

Cosa Ha Cambiato Lo Screening Esteso Per Le Malattie Metaboliche?

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SISMME SISN GENCLI
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Outline

- The ACMG uniform panel
- From **WHAT** we screen for (how many conditions) to **HOW WELL** we do it
 - Performance metrics (MS/MS)
 - Clinically defined cutoff values
 - The impact of 2nd tier tests

Newborn Screening

A Public Health Program

- Aimed at identification of conditions for which early intervention can prevent mortality, morbidity, and disabilities
- Performed by analysis of diagnostic markers in blood spots collected on filter paper at birth
- Extent of program is chosen (and upgraded) by each state independently

Conditions Traditionally Tested for by Newborn Screening (1960-2000)

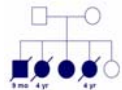
Condition	Incidence	States
• Sickle cell disease	1: 400	49/51
• Hypothyroidism	1: 4,000	51/51
• Phenylketonuria	1: 12,000	51/51
• CAH	1: 19,000	39/51
• Galactosemia	1: 50,000	50/51
• Biotinidase	1: 70,000	36/51
• MSUD	1: 250,000	29/51
• Homocystinuria	1: 275,000	35/51

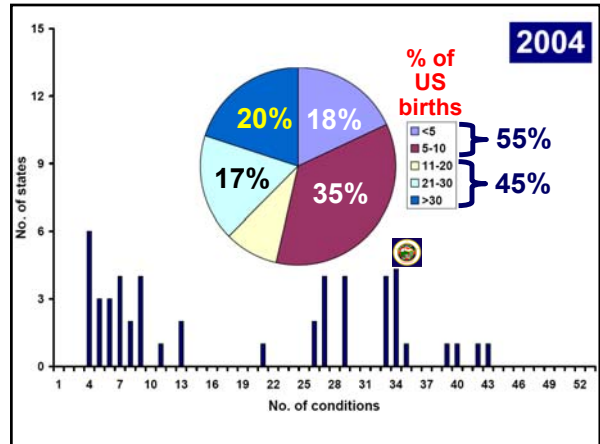
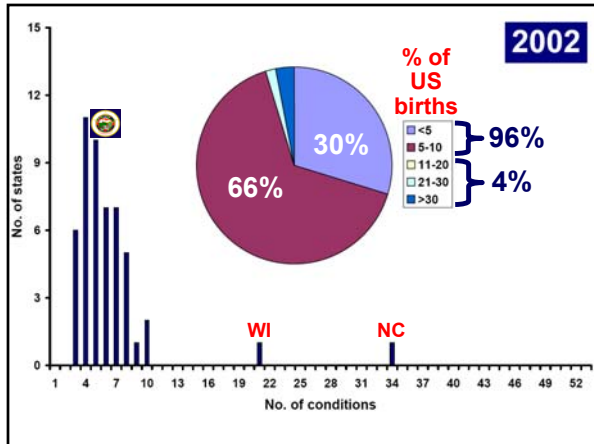
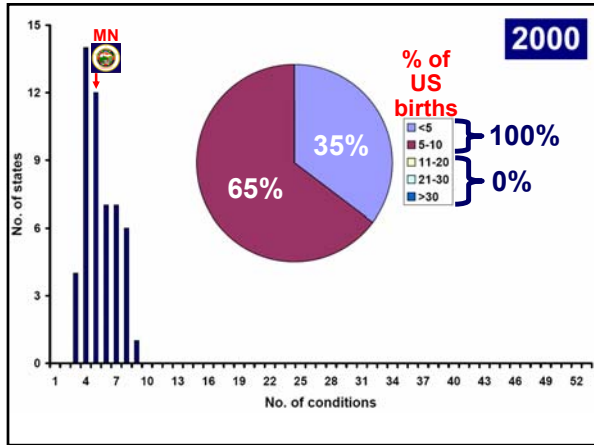
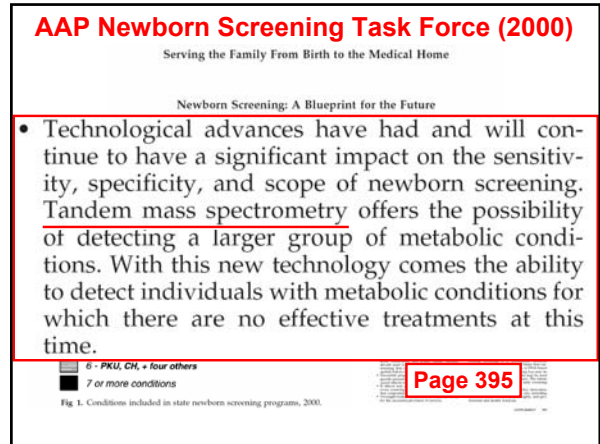
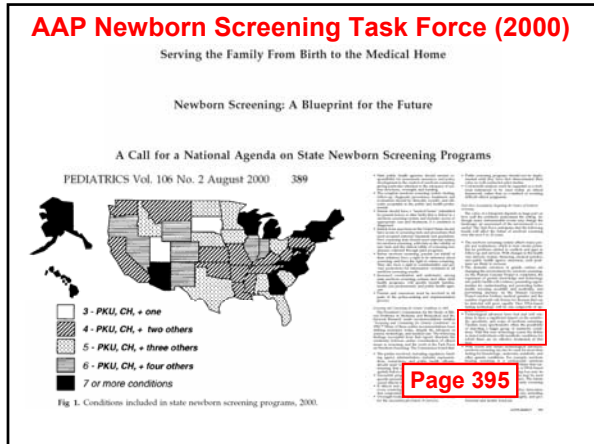
Other Conditions (2000)

- Hearing screening 27/51
- Cystic fibrosis (CO, WI, WY) 3/51
- **MCAD (ME, MA, NC) 3/51**
- Toxoplasmosis (MA) 2/51
- Tyrosinemia type I (GA, MD) 2/51
- G6PD (DC) 1/51
- HIV (NY) 1/51

Medium-Chain Acyl-CoA Dehydrogenase (MCAD) Deficiency

- Defect of mitochondrial fatty acid oxidation
- First report in 1976, defect confirmed in 1982
- Founder effect (common mutation 985A>G)
- Ethnic distribution (Caucasians)
- Incidence: 1:8,000-14,000 live births
- Normal growth and development
- 30-50% mortality (first acute episode)
- Screening method: **tandem mass spectrometry**



