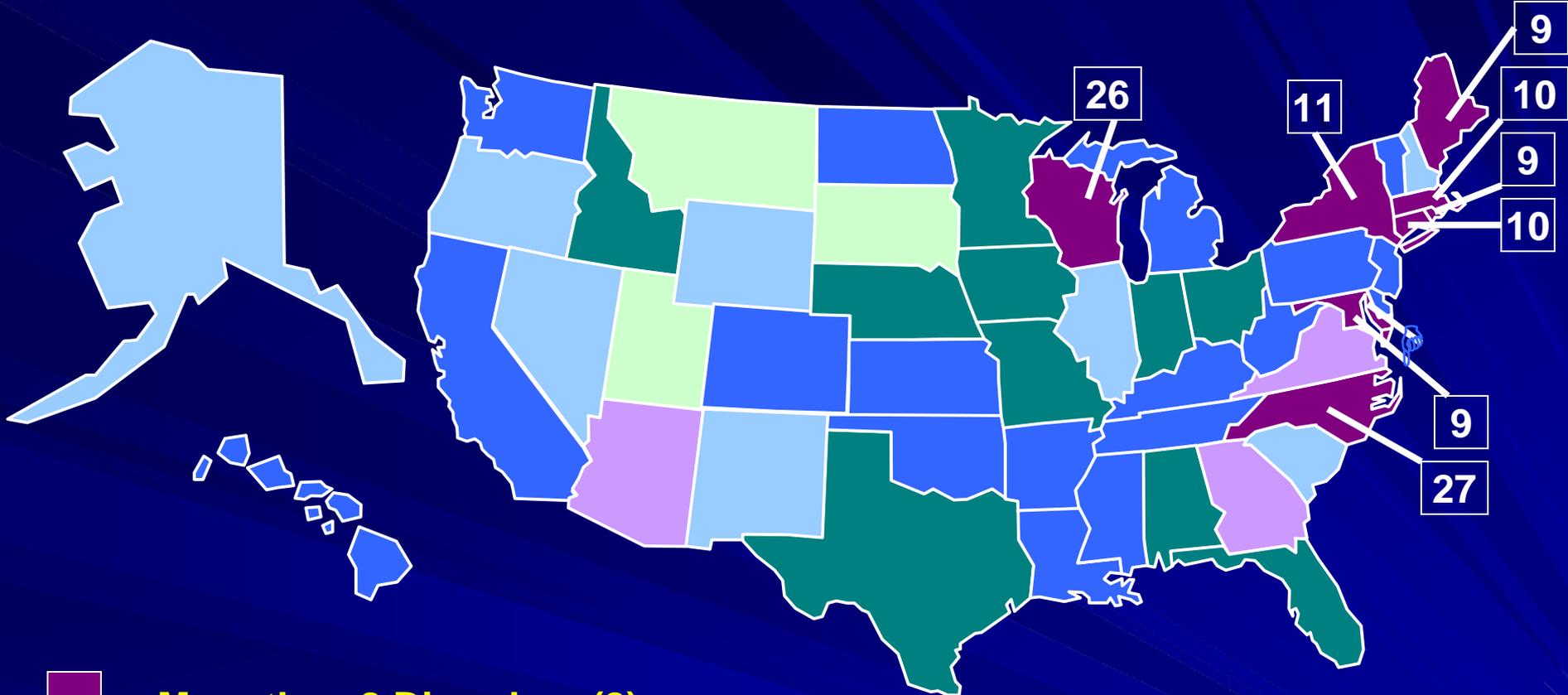
Sponsoring Organizations:

*Health Resources and Services Administration
American Academy of Pediatrics*

Co-Sponsoring Organizations:

*Agency for Healthcare Research and Quality
Association of Maternal and Child Health Programs
Association of Public Health Laboratories
Association of State and Territorial Health Officials
Centers for Disease Control and Prevention
The Genetic Alliance
National Institutes of Health*

*Funded in part by a grant (6MCJ-17R003) from the Maternal and
Child Health Bureau, HRSA.*



