Division of Laboratory Systems

Oregon State Public Health Laboratory Shares Lessons Learned from Its Newborn Screening Program

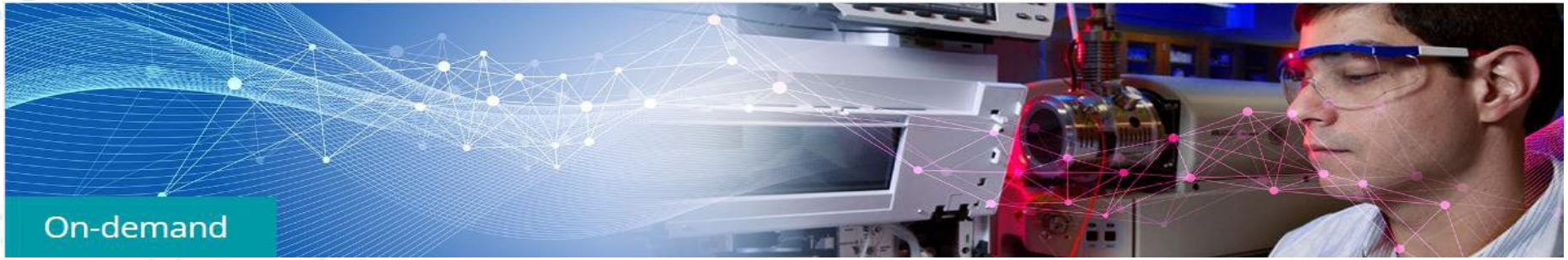
Patrice K. Held, PhD

July 25, 2023

Agenda

- Introduction
  - *Relevant OneLab™ Resources*
  - *Today's Presenter*
- *Oregon State Public Health Laboratory Shares Lessons Learned from Its Newborn Screening Program*
- Q&A
- Upcoming Events

Resources- eLearning Courses



cdc.gov/labtraining/training-courses/good-lab-practices-molecular-genetics-testing is for laboratory professionals who perform molecular genetics testing or may consider addingmolecular genetics to the laboratories testing menu.

cdc.gov/labtraining/training-courses/good-lab-practice-recs-biochem-genetic-testing_preanalytic-phase is for laboratory professionals working in biochemical genetic testing or reference laboratories and healthcare professionals who order biochemical genetic tests.

cdc.gov/labtraining/training-courses/lc_ms_ms_biochemical_genetics_laboratory is for laboratory professionals working or aspiring to work in a biochemical genetics laboratory.

Resources- Job Aids

reach.cdc.gov/jobaid/genetic-testing lists common questions and answers about genetic testing and results.

reach.cdc.gov/jobaid/health-professionals-and-genetic-testing contains basic information about molecular genetic testing and results.

reach.cdc.gov/jobaid/top-10-recommendations-laboratories-performing-molecular-genetic-testing contains recommendations for laboratory professionals performing molecular genetic testing.

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Presenter

Patrice K. Held

Manager of Oregon Newborn Screening Program,
Oregon State Public Health Laboratory
Co-Director of the Biochemical Genetics Laboratory,
Oregon Health & Sciences University

Newborn Screening Celebrates 60 Years

Oregon State Public Health Laboratory Shares Lessons Learned from Its Newborn Screening Program

Patrice K. Held, Oregon NBS Program Manager

July 25, 2023

Oregon Health Authority

What is Newborn Screening?

Newborn screening is a **state public health program** that identifies infants with **treatable disorders**, which may otherwise go **unrecognized**, to avoid or **prevent adverse outcomes**.

Newborn Screening Stats

- **97% of the nearly four million** newborns born in the United States each year are screened

  https://www.newsteps.org/about-newsteps

- Saves or improves the lives of over **12,000 babies** in the United States each year

  https://www.newsteps.org/about-newsteps

- In Oregon, approximately **40,000 babies are screened** each year and **more than 100** are diagnosed and treated for one of the conditions on the newborn screening panel.

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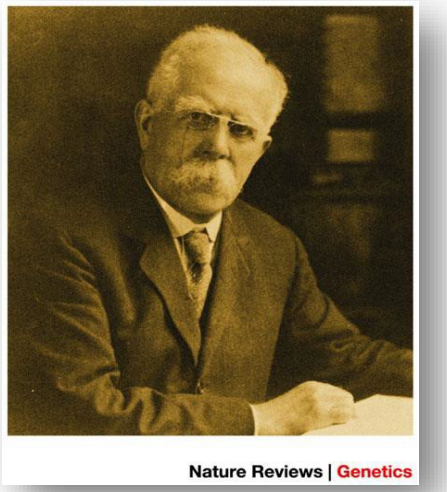
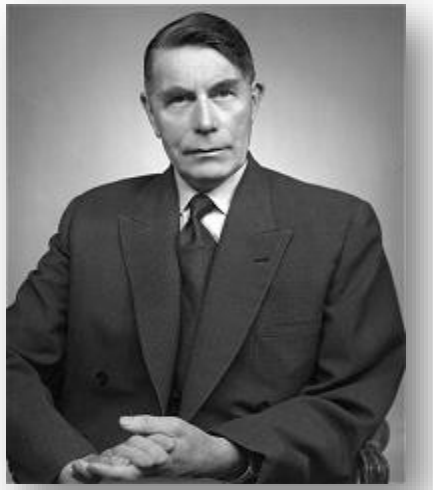
History of Newborn Screening

1908 Sir Archibald Garrod – "inborn errors of metabolism"

1934 Dr. Asbjorn Folling – discovery of PKU

1951 Dr. Horst Bickel – discovers a treatment for PKU





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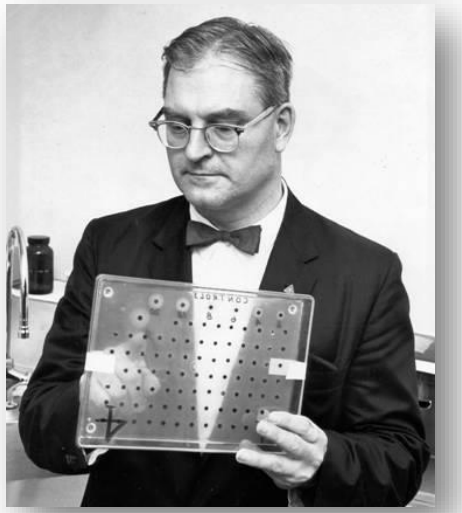
History of Newborn Screening

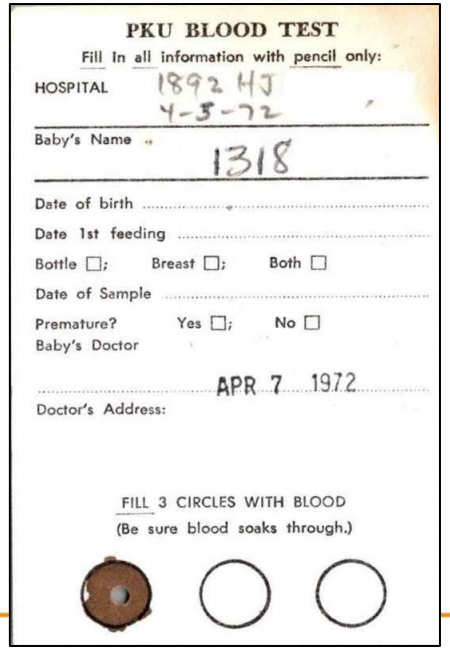
1960 Dr. Guthrie – developed bacterial inhibition assay to measure phenylalanine levels in dried blood spots

1963 Oregon passes law requiring universal PKU screening

*Other states include **Massachusetts**, Ohio, Maryland, New York.*

1965 All Oregon babies are screened





PKU BLOOD TEST

Fill in all information with pencil only:

HOSPITAL 1892 HJ 4-5-72

Baby's Name 1318

Date of birth

Date 1st feeding

Bottle ☐; Breast ☐; Both ☐

Date of Sample

Premature? Yes ☐; No ☐

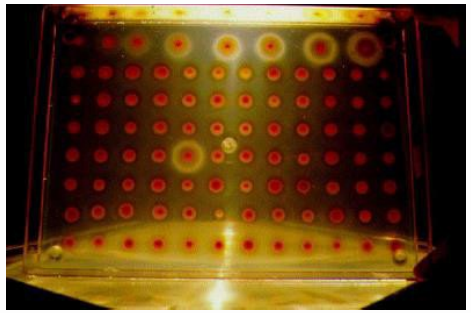
Baby's Doctor

APR 7 1972

Doctor's Address:

FILL 3 CIRCLES WITH BLOOD

(Be sure blood soaks through.)