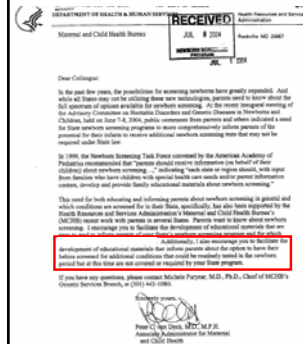


Status of Newborn Screening (2004)

- **Pervasive lack of uniformity in**
 - Extent of screening panels (~50/50)
 - Decision-making (no national process)
 - Analytical quality
 - Interpretation of results
 - Outcome data collection

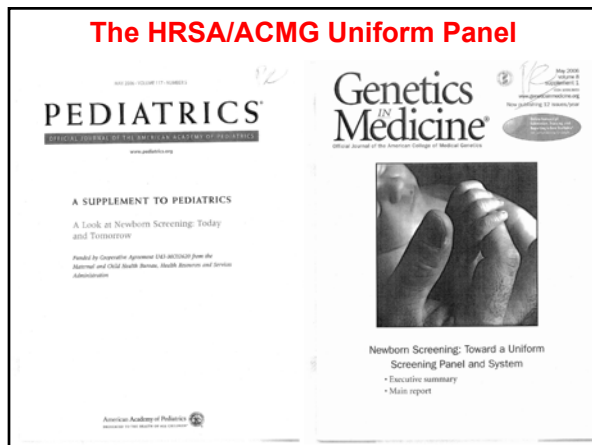
Expanded NBS left to consumer initiative!

Newborn Screening Left to Consumer Initiative

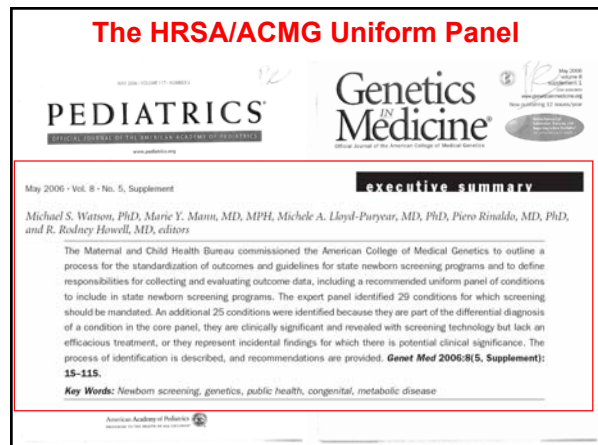


Additionally, I also encourage you to facilitate the development of educational material that inform parents about the option to have their babies screened for additional conditions that could be routinely tested in the newborn period but at this time are not covered or required by your State program.

The HRSA/ACMG Uniform Panel



The HRSA/ACMG Uniform Panel



Standardization of Outcomes and Guidelines for State Newborn Screening Programs

Contract No. 240-01-0038

Contractor

American College of Medical Genetics

Michael S. Watson, PhD, FACMG, Project Director

SPONSOR

Maternal and Child Health Bureau

Genetic Services Branch

Health Resources and Service Administration

Michele A. Lloyd-Puryear, MD, PhD, Chief

Marie Mann, MD, Project Officer

Primary Goals of HRSA/ACMG Contract

- Developing a uniform panel of newborn screening conditions
- Developing a decision-making tool for use in NBS program expansion or contraction
 - Criteria for assessing conditions for their appropriateness for newborn screening

Uniform Panel Survey

Work Group

- Donald Bailey
- Celia Kay
- Alex Kemper
- Michele Lloyd-Puryear
- Marie Mann
- Kenneth Pass
- Jennifer Puck
- (chair) Piero Rinaldo
- Brad Therrell
- Michael Watson



Conditions Included in Survey

- Endocrine disorders (CAH, CH, IDDM) 3
- Infectious diseases (HIV, Toxo, CMV) 3
- Hematologic disorders (Hb-pathies, G6PD) 5
- Genetic conditions (CF, DMD, FX, Wilson) 12
- IEM detectable by MS/MS (AA, AC)
 - Amino acid disorders (PKU, MSUD, HCY) 16
 - Fatty acid disorders (MCAD, VLCAD) 14
 - Organic acid disorders (PA, MMA, IVA, GA-I) 15
- Other IEM (± detectable by MS/MS)
 - Carbohydrate disorders (GALT, CDG) 4
 - Lysosomal disorders (Fabry, Krabbe, Pompe) 5
 - Others (BIOT, ALD, SLO) 6

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Criteria and Scoring System

- Incidence of conditions
- Identifiable at birth
- Burden of disease
- Availability of test
- Test characteristics
- Availability of treatment
- Cost of treatment
- Efficacy of treatment
- Benefits to individual
- Benefits to F&S
- Mortality prevention
- Diagnostic confirmation
- Acute management
- Simplicity of therapy

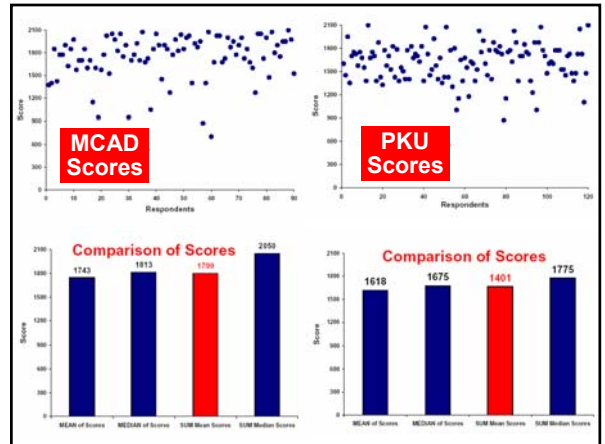
CRITERIA INCLUDED IN THIS SURVEY	CRITERIA	SCORE
Incidence of condition	1000	75
Sign & symptoms clinically identifiable in the first 48 hours	1000	75
Number of genes (total or by IEM)	1000	75
Does a variable gene specific identifying test currently exist?	1000	75
Test characteristics (How specific, how many)	1000	75
Availability of treatment	1000	75
Cost of treatment	1000	75
Potential efficacy of existing treatment	1000	75
Benefits of early intervention (PHYSIOLOGICAL, PSYCHOLOGICAL)	1000	75
Benefits of early identification (FAMILY & SOCIETY)	1000	75
Early diagnosis and confirmed genetic morbidity	1000	75
Diagnostic confirmation	1000	75
Acute management	1000	75
Simplicity of therapy	1000	75

