Between now and tomorrow

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Transforming Public Health in a Changing World
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Anticipating future applications of genomic technology in NBS

- Expand the list of treatable conditions that can be screened
- Strengthen interpretations of current screening results
- Provide that single black box?

- Generate a knowledge base from which we develop other (non-genomic) screening assays

Tomorrow

- Pre-determined pathogenic profiles for
- Preventable disease

Hmmm

- Some new instrumentation, software, skilled technical staff
- Genomic info from baby
- List of preventable diseases
- List of pathogenic profiles
- Flexibility to modify profiles
- Your understanding

Anticipating future applications of genomic technology in NBS

- Is it here to stay? - *likely*
- Is it a transient fad? - *parts may be*
- What is IT?
- Can we do this? -*Yes*
- Should we do this? - *May need to*
- How do we do this? - *Carefully*

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Current It:
Next-Generation Sequencing

Star Trek: **The Next Generation** 1987-1998

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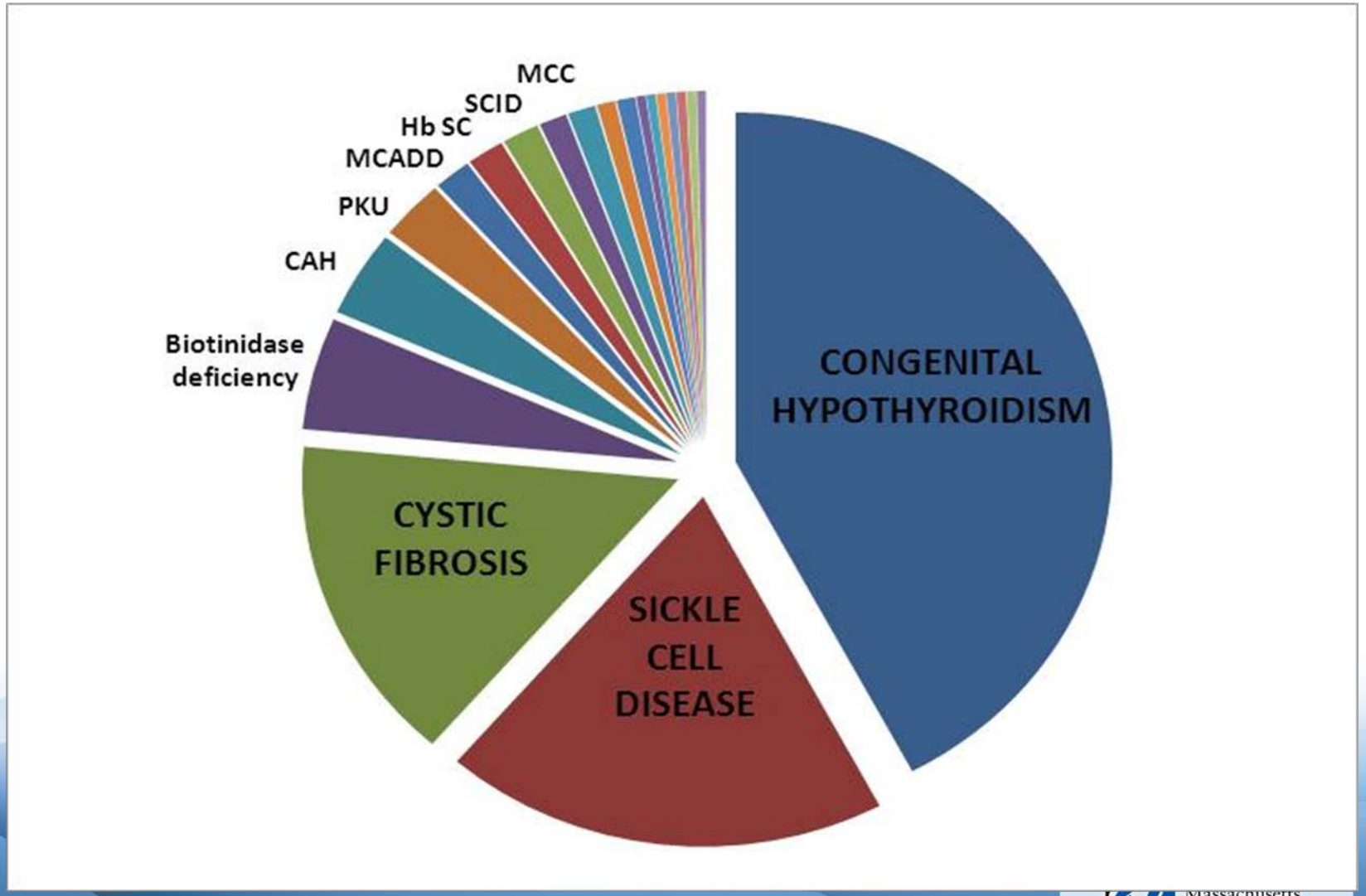
Newborn Screening is …

a public health program that provides an opportunity for early identification and early treatment of infants with conditions that otherwise would go unrecognized prior to irreversible clinical damage.