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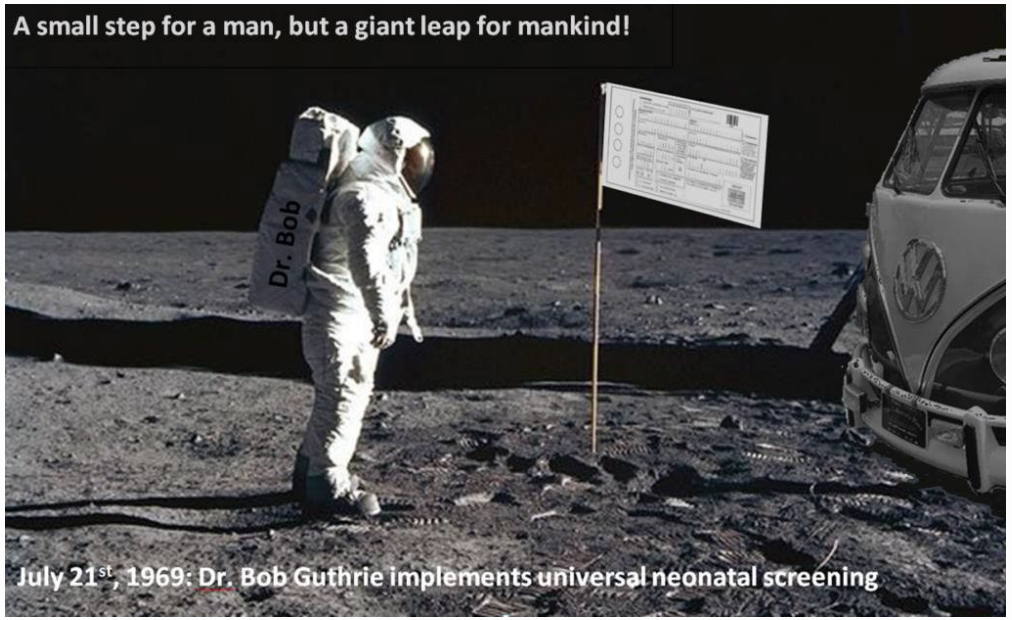
Dr. Robert Guthrie



"No child should die or suffer disabilities if a simple blood spot can prevent it."

Robert Guthrie, PhD, MD, 1916-1995
Developer of the first newborn screening test
(the Guthrie test for PKU)

https://robertguthriepku.org/blog/

History of Newborn Screening

Years	Conditions in NBS
1960s	PKU
1970s	Sickle cell (SS) disease (SCD) and other S allele conditions, congenital hypothyroidism (CH),
1980s	Galactosemia (GAL), maple syrup urine disease (MSUD), congenital adrenal hyperplasia (CAH), biotinidase def. (BIO)
1990s	No uniform approach to screened conditions
2000s	Cystic fibrosis (CF); Medium-chain acyl CoA Dehydrogenase deficiency (MCAD); Very Long-chain acyl CoA Dehydrogenase deficiency (VLCAD); Long-chain acyl CoA Dehydrogenase deficiency (LCHAD); Trifunctional Protein deficiency (TFP); Carnitine uptake/transport; Methylmalonic aciduria (MMA) (mutase); MMA (cobalamin); Propionic Acidemia (PA); isovaleric acidemia (IVA); 3-methyl crotonyl carboxylase deficiency (3MCC);3-hydroxy 3-methylglutaryl-CoA lyase deficiency (3H3MG); Holocarboxylase def.; Beta-keto-thiolase deficiency (BKT); Glutaric acidemia (GA 1); ASA; Citrullinemia Type 1 (CIT 1); Homocystinuria (HCU); Tyrosinemia type 1 (TYR) 1; Severe Combined Immunodeficiency (SCID); hearing loss (HL)
2010s	Spinal Muscular Atrophy (SMA); Pompe; Mucopolysaccharidosis I; Critical Cyanotic Congenital Heart Disease (CCHD); X-linked adrenoleukodystrophy (X-ALD)
~~2020–2021~~	~~None added to RUSP~~ 2022 Mucopolysaccharidosis II, 2023 GAMT deficiency

Int. J. Neonatal Screen. 2022, 8(3), 41; https://doi.org/10.3390/ijns8030041

Recommended Uniform Screening Panel

- May 2010 RUSP was adopted. RUSP is a list of disorders supported by the Advisory Committee on Heritable Disorders in Newborns and Children and recommended by the Secretary of HHS.

- **37 Core Conditions** listed on the RUSP
  - Inborn errors of metabolism
  - Endocrine Disorders
  - Hemoglobinopathies
  - Cystic Fibrosis
  - Severe Combined Immunodeficiencies
  - Hearing loss
  - Critical congenital heart disease

ACMG Code	Core Condition	Metabolic Disorder			Endocrine Disorder	Hemoglobin Disorder	Other Disorder
		Organic acid condition	Fatty acid oxidation disorders	Amino acid disorders			
PROP	Propionic acidemia	X					
MUT	Methylmalonic acidemia (methylmalonyl-CoA mutase)	X					
Cbl A,B	Methylmalonic acidemia (cobalamin disorders)	X					
IVA	Isovaleric acidemia	X					
3-MCC	3-Methylcrotonyl-CoA carboxylase deficiency	X					
HMG	3-Hydroxy-3-methyglutaric aciduria	X					
MCD	Holocarboxylase synthase deficiency	X					
BKT	ß-Ketothiolase deficiency	X					
GA1	Glutaric acidemia type I	X					
CUD	Carnitine uptake defect/carnitine transport defect		X				
MCAD	Medium-chain acyl-CoA dehydrogenase deficiency		X				
VLCAD	Very long-chain acyl-CoA dehydrogenase deficiency		X				
LCHAD	Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency		X				
TFP	Trifunctional protein deficiency		X				
ASA	Argininosuccinic aciduria			X			
CIT	Citrullinemia, type I			X			
MSUD	Maple syrup urine disease			X			
HCY	Homocystinuria			X			
PKU	Classic phenylketonuria			X			
TYR I	Tyrosinemia, type I			X			
CH	Primary congenital hypothyroidism				X		
CAH	Congenital adrenal hyperplasia				X		
Hb SS	S,S disease (Sickle cell anemia)					X	
Hb S/βTh	S, βeta-thalassemia					X	
Hb S/C	S,C disease					X	
BIOT	Biotinidase deficiency						X
CCHD	Critical congenital heart disease						X
CF	Cystic fibrosis						X
GALT	Classic galactosemia						X
GSD II	Glycogen Storage Disease Type II (Pompe)						X
HEAR	Hearing loss						X
SCID	Severe combined Immunodeficiencies						X