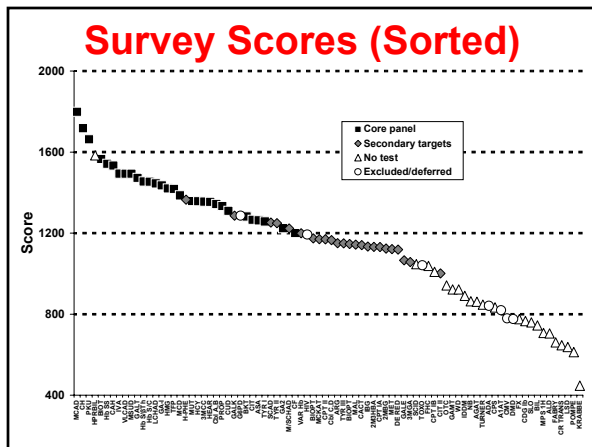
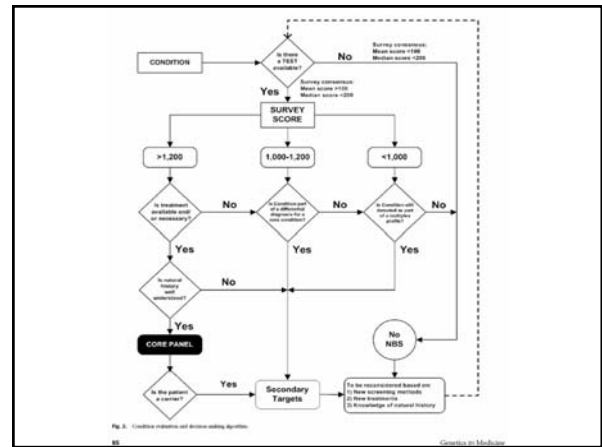
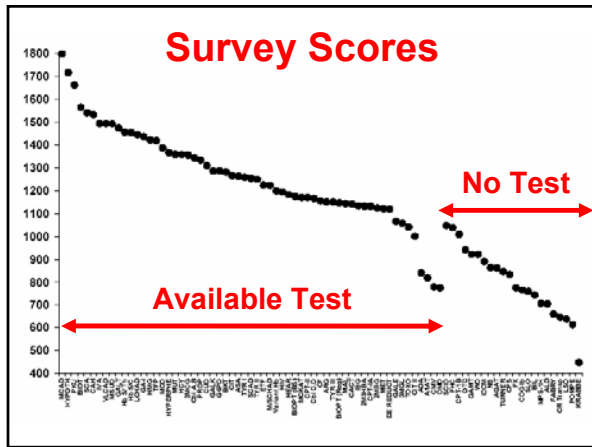
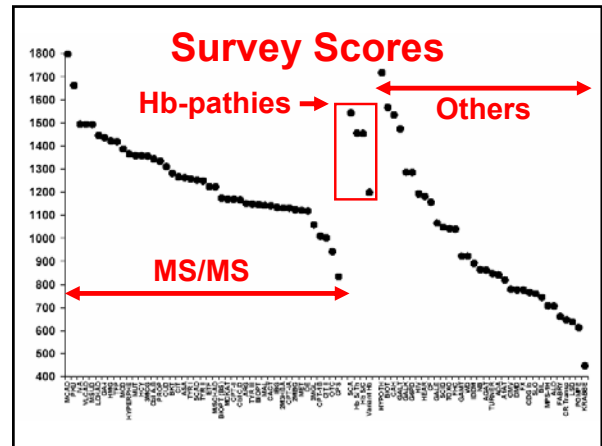
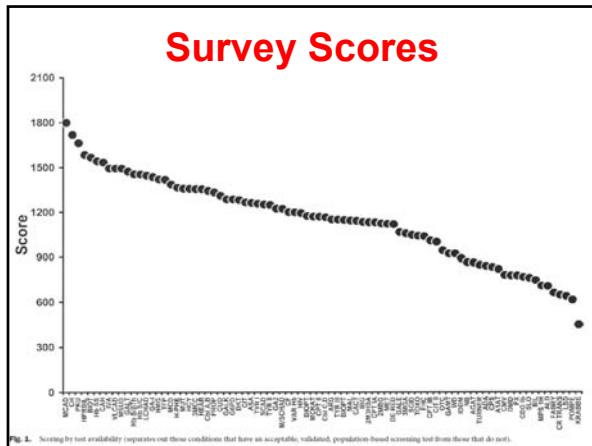
Final Results

- Responses 275
- Respondent "profiles" 560
- Conditions scored 3,927
- Individual scores 65,054

Criteria Scores (MCAD)

MCAD	RE-29	RE-17	RE-28	RE-29	RE-30	RE-31	RE-32	RE-44	RE-52	RE-53	RE-54	RE-55	RE-56	RE-57	RE-58	RE-59	RE-60
Incidence	1000	75	75	75	75	75	75	1000	75	75	75	75	75	75	75	75	75
Phenotype of birth	1000	75	100	100	75	100	100	1000	100	100	75	100	100	100	100	100	75
Diabetes if untreated	75	100	75	50	100	75	100	1000	75	100	75	75	100	100	100	75	75
Without evidence	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
Blood spot or Physical	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Yeast/urine	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Cost	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Multiple markers	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Secondary targets	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
Multiple platforms	200	200	200	0	200	200	200	200	200	200	200	200	200	200	200	0	200
Treatment availability	50	100	100	100	100	50	100	100	100	100	100	100	100	100	100	100	100
Efficacy of treatment	50	200	200	200	200	50	200	100	200	200	100	200	200	200	200	100	100
Early intervention (Hx)	100	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
Early identification (F&S)	50	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Mortality prevention	0	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Diagnostic confirmation	50	100	100	50	100	0	100	50	100	50	100	100	100	100	100	100	100
Acute management	0	100	100	100	20	100	100	100	100	100	100	100	100	100	100	100	100
Simplicity of therapy	50	200	200	200	200	50	200	100	100	50	200	200	200	200	100	200	200