US Newborn Screening Conditions Required October, 2000

Newborn screening: Toward a Uniform Screening Panel and System

American College of Medical Genetics

- September 2004 – ACMG draft report delivered to HRSA and the HHS Secretary's Advisory Committee on Genetic Diseases in Newborns and Children
- March 2005 – Public release and comment
- January 2006 – Report sent to Secretary of Health and Human Services
- May 2006, Special issue of *Pediatrics* (Vol 117, no 5)

29 Conditions in Core Panel

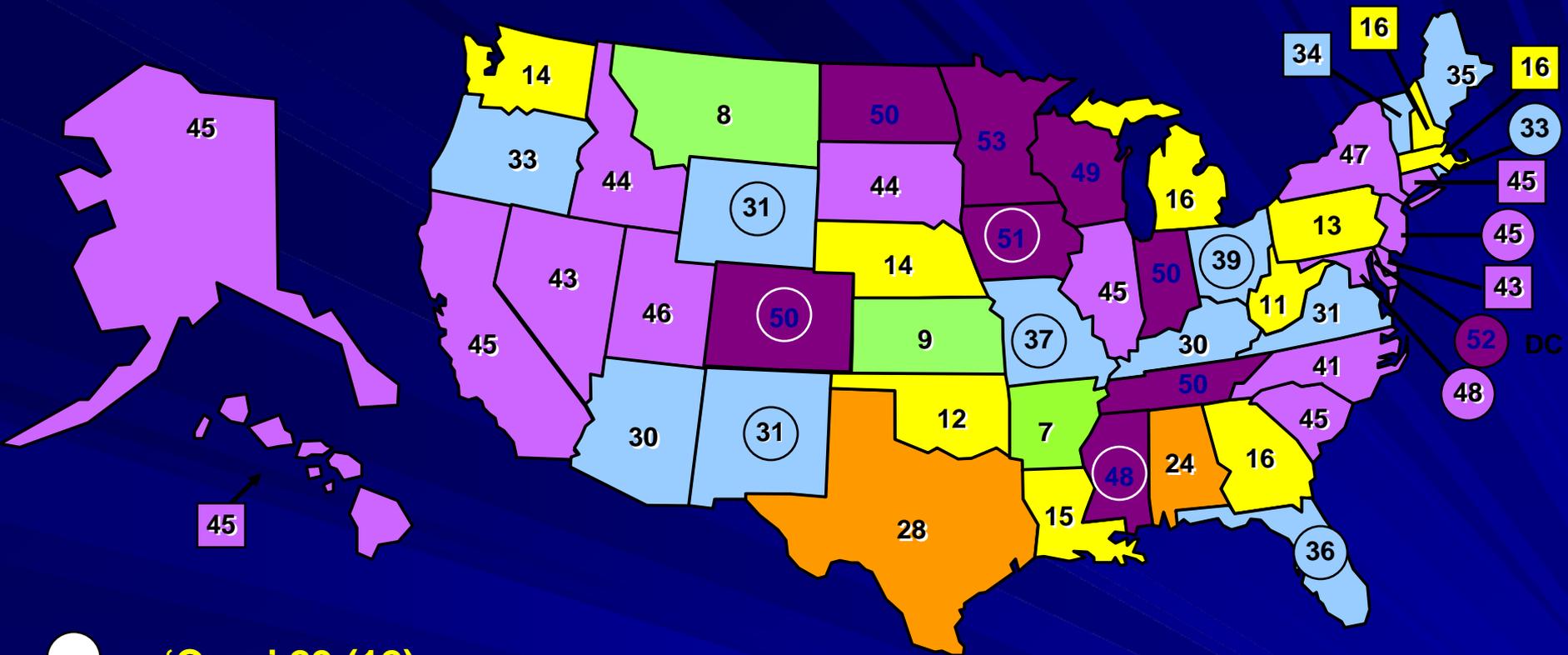
Uniform Panel (Primary Targets)				
MS/MS				
Acylcarnitines	Amino acids			
(9)	(5)	(6)	(3)	(6)
OA	FAO	AA	Hematology	Others
IVA GA-I HMG MCD MUT Cbl A,B 3MCC PROP BKT	MCAD VLCAD LCHAD TFP CUD	PKU MSUD HCY TYR I ASA CIT	SCA Hb S/ Th Hb S/C	HYPOTH BIOT CAH GALT HEAR CF