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Newborn Screening System

Pre-analytic | Analytic | Post-analytic

- Prenatal Education
- Specimen Collection
- Transport
- Laboratory Testing
- Short Term Follow-up
- Long Term Follow-up

baby's first test

www.babysfirsttest.org

OHSU

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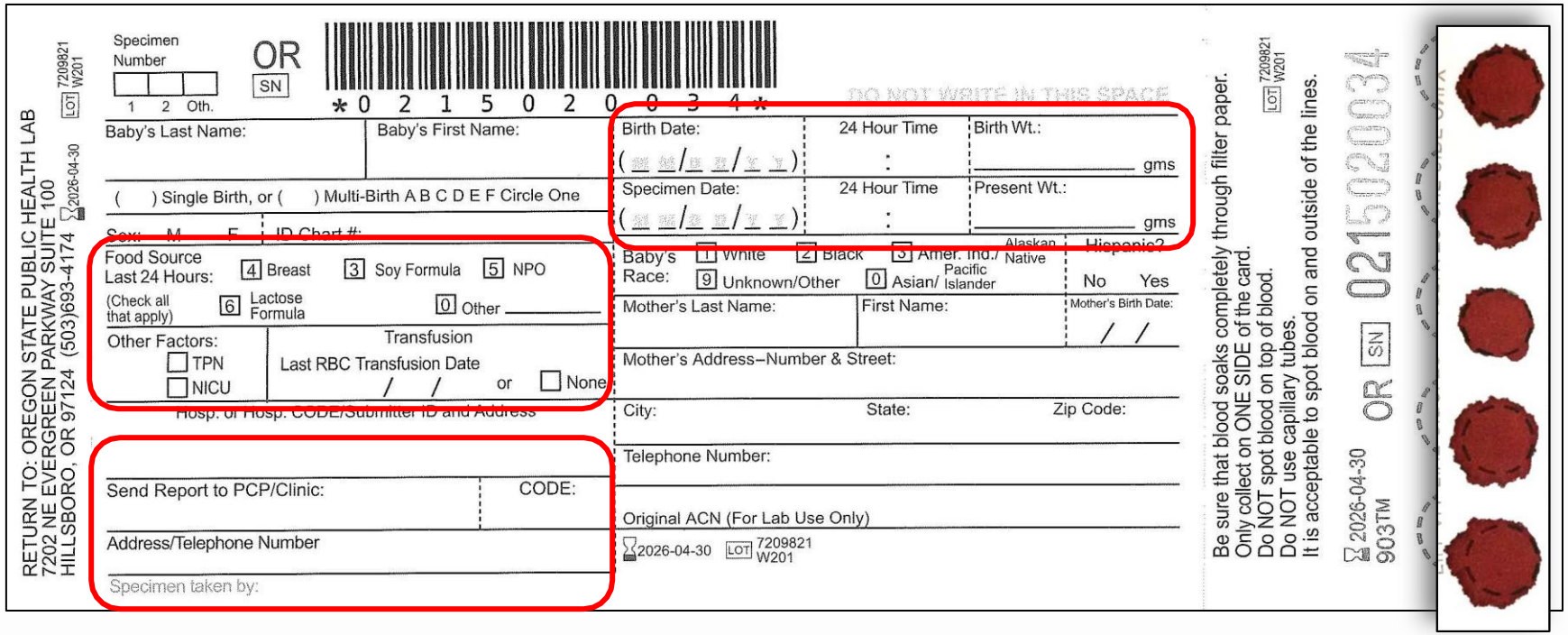
Collection of the Newborn Screen



incomplete saturation

blood clots

Specimen Transport

A JOURNAL SENTINEL WATCHDOG REPORT

Deadly Delays

The nation's newborn screening programs depend on speed and science to save babies from rare diseases. But thousands of hospitals fall short, deadly delays are ignored and failures are hidden from public view — while babies and their families suffer.

Kristyna Wentz-Graff/Journal Sentinel

Delays at hospitals across the country undermine newborn screening programs, putting babies at risk of disability and death

November 16, 2013

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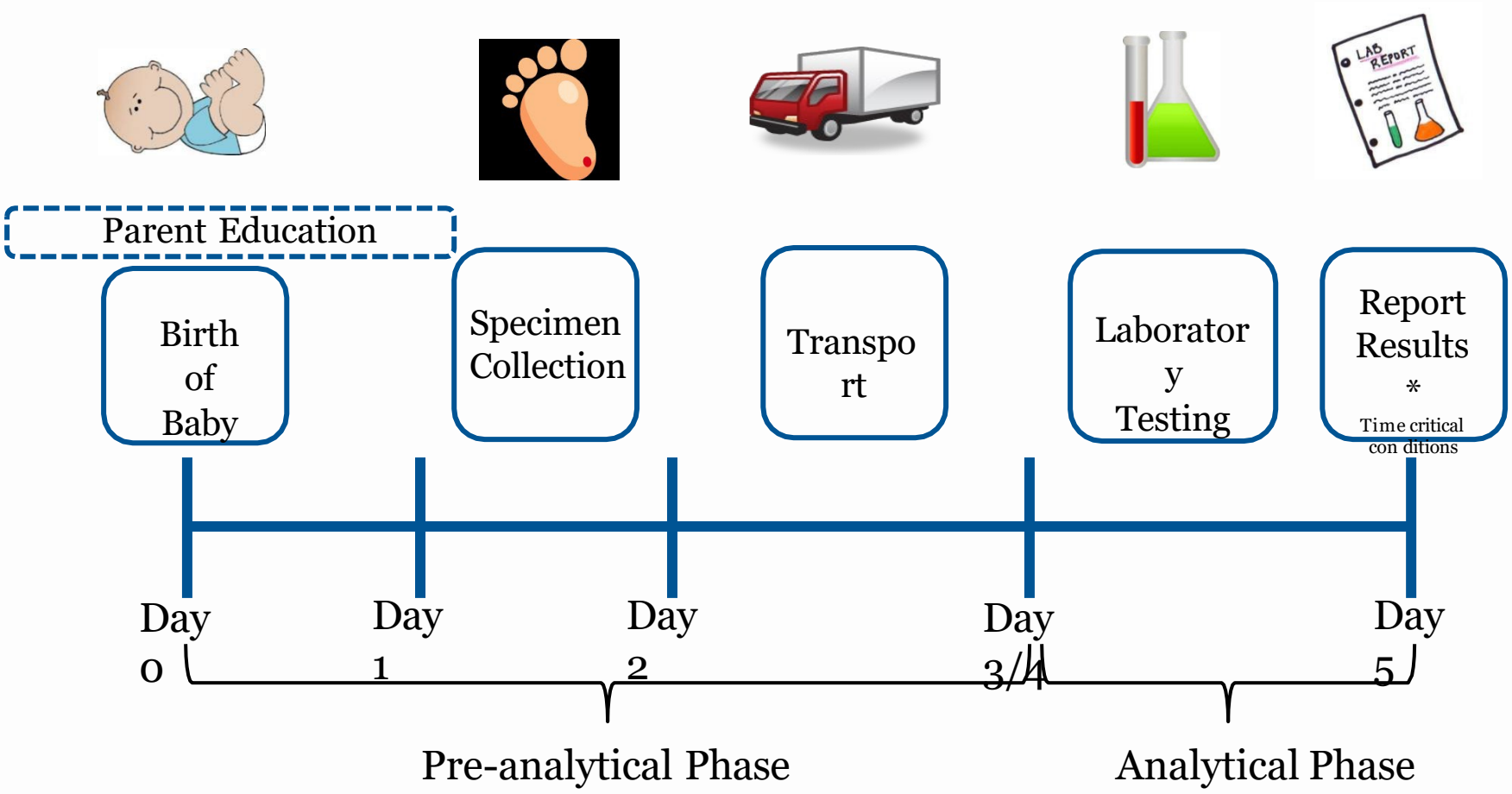
Timeliness of Newborn Screening

- Advisory Committee on Heritable Disorders in Newborns and Children provided recommendations for timeliness in newborn screening – March 2015
  - Initial screen collected with 48 hours after birth
  - Specimens should be received at laboratory within 24 hours of collection
  - Presumptive positive results for time-critical conditions reported within 5 days of life
  - Presumptive positive results for time-sensitive conditions reported within 7 days of life
  - All results should be reported within 7 days of life