- ### Uniform Screening Panel (2005)
- 29 primary conditions
 - 20 detected by MS/MS (AA, FAO, OA)
 - 3 Hb-pathies (S/S, S/βThal, S/C)
 - 6 others (BIOT, CAH, CF, CH, GALT, HEAR)
 - 25 secondary targets
 - 22 detected by MS/MS (AA, FAO, OA)
 - 1 Hb-pathy (many variants counted as one)
 - 2 others (GAL-epimerase, GAL-kinase)

U.S. Department of Health and Human Services | HRSA | MCHB Home | Questions? | Search

Health Resources and Services Administration | MCHB | **Maternal and Child Health Bureau**

Regional Genetics and Newborn Screening Collaboratives (HRSA-04-085)

Project 2: Regional Genetics and Newborn Screening Collaboratives
 The Regional Genetics and Newborn Screening Collaboratives are to be responsive to the priorities of the Heritable Disorders Program as indicated under Section 1109 of Title XI of the PHS Act. The Regional Genetics and Newborn Screening Collaboratives project will enhance and support the genetics and newborn screening capacity of States across the nation by undertaking a regional approach toward addressing the maldistribution of genetic resources. These grants are expected to improve the health of children and their families by promoting the translation of genetic medicine into public health and health care services. In order to address capacity needs nationally, seven regions have been identified. These regions are:

Region 1: CT, MA, ME, NH, RI, VT
 Region 2: DC, DE, MD, NY, NJ, PA, VA, WV
 Region 3: AL, FL, GA, LA, MS, NC, PR, SC, TN, VI
 Region 4: IL, IN, KY, MI, MN, OH, WI
 Region 5: AR, IA, KS, MO, ND, NE, OK, SD
 Region 6: AZ, CO, MT, NM, TX, UT, WY
 Region 7: AK, CA, HI, ID, NV, OR, WA, Pacific Basin

Applicants must propose to serve one of the defined regions.

A Regional Approach to Improve the Health of Children and Families with Heritable Disorders in Illinois, Indiana, Kentucky, Michigan, Minnesota, Ohio, and Wisconsin (Region 4)

**Cynthia A. Cameron, PhD
 Program Director**



Goals of Regional Collaborative

- Implement universal screening and confirmatory testing of newborns for inborn errors of amino acid, organic acid, and fatty acid metabolism
- Reduce inequities in access to genetic services
- Utilize a regional approach to improve public health infrastructure for supporting optimal diagnosis, follow up and management of children with heritable disorders and birth defects

Objectives of Project 1

- Achieve uniformity of testing panel by MS/MS to maximize detection of affected newborns within the region
- Improve overall analytical performance



**Performance Metrics TARGETS*
 (Full MS/MS Panel)**

Detection rate	1:3,000
FPR	<0.30%
PPV	>20%

*** Period & Volume MUST be specified**

Performance Metrics in MN

Period	Jul 04 - Aug 06
Volume	213,126
Detection rate	1:1,791
False Pos. Rate	0.08%
Pos. Pred. Value	42%

Very nice, but that is Minnesota.

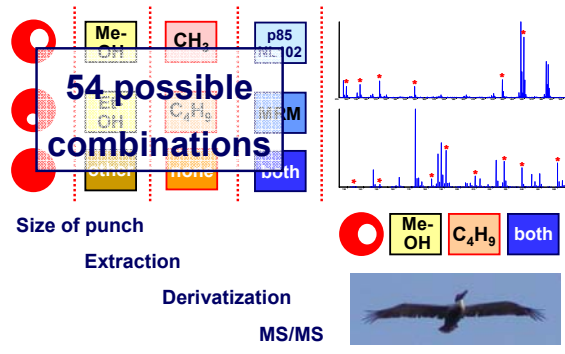
This is _____ (State's name)

and our lab is **DIFFERENT**

Conventional Wisdom ("Different" we stand)

- Results obtained using different procedures are not comparable
- Even instruments in the same labs are to be considered separately (different cut-offs)
- Every lab must develop own cutoffs based on local (normal) population
- Inter-laboratory comparison is not possible

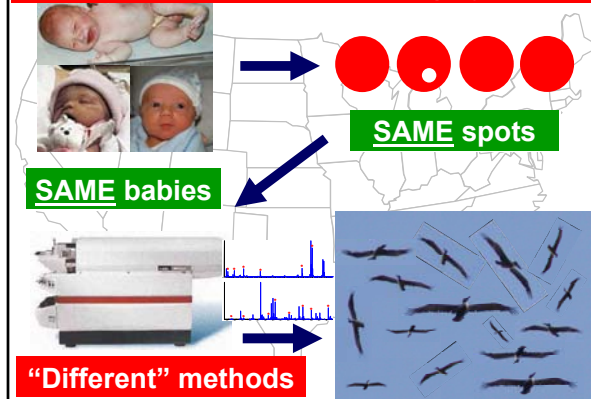
What Are the Differences?



The Sky of Newborn Screening by MS/MS



The Land of Newborn Screening by MS/MS



Can We Compare Something Like This?



Avoid Unrealistic Expectations



Seek Clinical Significance

...and have no fear of comparison



Do We Need Inter-Laboratory Comparison?

The “independence” of state NBS laboratories has created a situation of increasing **loss of consideration for the clinical significance** of test results