Relative Proportions of Infants Identified by Newborn Screening

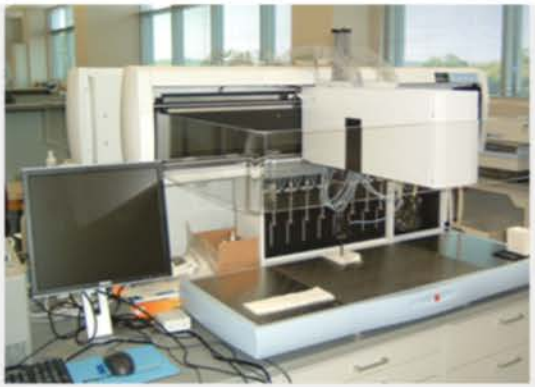


Texas Newborn Screening Laboratory

8 plates are distributed to 5 areas to test for 29 disorders.

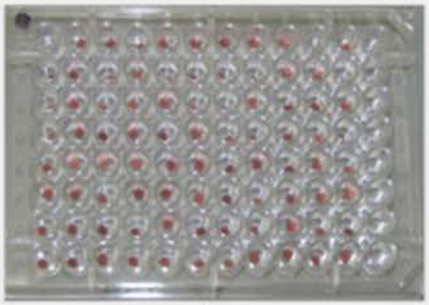
Hemoglobinopathy Screening:

<u>One test is used to identify:</u>
Sickle Cell Anemia
Sickle Hemoglobin C Disease
Sickle/Beta Thalassemia Disease
Other hemoglobinopathy diseases and traits



Galactosemia & Biotinidase Screening:

<u>Two tests are used to identify:</u>
Galactosemia
Biotinidase Deficiency



Endocrine & Cystic Fibrosis Screening:

<u>Three tests are used to identify:</u>
Congenital Hypothyroidism
Congenital Adrenal Hyperplasia
Cystic Fibrosis

SCID Screening:

<u>One molecular test is used to identify:</u>
Severe Combined Immunodeficiency

Tandem Mass Spectrometry Screening:

<u>One test is used to identify:</u>
6 amino acid disorders (e.g. PKU)
5 fatty acid disorders (e.g. MCAD)
9 organic acid disorders (e.g. glutaric acidemia type 1)

Hi Throughput – Large Menus

New York NBS:

30	Conditions
29,299	Daily Tests
782	Confirmed Cases
242,208	Newborns Tested

New England NBS:

30	Conditions
12,602	Daily Tests
301	Confirmed Cases
116,236	Newborns Tested

Wisconsin NBS:

30	Conditions
7,099	Daily Tests
143	Confirmed Cases
67,057	Newborns Tested

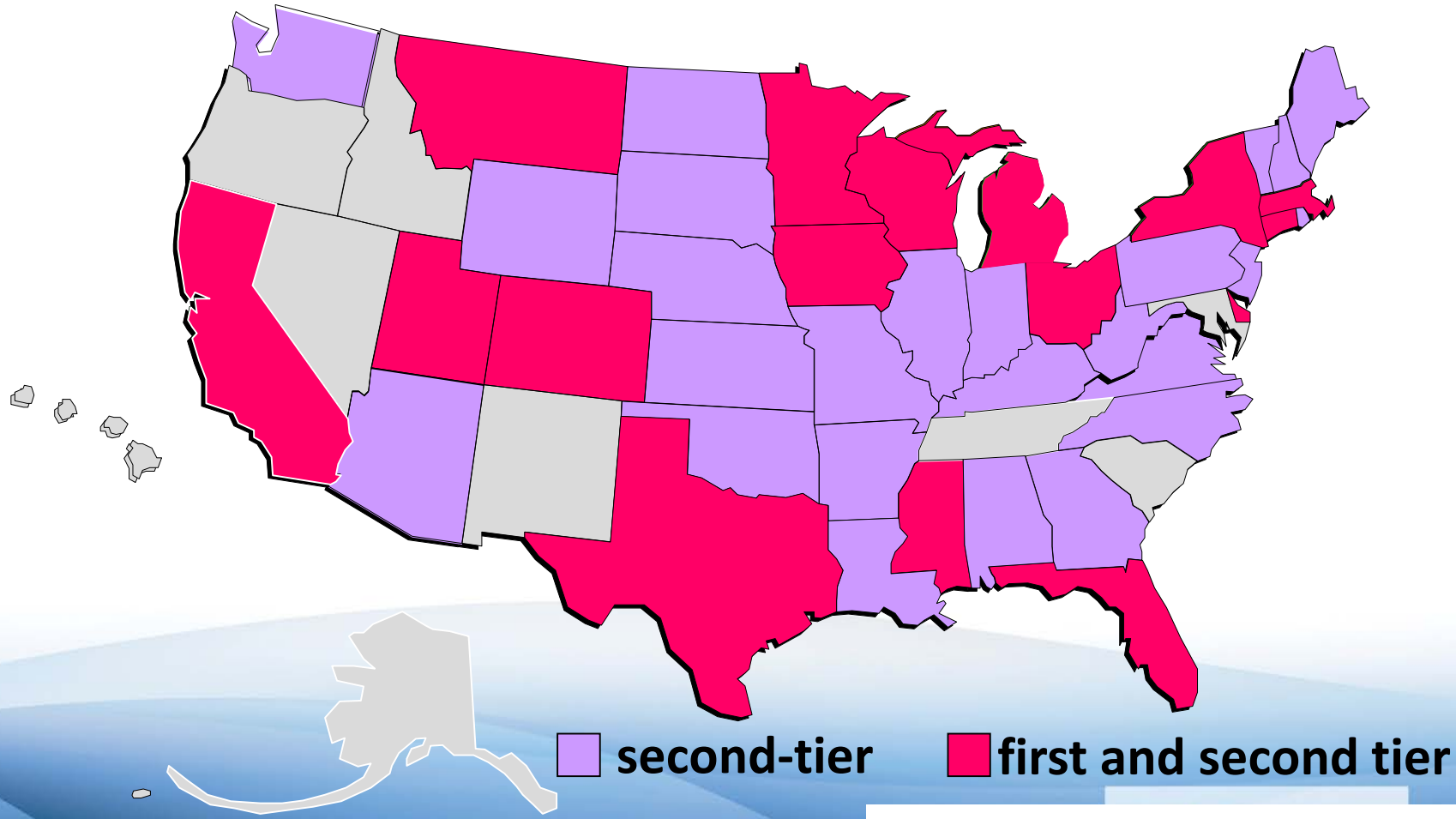
Minnesota NBS:

30	Conditions
6,780	Daily Tests
155	Confirmed Cases
67, 780	Newborns Tested

TXNBSP:

29*	Conditions
71,740	Daily Tests
743	Confirmed Cases
379,255	Newborns Tested

Molecular Assays in Use in Newborn Screening 2013



Courtesy, CDC

NEWBORN SCREENING CALLS TO THE FRONTLINE OF DEFENSE

NEWBORN SCREENING CALLS TO THE FRONTLINE OF DEFENSE

EVERY 3 MINUTES:

- 1 high risk
- 6 additional actionable

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Current Purposes of DNA in NBS

(data generated prior to full diagnostic evaluation)

- Enhance capacity of screening for conditions not otherwise included...

  TREC assay for SCID: molecular in **FIRST TIER**

- Enhance specificity of 1st tier test....

  CFTR mutation assay after IRT: molecular in **SECOND TIER**

- Supplemental just-in-time

  Increase available information to aid diagnostic evaluation…

  GALT mutation assay: molecular in **SECOND TIER**

Current DNA testing:

Regardless of purpose, the DNA target might be

A specific mutation
- A specific structure
- A foreign element
- Qualitative or Quantitative

Like other targets, these can be multiplexed.

DNA Testing in the 2nd Tier

(data generated prior to full diagnostic evaluation)

- Enhance capacity of screening for conditions not otherwise included...
  (Conventional genetic)
  TREC assay for SCID: molecular in **FIRST TIER**

- Enhance specificity of 1st tier test....
  CFTR mutation assay after IRT: molecular in **SECOND TIER**

- Supplemental just-in-time
  Increase available information to aid diagnostic evaluation…
  GALT mutation assay: molecular in **SECOND TIER**

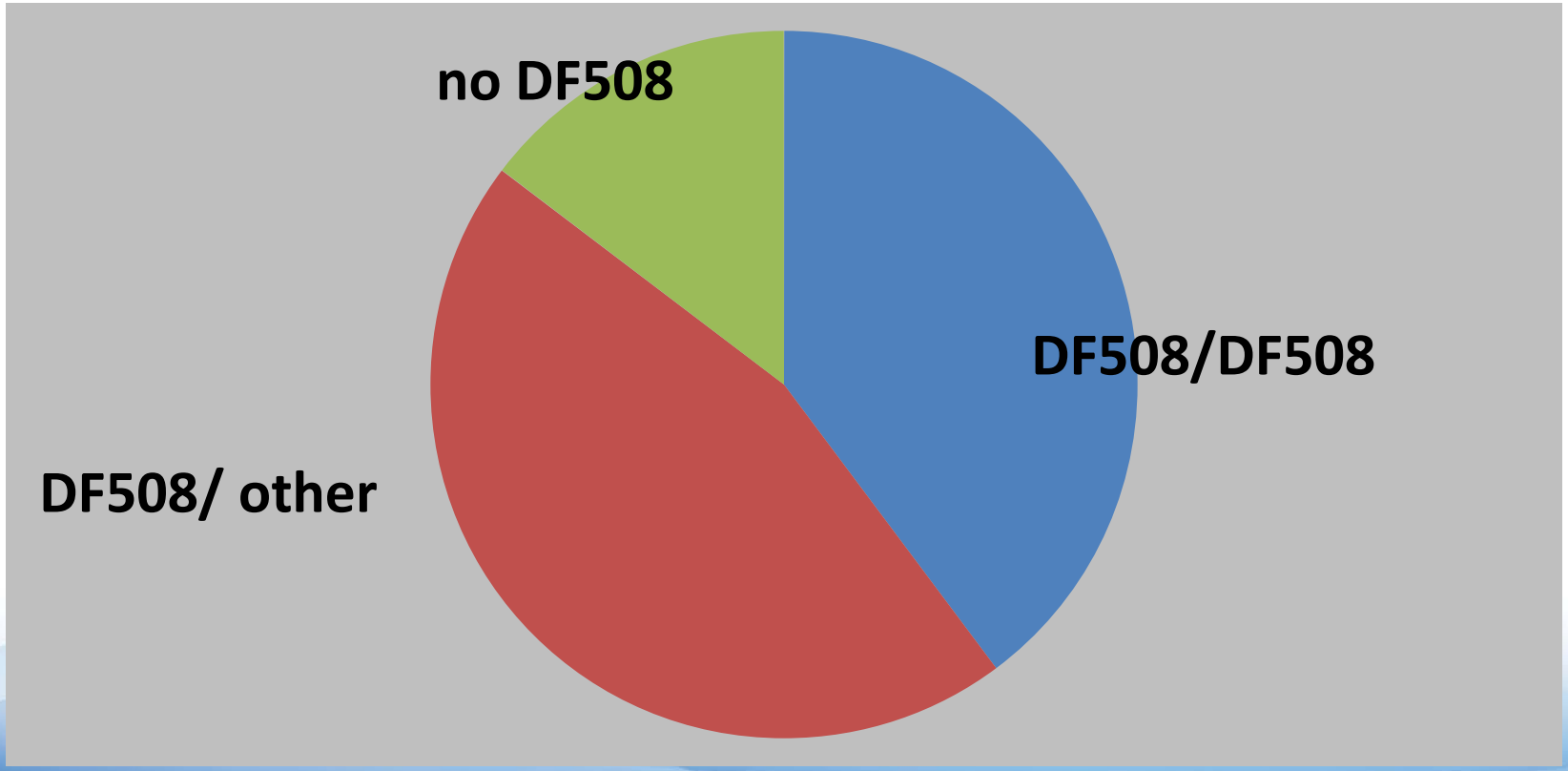
Current DNA testing:

Multiple mutations are already tested on a subset of babies

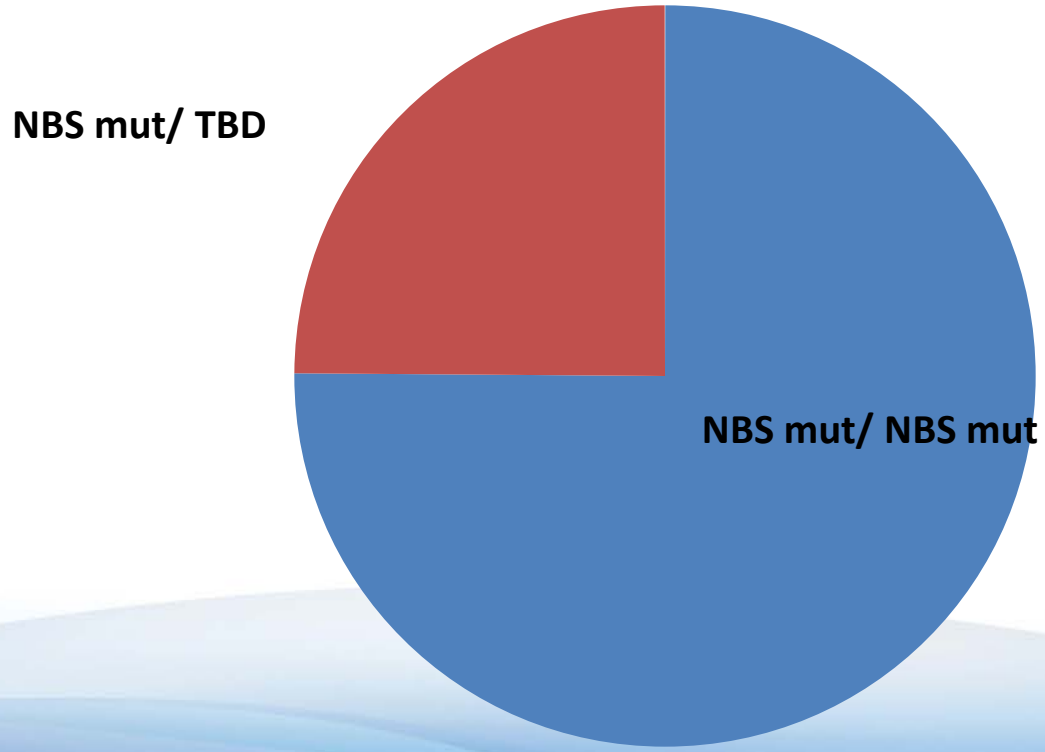
- IRT – top 5% infants tested for 39 mutations in CFTR

Genotype Distribution Among 450 New England CF infants

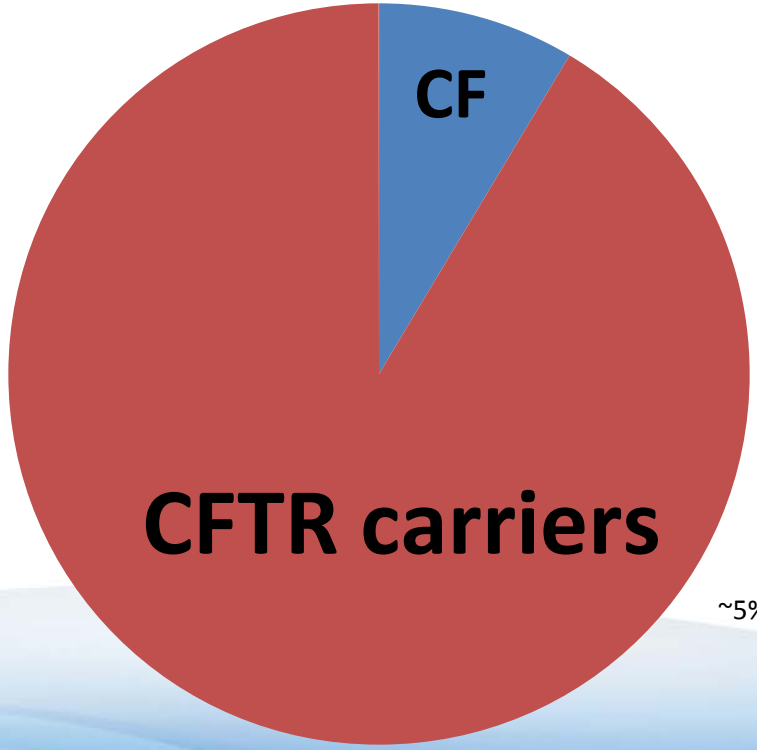
relative to common allele



Proportion of New England CF Infants shown to carry one or two mutations by newborn screening