Newborn Screening Timeline



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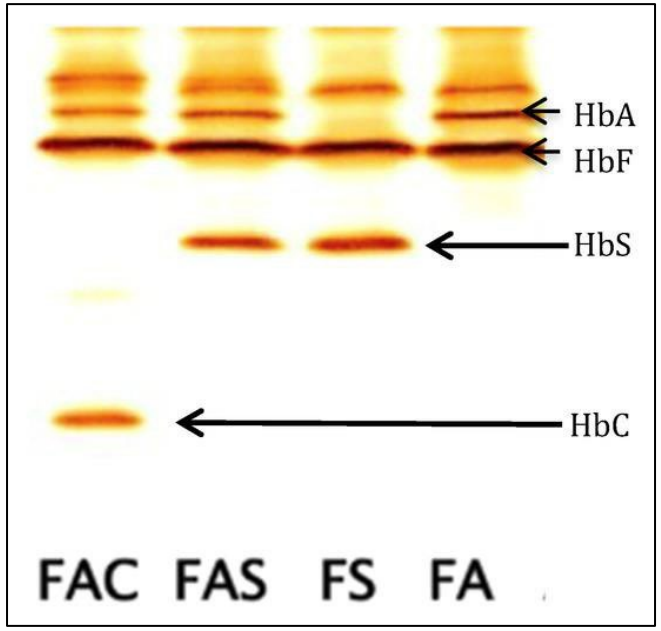
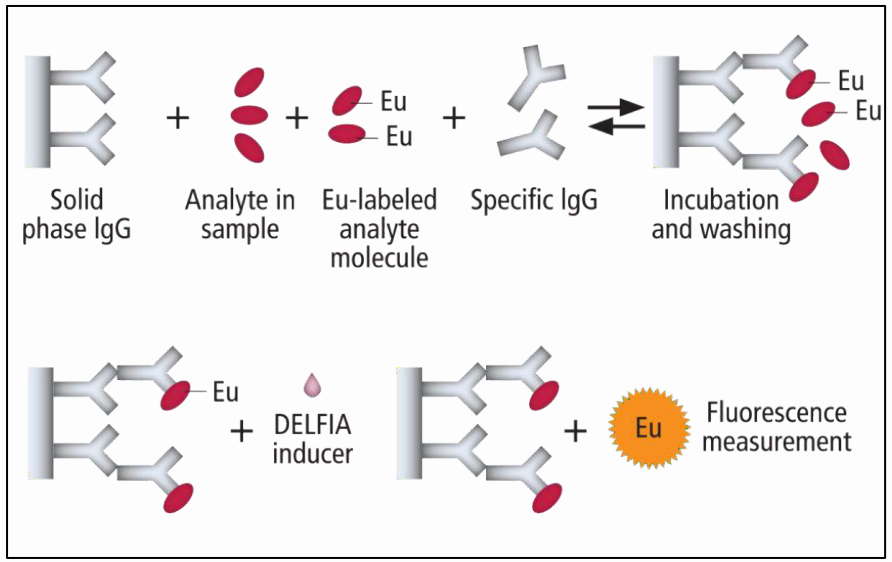
Technology Used in Screening



Screening for Hemoglobinopathies



Screening for Hypothyroidism, Congenital Adrenal Hyperplasia, and Cystic Fibrosis

Int. J. Neonatal Screen. 2018, *4*(4), 39; https://doi.org/10.3390/ijns4040039

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Technology Used in Screening

Screening for
Inborn Errors of Metabolism

Molecular Techniques
Quantitative PCR SCID and SMA

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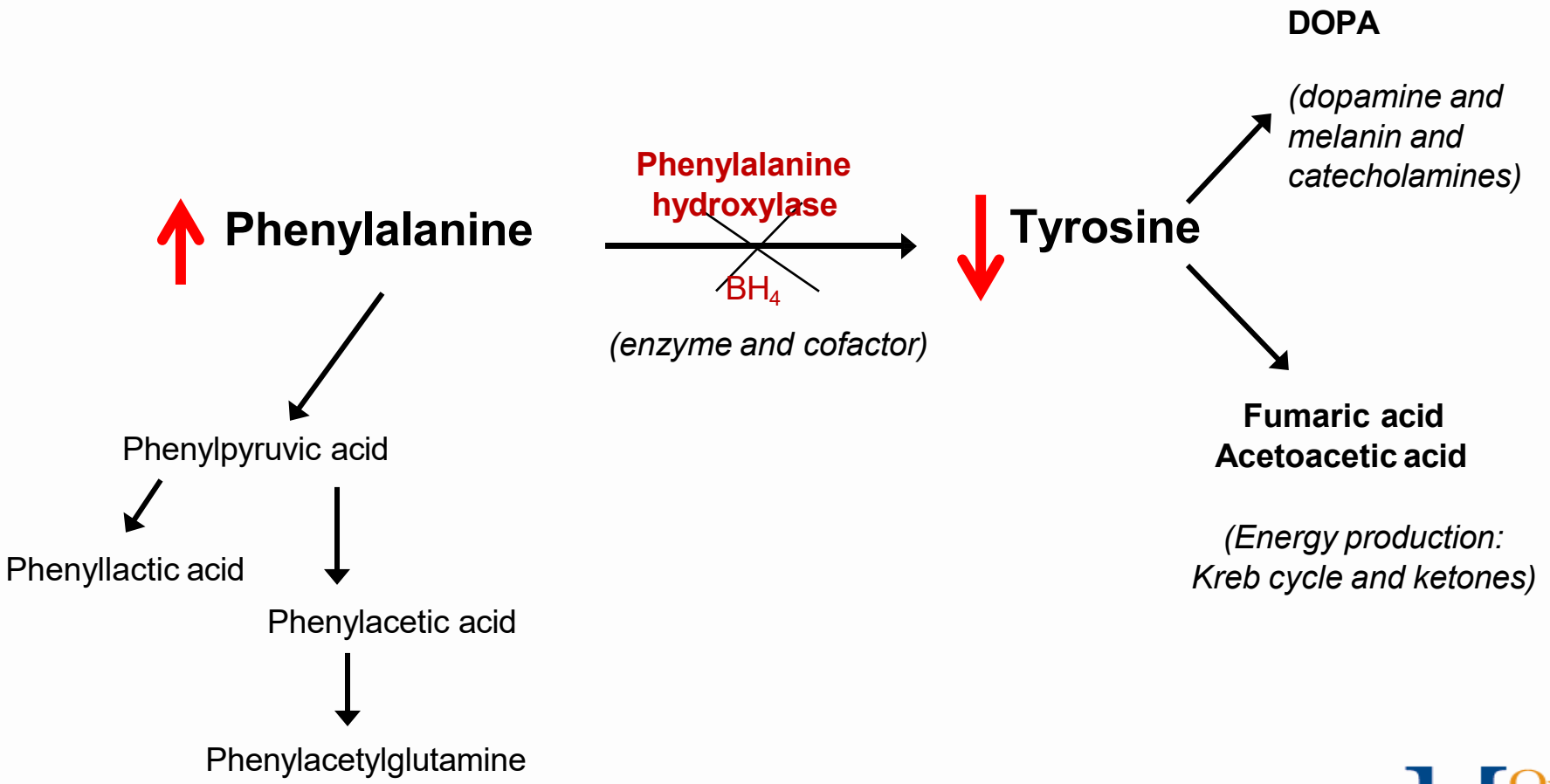
Phenylalanine Metabolism



Reporting of NBS Results

Risk Assessment

- **Screen Positive**
  - Marker(s) elevated above (or below) cutoff
  - Additional diagnostic testing is needed to confirm presence of disease
  - Lab notifies health care providers
- **Screen Negative**
  - Marker(s) within unaffected population distribution
  - No additional action needed
- **Inconclusive**
  - Unable to reliably detect markers
  - Lab notifies health care providers to repeat newborn screen