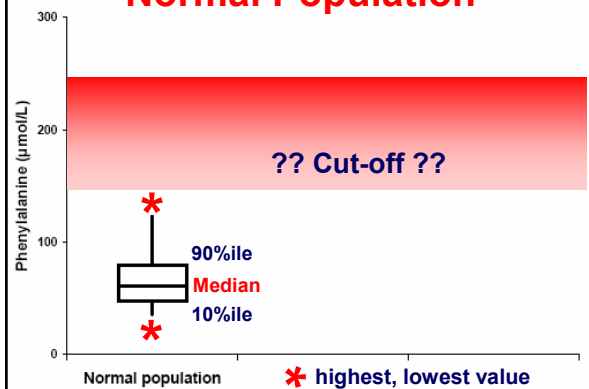
Outline

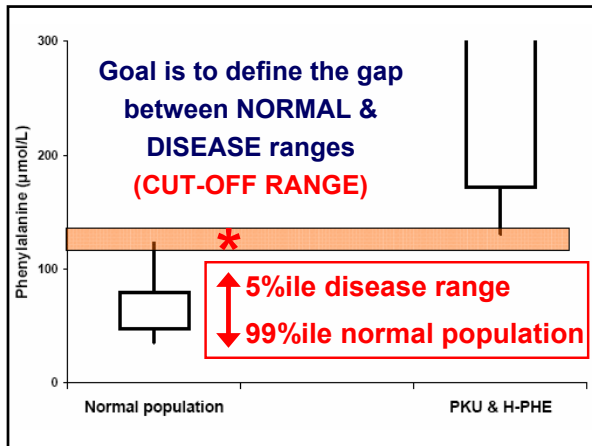
- The ACMG uniform panel
- From **WHAT** we screen for (how many conditions) to **HOW WELL** we do it
 - Performance metrics
 - Clinically defined cutoff values

Selection of Cut-Off Values

- Based on either fixed %ile or $(SD)_n$ above mean of NORMAL population
- Arbitrary adjustments driven by
 - Noise (false positives)
 - Missed cases (false negatives)
- Disconnected from clinical significance

Normal Population

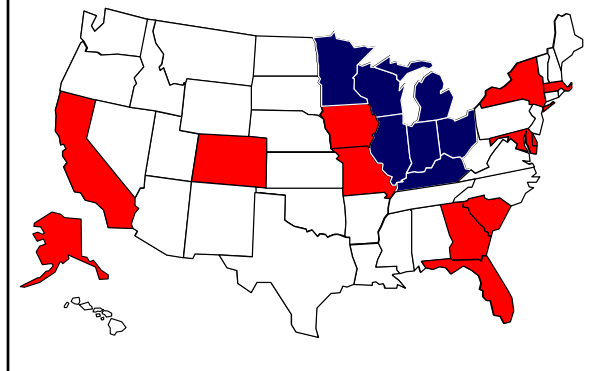




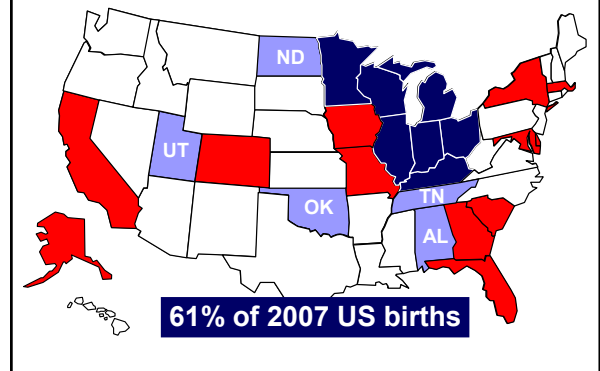
Cumulative Disease Ranges

- **2,213** confirmed cases (as 10/10/06)
 - 32 US states (sorted by region)
 - 18 International participants
 - Published reports (8%)
- Anonymized data
- Collection 0-7 days
- Only first specimens (no repeats)

19 Active Participants (USA)



Imminent Additions (USA)



International Participants

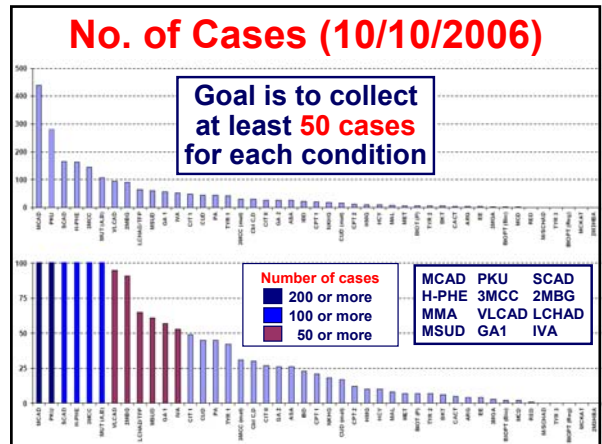
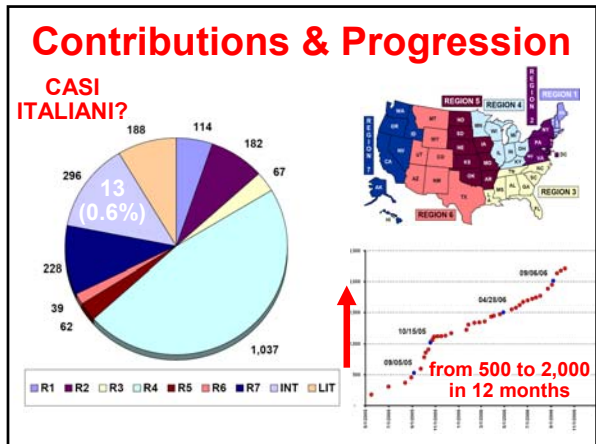
- Argentina
- Australia (1 state)
- Canada (3 provinces)
- Germany (2 labs)
- Italy (2 labs)
- Japan (1 lab)
- Saudi Arabia

Imminent Additions

- China (1 lab)
- Bulgaria
- Portugal
- Singapore
- Switzerland (1 lab)