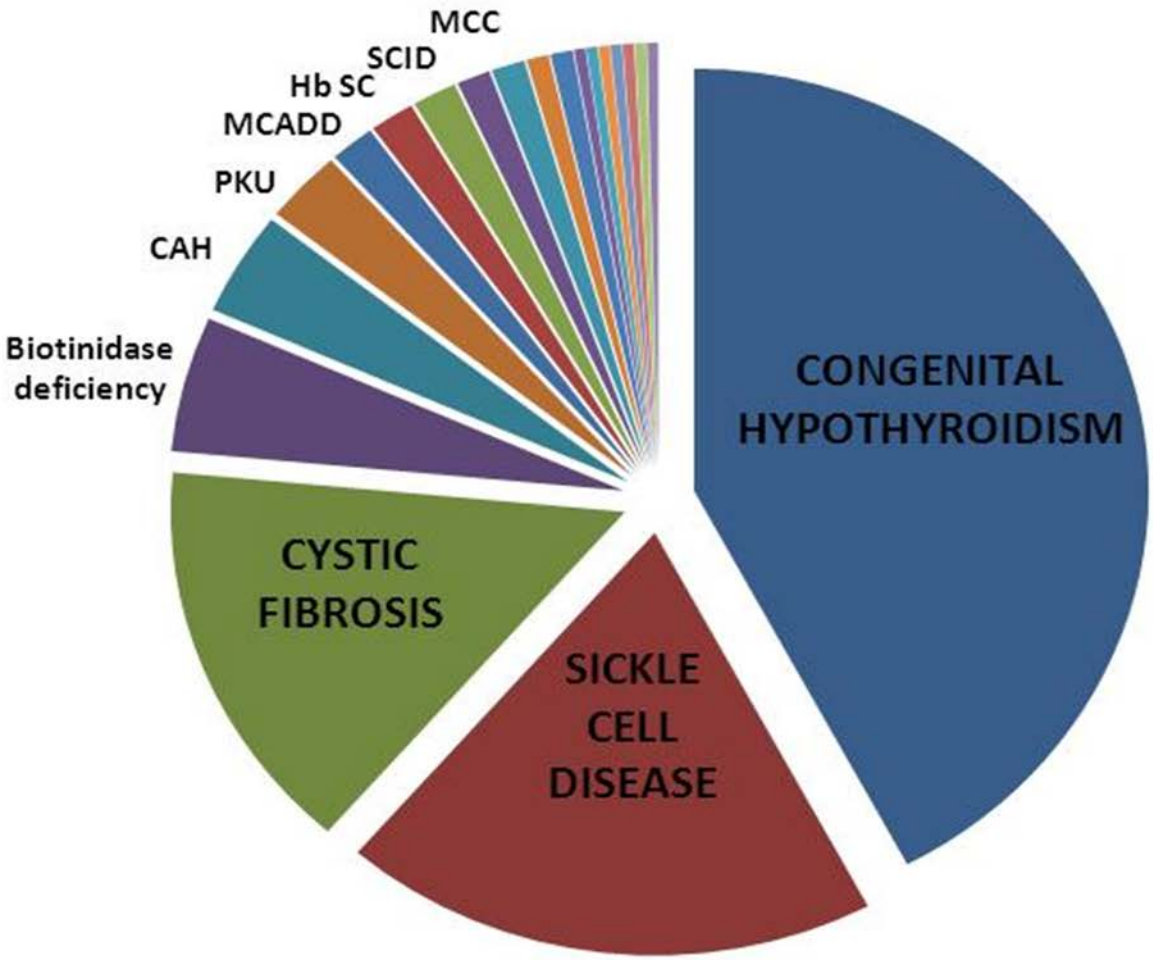


Carriers confirmed after diagnostic testing - identified in order to find CF



~5% will have two carrier parents

Relative Proportions of Infants Identified by Newborn Screening



Nucleic Acid Testing	Examples
Applications	Genetic mutations, viral load,
Multiple	Accuracy, precision,
Different	Traditional PCR followed by post-amplification analysis. Detection of
Varying C	
Lumi	
Quantit	

Advantages of Real-Time Q PCR	Disadvantages
Quantitative results in real-time	Limited multiplexing capability
Closed tube, reduced risk of contamination	Can be complex to set up, particularly for multiplexed reactions
Rapid cycling time (30 minutes to 2 hours)	
Highly sequence specific	Intra- and inter-assay variation, hence the need for an internal monitoring control

To be determined:

Analytic validity

- Promising –
- known issues with large deletions, rearrangements, copy number variants

Analytic validity in high throughput

- Promising –
- Scan or target…

Clinical validity

- Ongoing learning…complex traits…

DATA

Next Gen interrogates

- A whole genome
- A whole exome
- Targeted genes
- A targeted gene
- ….there is the capacity to target regions for sequencing

GENE	REFERENCE	POSSIBLE SEQUENCE VARIANTS		
CFTR	COLOR	CAWPR	COLAR	COLOUR
PKU	RED	REE	DEAD	READ
MCAD	BLUE	BECN	BLOO	BLEU
SCID	SOUND	SWIMD	SOUDD	SOWND
GALT	QUACK	HONK	QUICK	QUAKK
HGB	BELL	BLOB	BALL	BELLE

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		CYSTIC FIBROSIS?		