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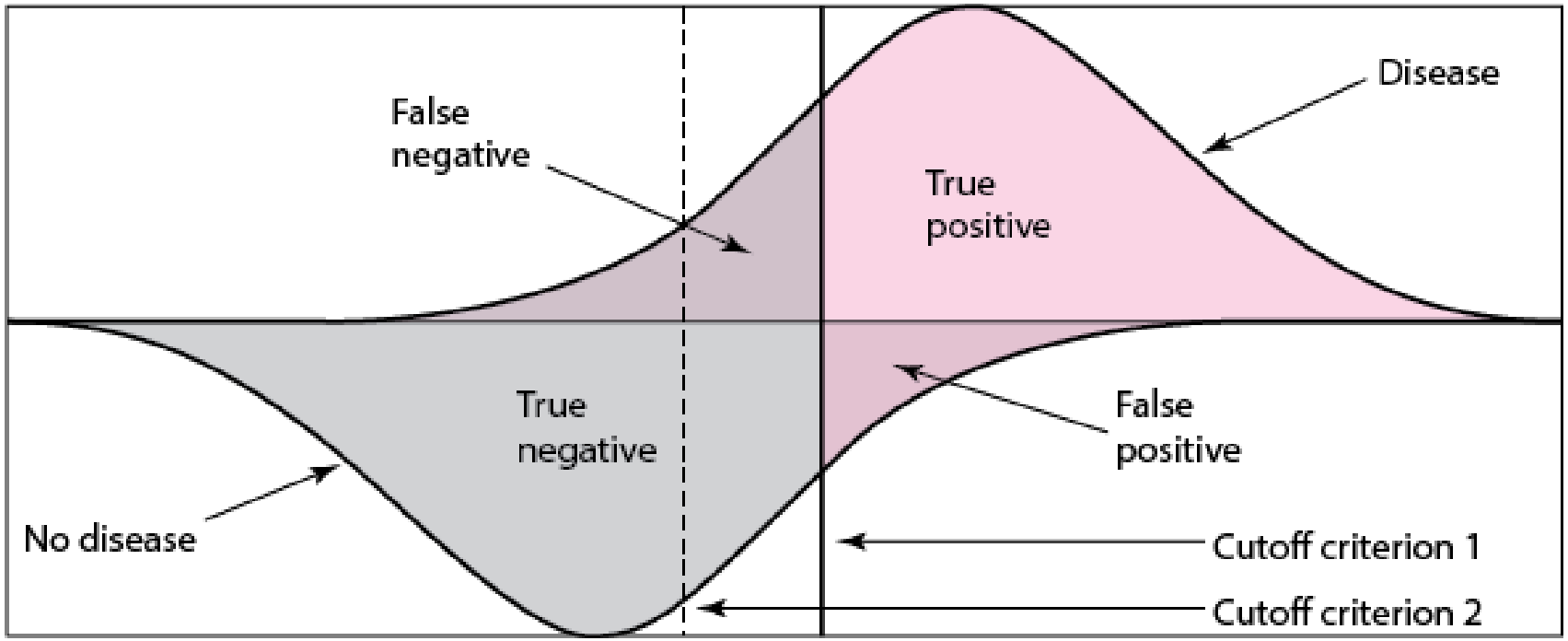
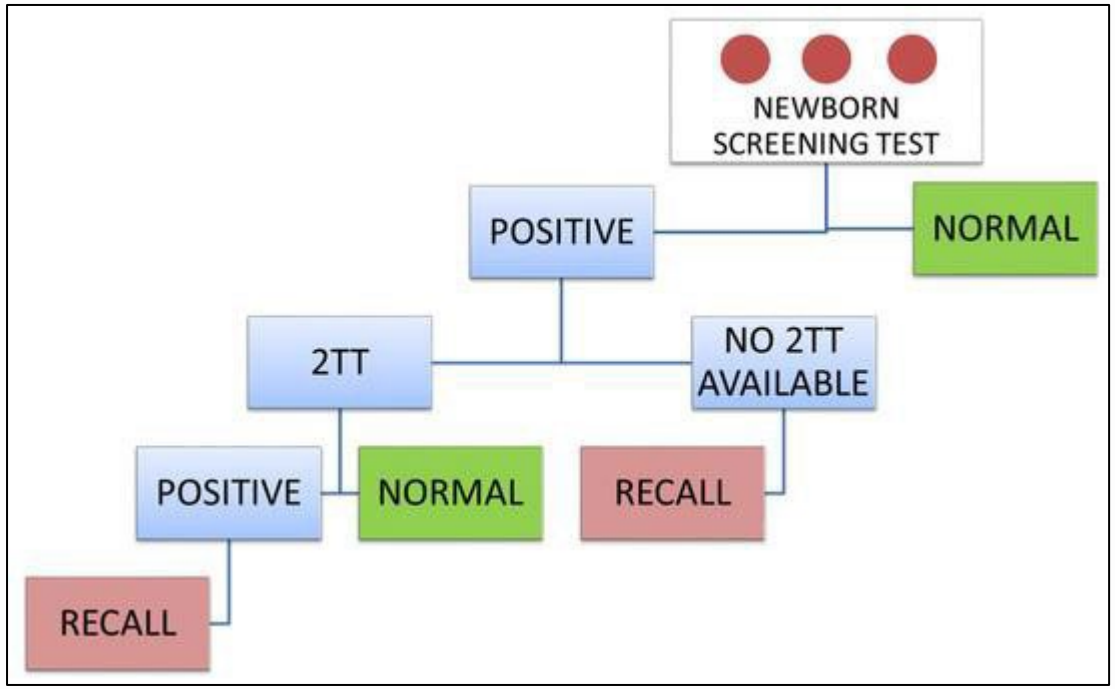
Screening Test Performance



Tiered Testing To Improve Screening Performance



Int. J. Neonatal Screen. 2020, 6(4), 84; https://doi.org/10.3390/ijns6040084

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Newborn Screening Follow-Up

Short Term Follow-up

To ensure that all newborns receive a valid screening test, and that those with a screen positive results receive a definitive diagnosis, in the most expedient manner possible.

Long Term Follow-up

Comprises the assurance and provision of quality chronic disease management, condition-specific treatment, and age-appropriate preventive care throughout the lifespan of individuals identified with a condition included in newborn screening.

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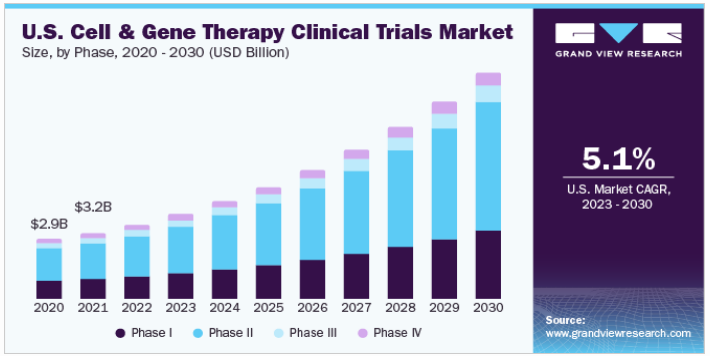
Candidate Conditions for Newborn Screening

1. Expanding number of conditions for which the molecular basis is known

Total number of phenotypes* for which the molecular basis is known	7,544
Total number of genes with phenotype-causing mutation	4,853

OMIM Gene Map Statistics: OMIM Morbid Map Scorecard (Updated July 21st, 2023)

2. Rapidly growing list of new therapies entering market



3. Candidate conditions

Duchenne Muscular Dystrophy, Krabbe Disease, Congenital Cytomegalovirus

Watson et al., Int. J. Neonatal Screen. 2022, 8, 41.

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Selection Criteria for Conditions

Adapted from 1968 Wilson & Jungner: Principles and Practice of Screening for Disease.