Conditions in red are treated by diet

Secondary Targets

MS/MS			Hb Pathies	Others
Acylcarnitines		Amino acids		
OA	FAO	AA		
Cbl C,D	M/SCHAD	Hyper-PHE	Variant Hb	GALE
2M3HBA	SCAD	TYR-II		GALK
IBG	MCKAT	BIOPT (BS)		
2MBG	GA-II	TYR-III		
3MGA	CPT-IA	ARG		
MAL	CPT-II	BIOPT (REG)		
	CACT	MET		
	DE REDUCT	CIT-II		





- 'Core' 29 (12)
- 50+ Disorders (9)
- 40-49 Disorders (13)
- 30-39 Disorders (12)
- 20-29 Disorders (2)
- 10-19 Disorders (10)
- <10 Disorders (3)

US Newborn Screening Conditions Required June, 2006

Military Health System Initiative

- Newborn Metabolic Screening Integrated Project Team (ITP)
 - Reports to Tricare Management Agency (TMA)/Health Affairs (HA)
- Comprehensive, uniform NBS Program for all DoD infants
(Chartered June 2005)

Components

- Centralized laboratory
 - All infants born in the military system will be screened in exactly the same way
- Results within days, not weeks
- Secure, internet-accessible data
- Immediate access to “cookbook” response guidelines if a result is abnormal

Components

- Integrated education and training for providers, laboratory personnel, and families
 - Online resources, brochures, workshops, lectures, etc.
- Responsive case management support team
- Registry of newborns to track quality and facilitate follow-up

Fact sheets and Act sheets

- Kaye CI et al. Newborn screening fact sheets. *Pediatrics* 2006;118:e934-e963.
 - Biotinidase Deficiency
 - Congenital Adrenal Hyperplasia
 - Congenital Hearing Loss
 - Congenital Hypothyroidism
 - Cystic Fibrosis
 - Galactosemia
 - Homocystinuria
 - Maple Syrup Urine Disease
 - Medium-Chain Acyl-Coenzyme A Dehydrogenase Deficiency
 - Phenylketonuria
 - Sickle Cell and Other Hemoglobinopathies
 - Tyrosinemia

ACMG ACT Sheets and Confirmatory Testing Algorithms

You Should Take the Following Actions:

- Contact family **IMMEDIATELY** to inform them of the newborn screening test result.
- Consult pediatric endocrinologist; referral to endocrinologist if considered appropriate.
- Evaluate infant (see clinical considerations below).
- Initiate timely confirmatory/diagnostic testing as recommended by the specialist.
- Initiate treatment as recommended by consultant as soon as possible.
- Educate parents/caregivers that hormone replacement prevents mental retardation.
- Report findings to state newborn screening program.

Diagnostic Evaluation: Diagnostic tests should include serum **free T4** and **thyroid stimulating hormone (TSH)**; consultant may also recommend **total T4** and **T3 resin uptake**. Test results include **reduced free T4** and **elevated TSH** in primary hypothyroidism; if done, **reduced total T4** and **low or normal T3 resin uptake**.

Controversies and Criticisms

■ False Positives of MS/MS alone

– Best case scenario:

■ Specificity of 99.995%

■ 2575 False Positives in US

■ 64 False positives in Military

– Worst case

■ Specificity of 99.9%

■ **>51,000 False Positives in US**

■ **1275 in MHS → GRIDLOCK !!**



Controversies and Criticisms

- Shallow reservoir of clinical metabolic expertise
- Follow-up and treatment under-funded



Controversies and Criticisms

- Informed Consent - necessary in only a few states
- One vs two screening tests
- ACMG Recommendations - based on a flawed analytic framework?
- Secondary Targets – many of these diseases cannot be treated
- Changing paradigm for diseases screened



In the final analysis

- Impetus and momentum
 - Public demand
 - Political mandate
 - Good medicine
- Continued expansion
- Growing pains
- Paradigm for genomic medicine in the rest of the population