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GALT	QUACK	HONK	QUICK	QUAKK
HGB	BELL	BLOB	BALL	BELLE
		DEAD DUCK DISEASE?		

Bioinformatics will need to be able to

- Target specific mutations,
- Detect a pathogenic profile
- Be flexible to the user

- Be Unidirectional?

Between now and tomorrow

- Some new instrumentation, software, skilled technical staff
- Genomic info from baby
- List of preventable diseases
- List of pathogenic profiles
- Flexibility to modify profiles
- Your understanding

Examples of pediatric onset actionable conditions for consideration in expansion

Disorder	Age of Onset	Gene/s	Inheritance	Clinical Features	Management (in addition to treatment of manifestations)	Prevention of Manifestations (Primary or Secondary)	Comments	Prevalance
AASE (aka Diamond Blackfan Anemia)	Infancy->	RPL5, RPL11,	AD	Anemia, increased risk (MDS, AML,	Surveillance/Supportive			1:200, 000
Abetalipoproteinemia	Infancy->	MTTP	AR	FTT, diarrhea; acanthocytosis); ataxi	–	? Primary-Vit E supplementation		Rare
Aceruloplasminemia	Young adulthc	CP	AR	Retinal degeneration, DM, anemia &	Surveillance	Primary/Secondary -Iron Chelators		
Achromatopsia	Neonatal/Infa	CNGA3, CNG	AR	Reduced visual acuity, photophobia,	Surveillance			
ADA Deficiency	Neonatal->	ADA	AR	Disorder of lymphocyte developmen	Surveillance	Primary-BMT/SCT & ER	Spectrum includes SCID	
Adenine phosphoribosyltransferase deficiency	Childhood->	APRT	AR	Kidney stones & chronic kidney dise	Surveillance	Primary- Allopurinol, Dietary modificat	1:40,000-1:100,000	
AIP-related isolated familial pituitary adenoma	Childhood ->	AIP	AD	Familial Pituitary Adenoma	Surveillance			
Alacrima-achalasia-adrenal insufficiency neurologic disorder	Infancy->	AAAS	AR	Achalasia, Addison disease, Alacrim	Surveillance/Supportive			Rare
Alagille syndrome	Neonatal->	JAG1	AD	Bile duct paucity, liver disease, card	Supportive/Surveillance		Variable penetr	1:70,000
ALK-related neuroblastoma	Neonatal ->	ALK	AD	Neuroblastoma susceptibility	Surveillance			
Alpha1-antitrypsin deficiency	Neonatal/Adu	SERPINA1	AR	COPD (adulthood); liver disease (ne	Surveillance/Supportiv	Primary/Secondary -avoidance of smok	1:500- 3500 (Europ	
Alpha-Mannosidosis (lysosomal)	Neonatal->	MAN2B1	AR	Progressive CNS involvement, impair	Supportive	Primary-BMT/SCT (Experimental)		
Alström syndrome	Neonatal/Infa	ALMS1	AR	Progressive hearing & vision loss, ca	Surveillance/Supportiv	Primary/Secondary -lifestyle modification		
Alström syndrome	Neonatal/Infa	ALMS1	AR	Progressive hearing & vision loss, ca	Surveillance/Supportiv	Primary/Secondary -lifestyle modification		
Andersen-Tawil syndrome	Childhood->	KCNJ2	AD	Muscle weakness, prolonged QT int	Surveillance/Supportive			
Androgen insensitivity syndrome	Neonatal->	AR	X-Linked	46XY; Ambiguous genitalia, abnorma	Surveillance			
APC-associated polyposis	Infancy ->	APC	AD	Colon polyps; colon cancer predispo	Surveillance	Secondary-Colonic resection		
Arginine:glycine amidinotransferase deficiency	Infancy->	GATM	AR	FTT, developmental delays, autistic	–	? Primary-Creatine supplementation		Rare
Arrhythmogenic right ventricular dysplasia/cardiomyopathy (	Childhood->	TGFB3, RYR2	AD	Ventricular tachycardia	Surveillance	Primary-antiarrhythmi	Additional gene	1:1000 to 1:1250
Arylsulfatase A deficiency (metachromatic leukodystrophy)	Infancy->	ARSA	AR	Progressive neurologic dysfunction	Supportive	Primary-BMT/SCT (Experimental)		1:40,000 -1:160,00
Ataxia with Vitamin E Deficiency	Childhood->	TTPA	AR	Progressive ataxia, loss of proprioce	Supportive	Primary-Vit E supplementation		? 1:333,000
ATP7A -Related Copper Transport Disorders	Menkes/OHS-I	ATP7A	X-linked	Menkes-Neurological regression, hy	Supportive	Primary-Rx with copper shows promise		
Autoimmune lymphoproliferative syndrome (ALPS)	Childhood->	FAS	AD	Autoimmune disorders, increased ri	Surveillance			Rare
Autoimmune polyglandular syndrome, Type 1	Childhood->	AIRE	AR	Mucocutaneous candidiasis, hypopa	Surveillance			Rare
Autosomal dominant lateral temporal lobe epilepsy	Infancy->	LGI1	AD	Focal-generalized seizures, auditory	Surveillance	Secondary-Prompt Rx for seizures		–