Laboratory Test for Screening

- Rapid and economical laboratory screening test is available
- High specificity and sensitivity
- High positive predictive value
- Confirmatory test is available to validate screening results

Public Health System Infrastructure

- Treatment
- Clinical care
- Counseling

Disorder

- Prevalence (>1/100,000)
- Natural history understood
- Significant morbidity/mortality
- Effective treatment available
- Early treatment changes outcome (prevents or reduces illness)
- Routine care will not reveal disorder

Cost

- Screening is cost-effective

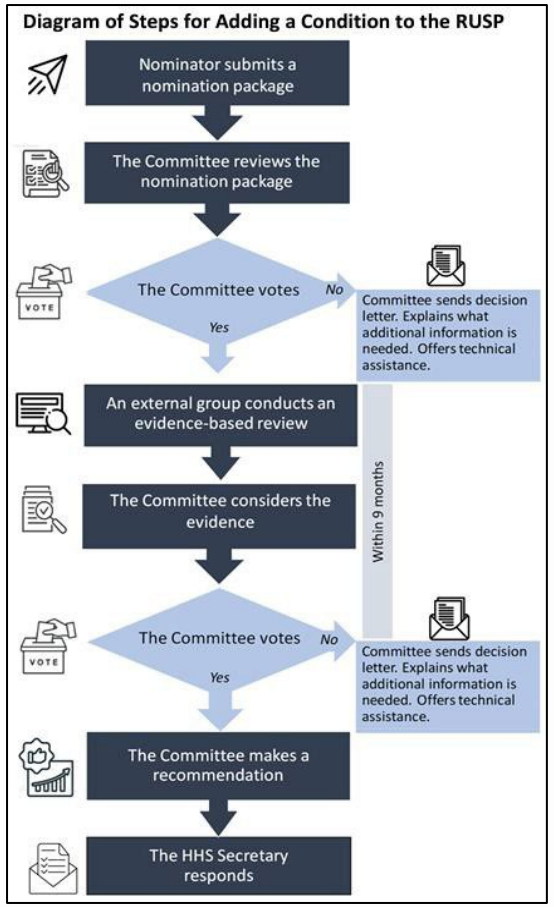
Emerging Criteria for Conditions

Box 2. **Synthesis of emerging screening criteria proposed over the past 40 years**

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.

Andermann et al., Bulletin of the World Health Organization, April 2008, 86(4)

Addition of Conditions to RUSP



NET BENEFIT/ CERTAINTY			READINESS			FEASIBILITY	
			Ready	Developmental	Unprepared		
SIGNIFICANT Benefit	Certainty	HIGH	**A1** Screening for the condition has a high certainty of significant net benefits, screening has high or moderate feasibility. Most public health departments are ready to screen.	**A2** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments have only developmental readiness.	**A3** Screening for the condition has a high certainty of significant net benefits and screening has high or moderate feasibility. Public health departments are unprepared for screening.	Feasibility	HIGH or MODERATE
			A4 There is high certainty that screening would have a significant benefit; however, most health departments have low feasibility of implementing population screening.				LOW
		MOD	**B 1-4** There is moderate certainty that screening would have a significant benefit.				---
Small to ZERO Benefit	Certainty	MOD/HIGH	**C 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a small to zero net benefit.				---
NEG Benefit			**D 1-4** There is high or moderate certainty that adoption of screening for the targeted condition would have a negative net benefit.				---
---		LOW	**L 1-4** There is low certainty regarding the potential net benefit from screening.				---

https://www.hrsa.gov/advisory-committees/heritable-disorders

Goals for Newborn Screening Programs

- **Harmonization between NBS programs**
  - Language used
  - Diseases Screened
  - Assessing effectiveness (quality) of program
- **Improvements in education and outreach**
  - Parental education
  - Communication of results
- **Improvements in long term follow-up**
- **Addressing health equity**

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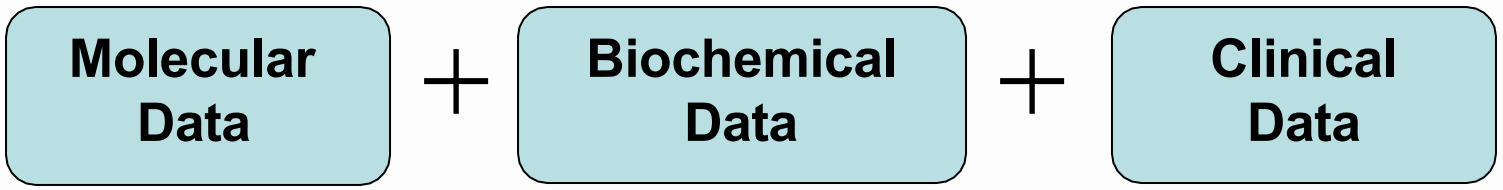
CDC: Role in Quality Assurance

- Newborn Screening Quality Assurance Program (NSQAP) develops analytical methods to measure substances in dried blood spots (DBSs) and produces certified DBS quality-control and reference materials for newborn screening tests.
- Initiated projects to look at harmonization of data across different testing platforms and laboratories
- Enhancing Data-driven Disease Detection in Newborns (ED3N) pilot program



https://www.cdc.gov/nceh/dls/ed3n.html

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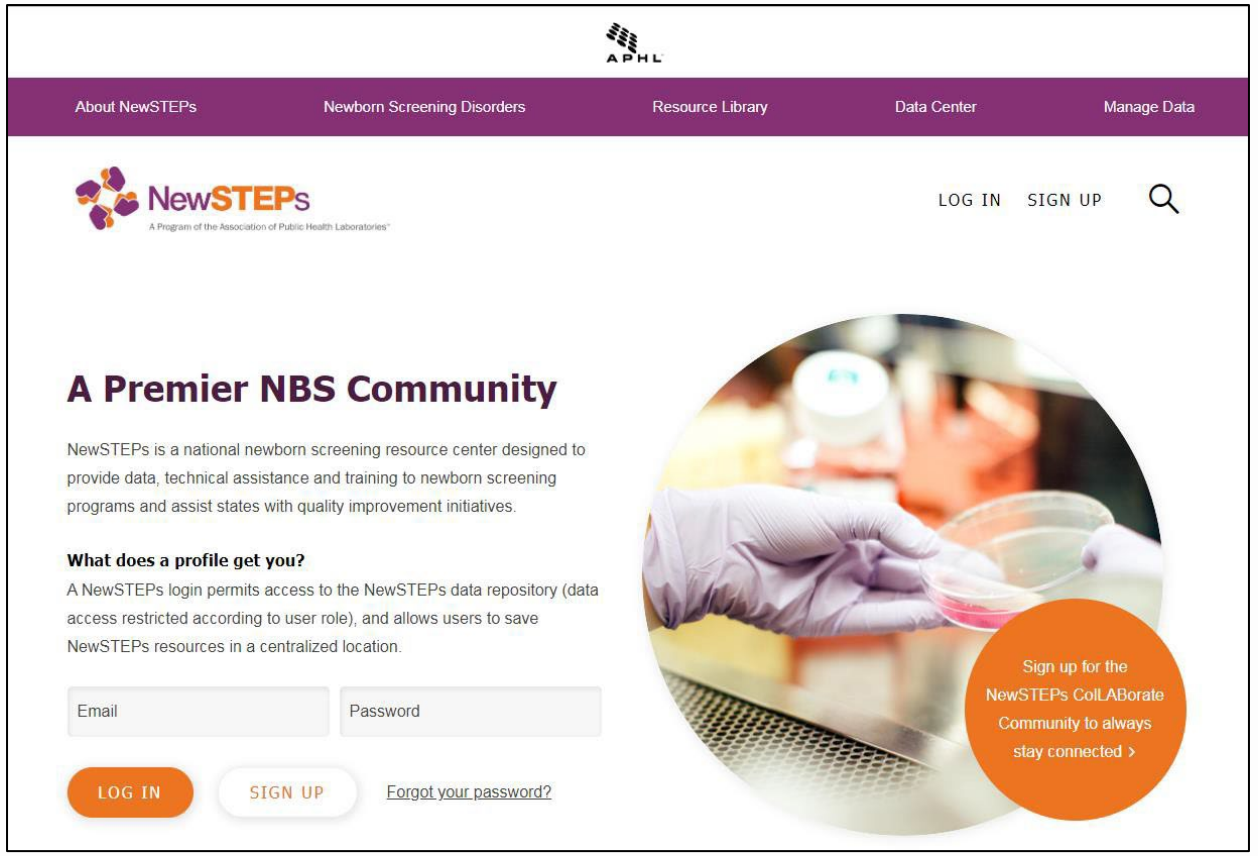
NewSTEPs: Role in Quality Improvement



https://www.newsteps.org/

APHL

https://www.aphl.org/

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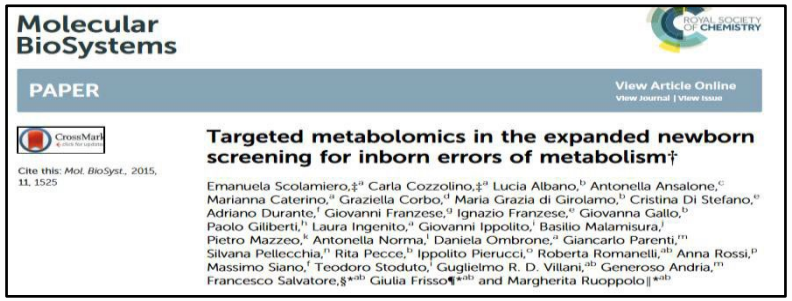
Future of Newborn Screening