A Tool for OBJECTIVE COMPARISON of Performance Metrics

Region 4 - Laboratory Quality Improvement Collaborative Project (NBS by MS/MS)																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																														
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GLY	80	100	184	310	812	700	98.97%	5.3	36%	5.8	812 - 700	98	407	810	581	388	939	1,197	1,312	1,426	1,540	1,654	1,768	1,882	1,996	2,110	2,224	2,338	2,452	2,566	2,680	2,794	2,908	3,022	3,136	3,250	3,364	3,478	3,592	3,706	3,820	3,934	4,048	4,162	4,276	4,390	4,504	4,618	4,732	4,846	4,960	5,074	5,188	5,302	5,416	5,530	5,644	5,758	5,872	5,986	6,100	6,214	6,328	6,442	6,556	6,670	6,784	6,898	7,012	7,126	7,240	7,354	7,468	7,582	7,696	7,810	7,924	8,038	8,152	8,266	8,380	8,494	8,608	8,722	8,836	8,950	9,064	9,178	9,292	9,406	9,520	9,634	9,748	9,862	9,976	10,090	10,204	10,318	10,432	10,546	10,660	10,774	10,888	11,002	11,116	11,230	11,344	11,458	11,572	11,686	11,800	11,914	12,028	12,142	12,256	12,370	12,484	12,598	12,712	12,826	12,940	13,054	13,168	13,282	13,396	13,510	13,624	13,738	13,852	13,966	14,080	14,194	14,308	14,422	14,536	14,650	14,764	14,878	14,992	15,106	15,220	15,334	15,448	15,562	15,676	15,790	15,904	16,018	16,132	16,246	16,360	16,474	16,588	16,702	16,816	16,930	17,044	17,158	17,272	17,386	17,500	17,614	17,728	17,842	17,956	18,070	18,184	18,298	18,412	18,526	18,640	18,754	18,868	18,982	19,096	19,210	19,324	19,438	19,552	19,666	19,780	19,894	20,008	20,122	20,236	20,350	20,464	20,578	20,692	20,806	20,920	21,034	21,148	21,262	21,376	21,490	21,604	21,718	21,832	21,946	22,060	22,174	22,288	22,402	22,516	22,630	22,744	22,858	22,972	23,086	23,200	23,314	23,428	23,542	23,656	23,770	23,884	24,000	24,114	24,228	24,342	24,456	24,570	24,684	24,798	24,912	25,026	25,140	25,254	25,368	25,482	25,596	25,710	25,824	25,938	26,052	26,166	26,280	26,394	26,508	26,622	26,736	26,850	26,964	27,078	27,192	27,306	27,420	27,534	27,648	27,762	27,876	27,990	28,104	28,218	28,332	28,446	28,560	28,674	28,788	28,902	29,016	29,130	29,244	29,358	29,472	29,586	29,700	29,814	29,928	30,042	30,156	30,270	30,384	30,498	30,612	30,726	30,840	30,954	31,068	31,182	31,296	31,410	31,524	31,638	31,752	31,866	31,980	32,094	32,208	32,322	32,436	32,550	32,664	32,778	32,892	33,006	33,120	33,234	33,348	33,462	33,576	33,690	33,804	33,918	34,032	34,146	34,260	34,374	34,488	34,602	34,716	34,830	34,944	35,058	35,172	35,286	35,400	35,514	35,628	35,742	35,856	35,970	36,084	36,198	36,312	36,426	36,540	36,654	36,768	36,882	36,996	37,110	37,224	37,338	37,452	37,566	37,680	37,794	37,908	38,022	38,136	38,250	38,364	38,478	38,592	38,706	38,820	38,934	39,048	39,162	39,276	39,390	39,504	39,618	39,732	39,846	39,960	40,074	40,188	40,302	40,416	40,530	40,644	40,758	40,872	40,986	41,100	41,214	41,328	41,442	41,556	41,670	41,784	41,898	42,012	42,126	42,240	42,354	42,468	42,582	42,696	42,810	42,924	43,038	43,152	43,266	43,380	43,494	43,608	43,722	43,836	43,950	44,064	44,178	44,292	44,406	44,520	44,634	44,748	44,862	44,976	45,090	45,204	45,318	45,432	45,546	45,660	45,774	45,888	46,002	46,116	46,230	46,344	46,458	46,572	46,686	46,800	46,914	47,028	47,142	47,256	47,370	47,484	47,598	47,712	47,826	47,940	48,054	48,168	48,282	48,396	48,510	48,624	48,738	48,852	48,966	49,080	49,194	49,308	49,422	49,536	49,650	49,764	49,878	49,992	50,106	50,220	50,334	50,448	50,562	50,676	50,790	50,904	51,018	51,132	51,246	51,360	51,474	51,588	51,702	51,816	51,930	52,044	52,158	52,272	52,386	52,500	52,614	52,728	52,842	52,956	53,070	53,184	53,298	53,412	53,526	53,640	53,754	53,868	53,982	54,096	54,210	54,324	54,438	54,552	54,666	54,780	54,894	55,008	55,122	55,236	55,350	55,464	55,578	55,692	55,806	55,920	56,034	56,148	56,262	56,376	56,490	56,604	56,718	56,832	56,946	57,060	57,174	57,288	57,402	57,516	57,630	57,744	57,858	57,972	58,086	58,200	58,314	58,428	58,542	58,656	58,770	58,884	59,000	59,114	59,228	59,342	59,456	59,570	59,684	59,798	59,912	60,026	60,140	60,254	60,368	60,482	60,596	60,710	60,824	60,938	61,052	61,166	61,280	61,394	61,508	61,622	61,736	61,850	61,964	62,078	62,192	62,306	62,420	62,534	62,648	62,762	62,876	62,990	63,104	63,218	63,332	63,446	63,560	63,674	63,788	63,902	64,016	64,130	64,244	64,358	64,472	64,586	64,700	64,814	64,928	65,042	65,156	65,270	65,384	65,498	65,612	65,726	65,840	65,954	66,068	66,182	66,296	66,410	66,524	66,638	66,752	66,866	66,980	67,094	67,208	67,322	67,436	67,550	67,664	67,778	67,892	68,006	68,120	68,234	68,348	68,462	68,576	68,690	68,804	68,918	69,032	69,146	69,260	69,374	69,488	69,602	69,716	69,830	69,944	70,058	70,172	70,286	70,400	70,514	70,628	70,742	70,856	70,970	71,084	71,198	71,312	71,426	71,540	71,654	71,768	71,882	71,996	72,110	72,224	72,338	72,452	72,566	72,680	72,794	72,908	73,022	73,136	73,250	73,364	73,478	73,592	73,706	73,820	73,934	74,048	74,162	74,276	74,390	74,504	74,618	74,732	74,846	74,960	75,074	75,188	75,302	75,416	75,530	75,644	75,758	75,872	75,986	76,100	76,214	76,328	76,442	76,556	76,670	76,784	76,898	77,012	77,126	77,240	77,354	77,468	77,582	77,696	77,810	77,924	78,038	78,152	78,266	78,380	78,494	78,608	78,722	78,836	78,950	79,064	79,178	79,292	79,406	79,520	79,634	79,748	79,862	79,976	80,090	80,204	80,318	80,432	80,546	80,660	80,774	80,888	81,002	81,116	81,230	81,344	81,458	81,572	81,686	81,800	81,914	82,028	82,142	82,256	82,370	82,484	82,598	82,712	82,826	82,940	83,054	83,168	83,282	83,396	83,510	83,624	83,738	83,852	83,966	84,080	84,194	84,308	84,422	84,536	84,650	84,764	84,878	84,992	85,106	85,220	85,334	85,448	85,562	85,676	85,790	85,904	86,018	86,132	86,246	86,360	86,474	86,588	86,702	86,816	86,930	87,044	87,158	87,272	87,386	87,500	87,614	87,728	87,842	87,956	88,070	88,184	88,298	88,412	88,526	88,640	88,754	88,868	88,982	89,096	89,210	89,324	89,438	89,552	89,666	89,780	89,894	90,008	90,122	90,236	90,350	90,464	90,578	90,692	90,806	90,920	91,034	91,148	91,262	91,376	91,490	91,604	91,718	91,832	91,946	92,060	92,174	92,288	92,402	92,516	92,630	92,744	92,858	92,972	93,086	93,200	93,314	93,428	93,542	93,656	93,770	93,884	94,000	94,114	94,228	94,342	94,456	94,570	94,684	94,798	94,912	95,026	95,140	95,254	95,368	95,482	95,596	95,710	95,824	95,938	96,052	96,166	96,280	96,394	96,508	96,622	96,736	96,850	96,964	97,078	97,192	97,306	97,420	97,534	97,648	97,762	97,876	97,990	98,104	98,218	98,332	98,446	98,560	98,674	98,788	98,902	99,016	99,130	99,244	99,358	99,472	99,586	99,700	99,814	99,928	100,042	100,156	100,270	100,384	100,498	100,612	100,726	100,840	100,954	101,068	101,182	101,296	101,410	101,524	101,638	101,752	101,866	101,980	102,094	102,208	102,322	102,436	102,550	102,664	102,778	102,892	103,006	103,120	103,234	103,348	103,462	103,576	103,690	103,804	103,918	104,032	104,146	104,260	104,374	104,488	104,602	1