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)		CHRNA4, CH	AD	Nocturnal motor seizures	Surveillance	Secondary-Prompt Rx for seizures		–
Axenfeld-Rieger syndrome		PITX2, FOXC	AD	Abnormalities of anterior segment,	Surveillance			
Bartter syndrome	Infancy->	SLC12A1, KC	AR	FTT, dehydration, polyuria, hypotale	Surveillance			1: 1,000,000
Biliary atresia					–			
Catecholaminergic polymorphic ventricular tachycardia	Infancy->	RYR2 and CASQ2		Ventricular tachycardia	Surveillance			1:10,000
Chronic granulomatous disease	Infancy->	CYBA, CYBB	AR/X-linked	Recurrent infections	Surveillance/Supportive			1:200,000
Complement Factor I deficiency	Infancy->	CF I	AR	Infections; autoimmune disorders	Surveillance			Rare
Congenital central hypoventilation syndrome (CCHS)	Neonatal ->	PHOX2B	AD	Hypoventilation, SIDS	Surveillance/Supportive			Rare
Creatine transport defect					–			
CV-AVM	Infancy->	RASA 1	AD	AV malformations	Surveillance			1:1,000,000
Fabry Disease	Childhood->	GLA	X-linked	Acroparesthesias, angiokeratomas,	Hypohidrosis, corneal c	? Primary-ERT		1: 40,000
Familial Atrial Fibrillation	Childhood->	KCNE2, KCNI	AD	Atrial fibrillation	Surveillance			Common
Familial acute myeloid leukemia with mutated CEBPA	Childhood ->	CEBPA	AD	AML	Surveillance/Supportive			1:50,000
Familial lipoprotein lipase	Infancy->	LPL	AR	Pancreatitis, hepatosplenomegaly	Surveillance/Supportiv	? Primary-Dietary modifications		1:1,000,000
Glycogen storage disease type III	Infancy->	AGL	AR	FTT, hypoglycemia, hyperlipidemia,	Supportive	? Primary-Dietary		1:100, 000, 1: 5 50
Gorlin syndrome	Infancy->	PTCH1	AD	Nevoid basal cell carcinomas, other	Surveillance/Supportive			1:30,000
Guanidinoacetate methyltransferase deficiency					–			
Hemophagocytic lymphohistiocytosis, Familial	Infancy->	PRF1, UNC1	AR	Acute illness with prolonged fever;	hepatosplenomegaly	? Primary-BMT		1:50,000 births
Hereditary angioedema	Infancy->	SERPING1; F	AD	Recurrent angioedema	Surveillance			1:50,000
Hereditary fructose intolerance	Infancy->	ALDOB	AR	Hypoglycemia, hepatic and renal dys	function	? Primary-Dietary		1:40,000
Hyperkalemic periodic paralysis	Infancy->	SCN4A	AD	Periodic paralysis	Surveillance			1:200, 000
Jervell and Lange Nielsen syndrome	Infancy->	KCNE1; KCNC	AD	Arrythmias; Hearing Loss	Surveillance/Supportive			1: 20, 000
Job syndrome	Infancy->	STAT3	AD	Immune disorder, High IgE	Surveillance/Supportive			Rare
Juvenile myoclonic epilepsy	Childhood, ad	CACNB4, CLCN2, EFHC1, GABRA1, GABRD	Variable	Myoclonic seizures, tonic-clonic seiz	Surveillance			1:1 000
Maternally inherited diabetes and deafness	Childhood->	MT-TL1, MT-	Mitochondrial	DM, Deafness	Surveillance			Common (1% of D
Methylene tetrahydrofolate deficiency (MTHFR Severe)	Infancy->	MTHFR		Microcephaly, seizures	–	Primary -SMTH		
Mucopolysaccharidosis type I	Infancy->	IDUA	AR	Storage disorder, hepatosplenomegaly, dysostosis multipl		? Primary-ERT		1: 100,000
Multiple endocrine neoplasia -Type 1		MEN1	AD	Tumors of parathyroid gland, pituita	Surveillance			1:30, 000
Multiple endocrine neoplasia -Type 2		RET	AD	Medullary thyroid carcinoma, parath	Surveillance			1:30, 000
Osteogenesis imperfecta (OI)	Neonatal ->	COL1A1, CO	AD/AR	Bone fragility, hearing loss	Surveillance/Supportive			4-5:100,000
Pyridoxine-dependent epilepsy	Neonatal	ALDH7A1	AR	Epilepsy, hypothermia, hypotonia, d	Supportive	Primary- Medications,		1:100,000
Wilson disease				Neuropsychiatric disorders, Liver dys		Primary- Medications,		
Wiskott-Aldrich syndrome	Neonatal->	WAS	X-linked	Microthrombocytopenia, immune dy	Surveillance			1: 1,000,000
X-linked adrenal hypoplasia congenita	Infancy/childh	NR0B1	X-linked	Adrenal insufficiency, hypogonadisr	Surveillance			1:12, 500
X-linked adrenal hypoplasia congenita	Infancy/childh	NR0B1	X-linked	Adrenal insufficiency, hypogonadisr	Surveillance			1:12, 500
X-linked adrenoleukodystrophy	Childhood->	ABCD1	X-linked	3 forms-Childhood cerebral, adrenoc		Primary-BMT		1:20, 000
X-linked agammaglobulinemia	Infancy->	BTK	X-linked	Recurrent infections		Prevention of infections		1:200, 000