Use of metabolomics to identify inborn errors of metabolism



Molecular BioSystems

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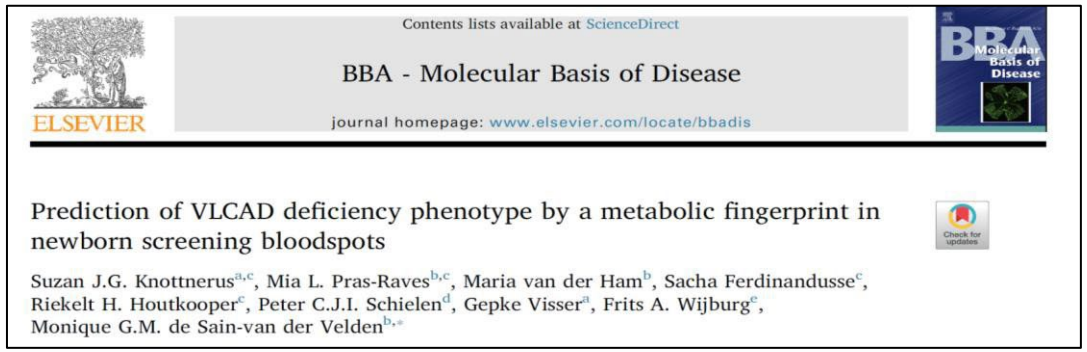
Targeted metabolomics in the expanded newborn screening for inborn errors of metabolism†

Cite this: *Mol. BioSyst.*, 2015, 11, 1525

Emanuela Scolamiero,‡[a] Carla Cozzolino,‡[a] Lucia Albano,[b] Antonella Ansalone,[c] Marianna Caterino,[a] Graziella Corbo,[d] Maria Grazia di Girolamo,[b] Cristina Di Stefano,[e] Adriano Durante,[f] Giovanni Franzese,[g] Ignazio Franzese,[e] Giovanna Gallo,[b] Paolo Giliberti,[h] Laura Ingenito,[a] Giovanni Ippolito,[i] Basilio Malamisura,[j] Pietro Mazzeo,[k] Antonella Norma,[l] Daniela Ombrone,[a] Giancarlo Parenti,[m] Silvana Pellecchia,[n] Rita Pecce,[b] Ippolito Pierucci,[o] Roberta Romanelli,[ab] Anna Rossi,[p] Massimo Siano,[f] Teodoro Stoduto,[i] Guglielmo R. D. Villani,[ab] Generoso Andria,[m] Francesco Salvatore,§*[ab] Giulia Frisso¶*[ab] and Margherita Ruoppolo‖*[ab]

Use of metabolomics to identify biomarkers of disease and predict clinical phenotype



Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

ELSEVIER

Prediction of VLCAD deficiency phenotype by a metabolic fingerprint in newborn screening bloodspots

Suzan J.G. Knottnerus[a,c], Mia L. Pras-Raves[b,c], Maria van der Ham[b], Sacha Ferdinandusse[c], Riekelt H. Houtkooper[c], Peter C.J.I. Schielen[d], Gepke Visser[a], Frits A. Wijburg[c], Monique G.M. de Sain-van der Velden[b,*]

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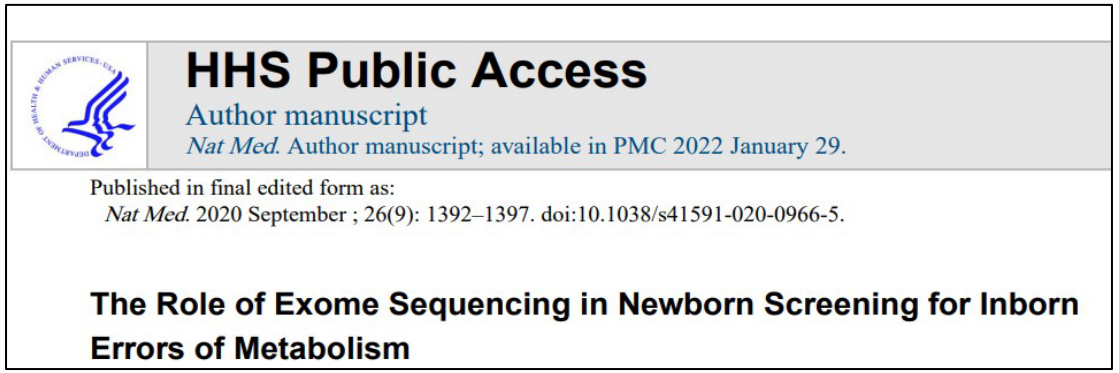
La Marca et al., Int. J. Neonatal Screen. 2023, 9, 15

Future of Newborn Screening

Use of whole exome (or genome) sequencing to identify conditions in newborns



HHS Public Access

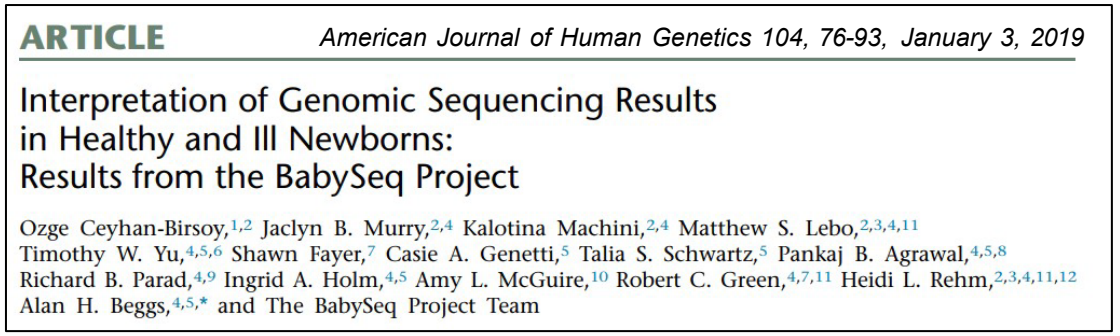
Author manuscript

Nat Med. Author manuscript; available in PMC 2022 January 29.

Published in final edited form as:

Nat Med. 2020 September ; 26(9): 1392–1397. doi:10.1038/s41591-020-0966-5.

The Role of Exome Sequencing in Newborn Screening for Inborn Errors of Metabolism



ARTICLE *American Journal of Human Genetics 104, 76-93, January 3, 2019*

Interpretation of Genomic Sequencing Results in Healthy and Ill Newborns: Results from the BabySeq Project

Ozge Ceyhan-Birsoy,[1,2] Jaclyn B. Murry,[2,4] Kalotina Machini,[2,4] Matthew S. Lebo,[2,3,4,11] Timothy W. Yu,[4,5,6] Shawn Fayer,[7] Casie A. Genetti,[5] Talia S. Schwartz,[5] Pankaj B. Agrawal,[4,5,8] Richard B. Parad,[4,9] Ingrid A. Holm,[4,5] Amy L. McGuire,[10] Robert C. Green,[4,7,11] Heidi L. Rehm,[2,3,4,11,12] Alan H. Beggs,[4,5,*] and The BabySeq Project Team

La Marca et al., Int. J. Neonatal Screen. 2023, 9, 15.
Watson et al., Int. J. Neonatal Screen. 2022, 8, 41.