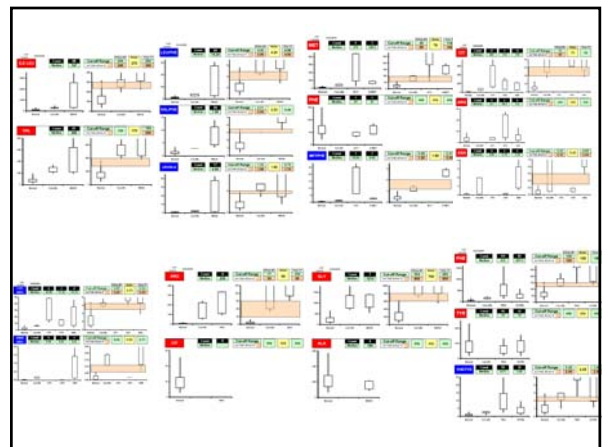
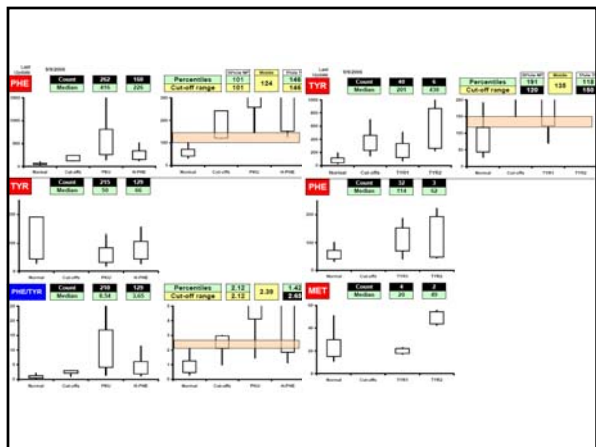
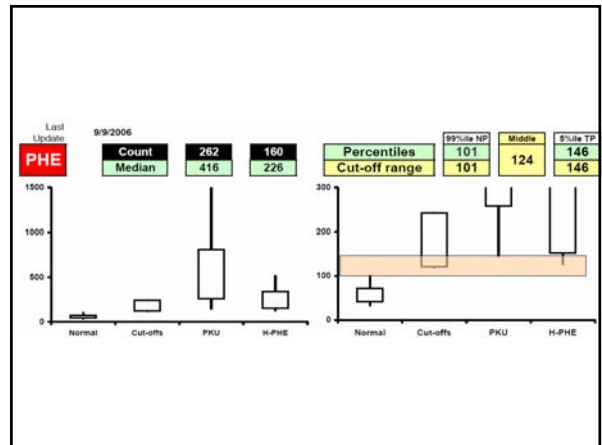


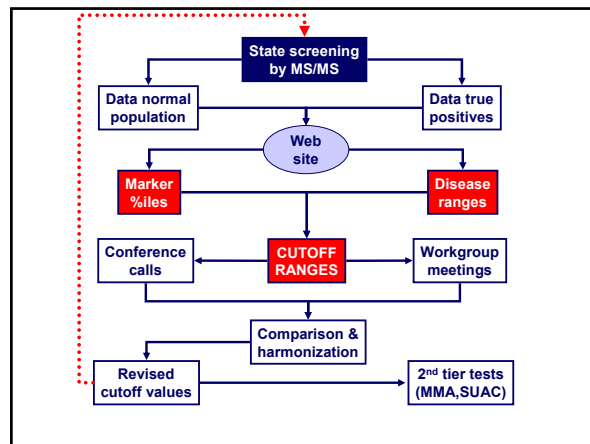
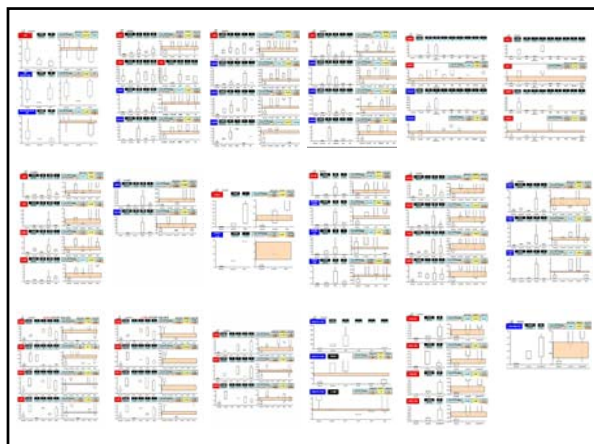
AA Ratios (7)