University of Massachusetts Medical School
UMASS
umassmed.edu

Challenges: the Report

Technical Report

- CLSI demographics
- Reason for testing
- Disease locus tested
- Result is In Range or Out of Range

  Out of Range:

  Number of DNA sequence variants **detected** by the screen

Report Content

- **Names** of DNA sequence variants **detected** by the screen (colloquial and (?) HGVS)
- **Names** of DNA sequence variants **TESTED**.

nomenclature

- colloquial: Delta F508
- HGVS: c.1521_1523delCTT

Human Genome Variation Society
http://www.hgvs.org/

Report Content

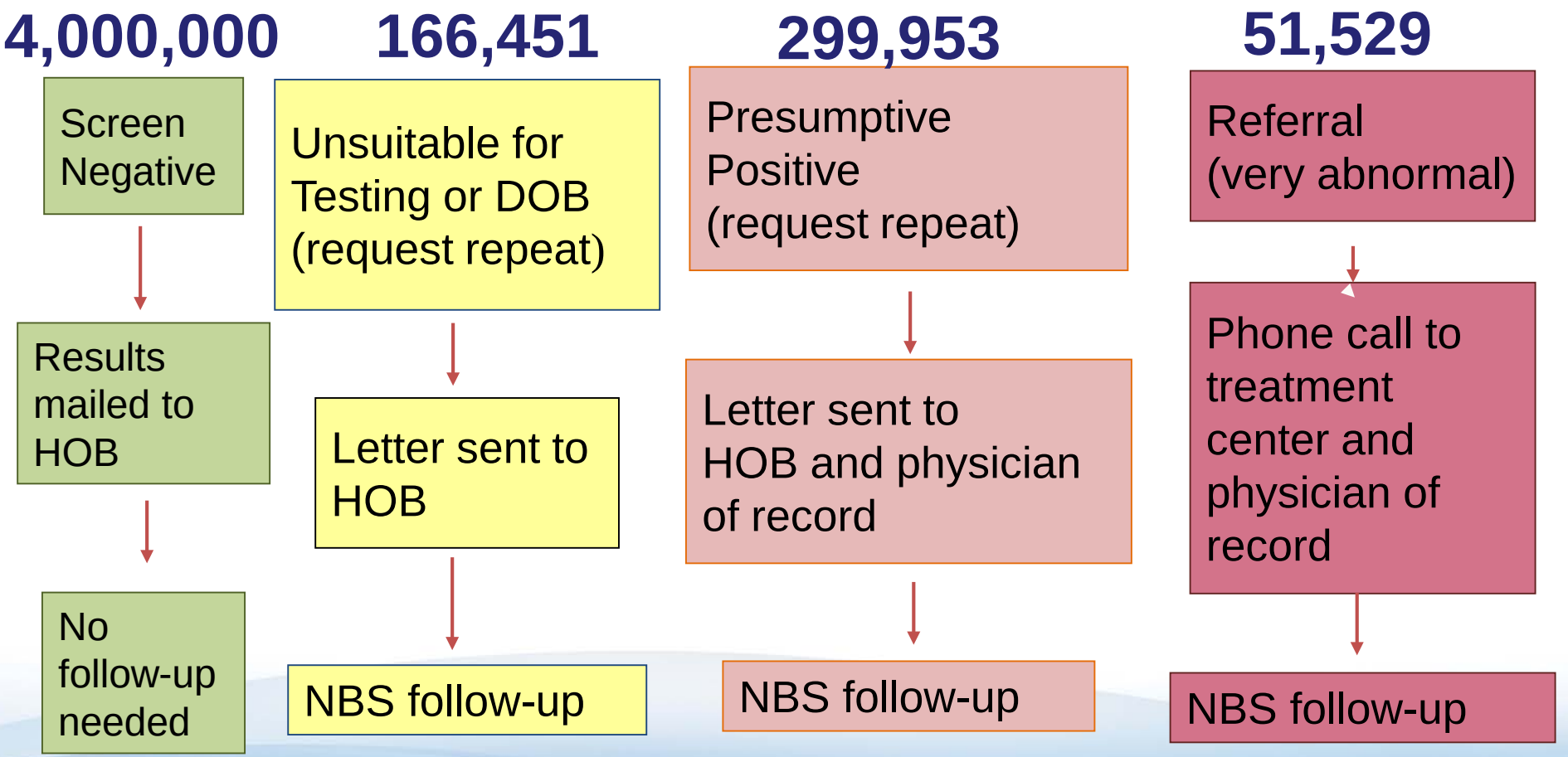
INTERPRETATION

- Interpretation of the overall NBS result for the condition
- State interpretation of the DNA result, e.g.,
  - *infant is (at least) a carrier*
  - *Infant with 2 variants is at high risk*

RECOMMENDED ACTION

Reporting:
Some adjustments needed

Risk Assessment Process



13,711 confirmed cases or 1/290 newborns have a NBS condition

Courtesy, NY

The public health challenges are

Justifying the transition instrumentation, labor

Defining pathogenic profiles interface with research

Technology public private partnerships, validations

Flexibility to modify assay as data grows

data mining – propose expiration dates

Public Trust