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Newborn Screening Future Considerations

Continual request to add conditions to the panel

- Is our program infrastructure able to handle additional conditions?

Impact of new molecular technologies

- Carrier detection
- Variants of unknown significance
- How/When to provide information to physicians and parents on results

Consent for Newborn Screening

- Is "opt out" an adequate form of consent?

Storage and Use of Dried Blood Spots for Research

- What are the appropriate uses of the DBS and data?

Questions?

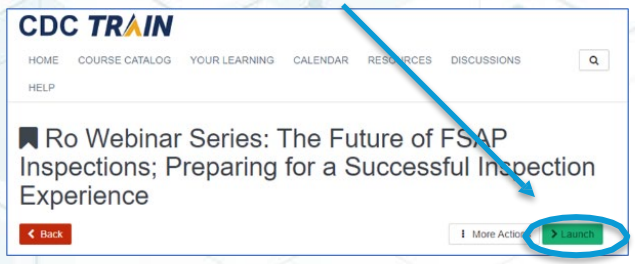
- Things that have evolved
- Number of conditions
- From a laboratory testing to a system
- Recognized timeliness of NBS
- **NBS is Equity Focused**
- **Improvements in testing by addition of tiers (biochemical / molecular)**

Continuing Education

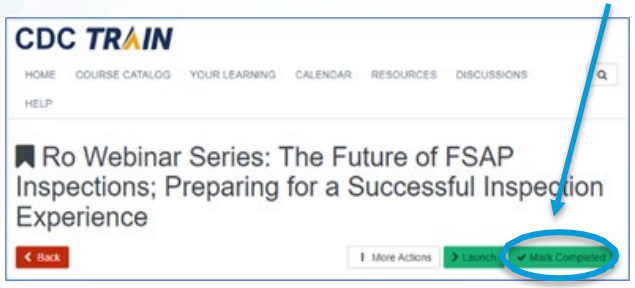
In order to receive continuing education credits, you must:

1. **Attend** entire webinar/**register** for course on TRAIN
   - Register for the course in TRAIN
   - Registration passcode: **V238**
   - Select **"PACE"** credit type

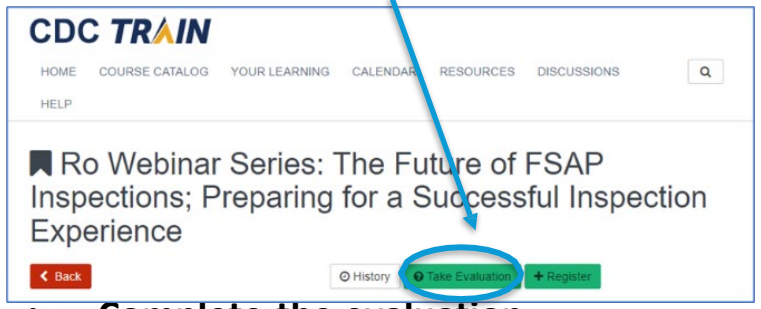
   - Click "**Launch**"



   - Click on green **"Mark Complete"**

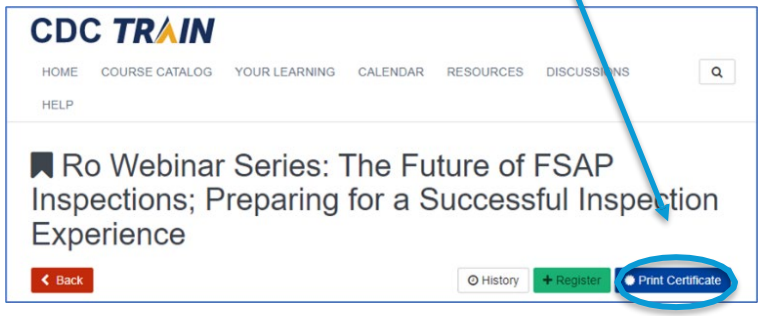


2. **Complete** webinar evaluation
   - Click green **"Take Evaluation"** button



   - **Complete the evaluation**

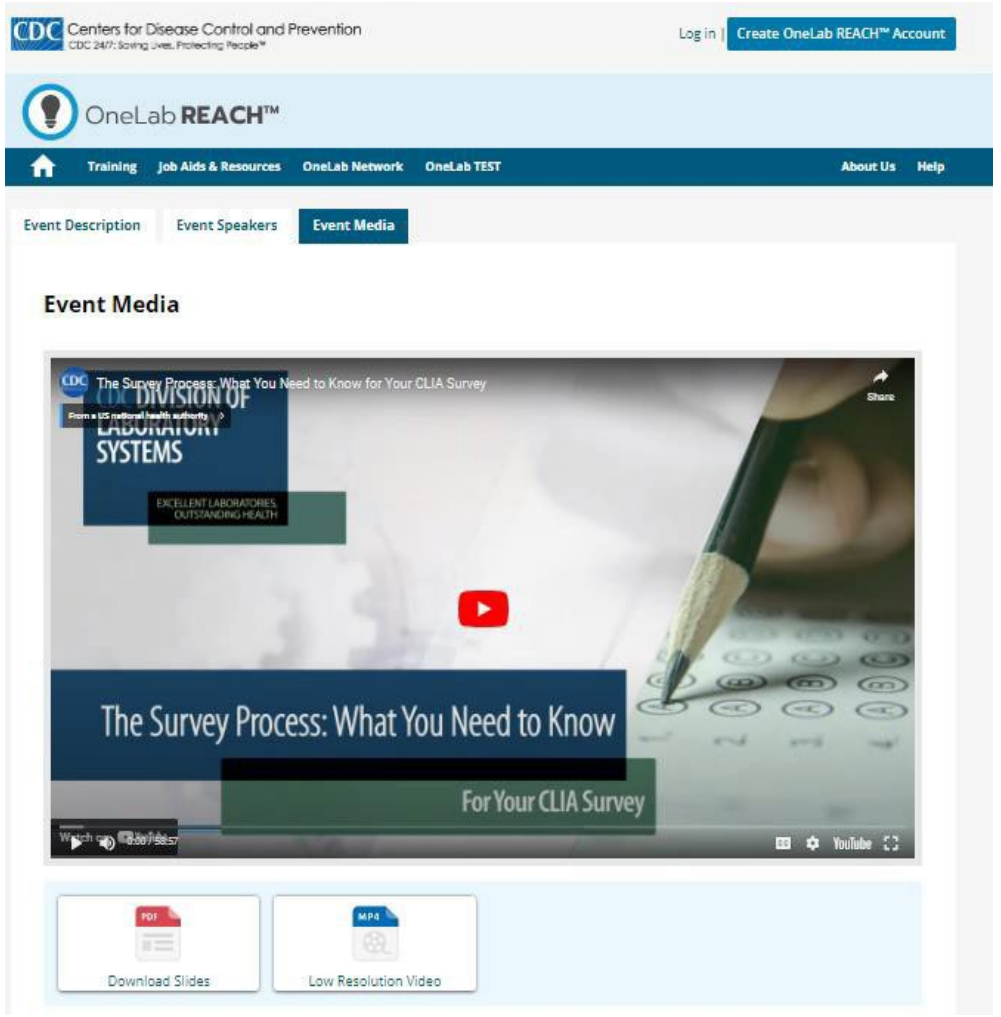
3. **Obtain** P.A.C.E Certificate
   - Click on the blue **"Print Certificate"** button to download



Previous OneLab Network Event Videos* now LIVE!

To access previous event videos:

1. Visit reach.cdc.gov/onelabnetwork/events/past-events page
2. Choose which webinar you would like to watch by clicking on the event title
3. Select the "Event Media" tab



*April and May 2023 videos coming soon!

Upcoming OneLab Events

OneLab Network:

September 7, 2023- CMS Proficiency Testing (PT) Final Rule, CMS-3355-F

September 26, 2023- How Clinical and Public Health Laboratory Professionals Should Plan for Possible B. pseudomallei Exposure and Cases

OneLab Summit 2023:

October 3-5, 2023- "Thrive: People. Planning. Preparedness

Registration details coming soon!