AA (9)

AC (25)

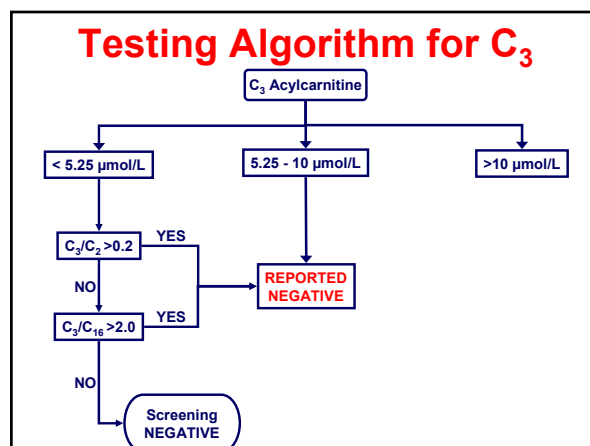
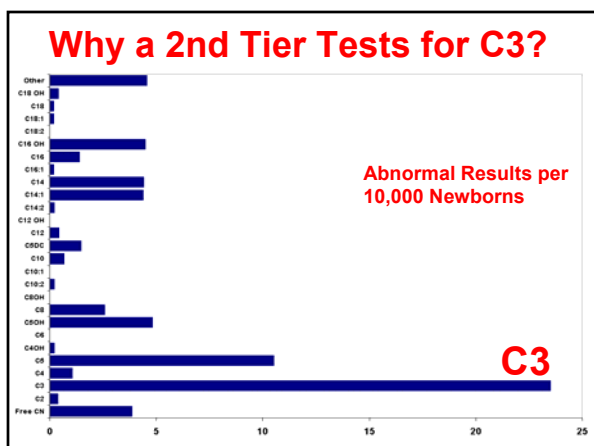
AC Ratios (20)

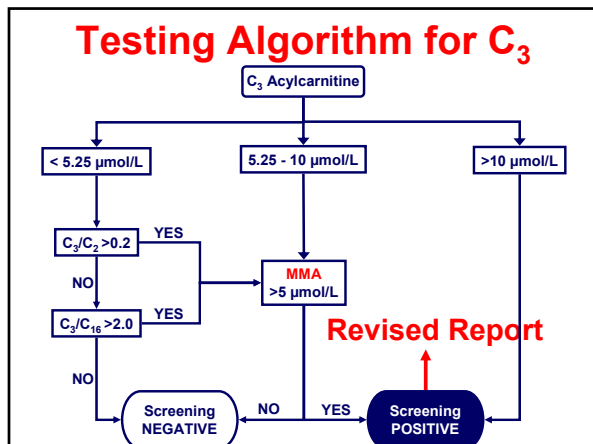




- ### Outline
- The ACMG uniform panel
 - From **WHAT** we screen for (how many conditions) to **HOW WELL** we do it
 - Performance metrics
 - Clinically defined cutoff values
 - **The impact of 2nd tier tests**

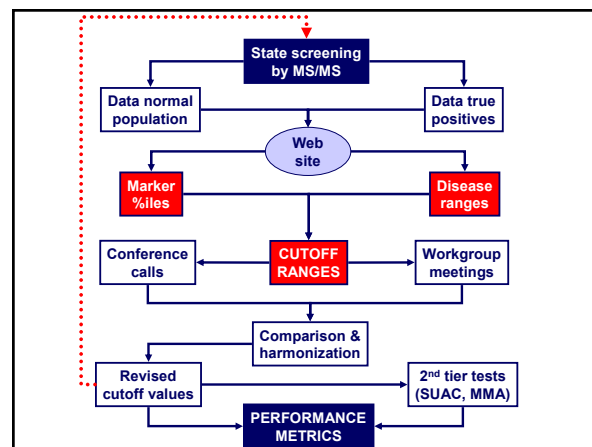
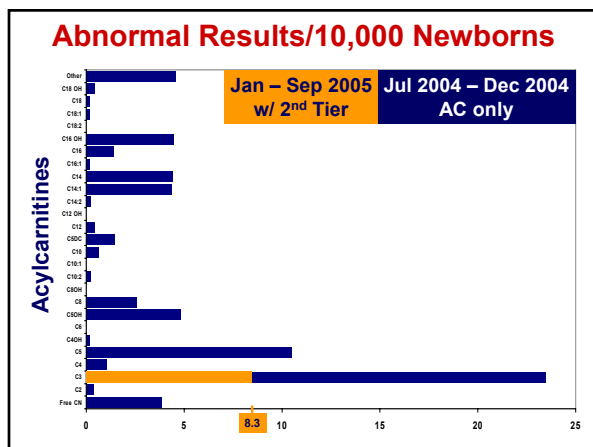
- ### Second Tier Tests
- Steroids (CAH)
 - Lacey JM, Clin Chem 2004;50:621
 - Minutti CZ, J Clin Endocrinol Metab 2004;89:3687
 - Succinylacetone (Tyrosine)
 - Magera MJ, Mol Genet Metab 2006;88:16
 - Methylmalonic acid (C3)
 - Homocysteine (Methionine, C3)





Impact of 2nd Tier test for MMA

	AC only	w/ 2 nd Tier
Period	7/1/04 - 12/31/04	1/1/05 - 9/30/05
Test volume	46,715	78,065
Abnormal C ₃	109	726
Reported abnormal	22	12
True positives	1	5 (1:15,613)
False positives	21 (0.045%)	7 (0.009%)
Pos. predict. Value	5%	42%



- ### Participation in Collaborative Project
- Everyone is very welcome to join in, everybody is needed!
 - Participation is based on monthly submission of data:
 - Percentiles of normal population (cumulative)
 - Performance metrics (period, volume)
 - Cutoff values (willingness to explore new ones)
 - All data (AA, AC) of true positive cases

- ### Conclusions
- Newborn screening is undergoing major changes
 - Number of conditions, uniformity
 - Awareness of performance metrics
 - Collaborative effort is critical
 - 2nd tier tests reduce false positive rates without compromising sensitivity
 - How do we measure success?