Newborn screening today: A dynamic application of precision public health

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Disclosures

- Speaking honorariums received from Takeda, Spark Therapeutics, Orchard Therapeutics, and Worldwide Clinical Trials.

Very brief background on newborn screening

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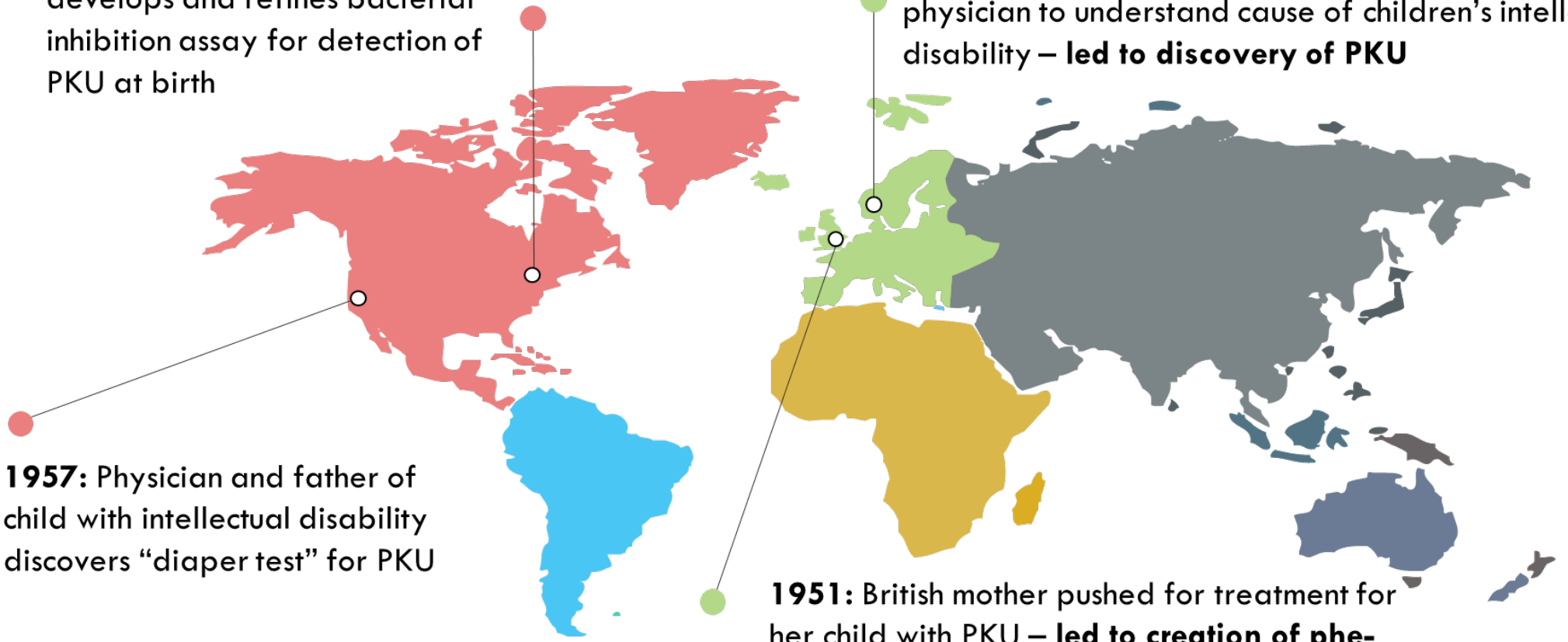
Newborn screening and the role of advocacy

1958-61: Dr. Robert Guthrie develops and refines bacterial inhibition assay for detection of PKU at birth

1934: Norwegian mother relentlessly pushed her physician to understand cause of children's intellectual disability – **led to discovery of PKU**



1957: Physician and father of child with intellectual disability discovers "diaper test" for PKU

1951: British mother pushed for treatment for her child with PKU – **led to creation of phe-free formula**

Wilson and Jungner Criteria

1. Important health problem
2. Accepted treatment
3. Available centers for diagnosis and treatment
4. Recognizable latent or early symptomatic stage
5. Suitable test or examination
6. Acceptable to the population
7. Natural history should be understood
8. Agreed policy on whom to treat
9. Cost of screening/diagnosis/treatment should be weighed against possible expenditure on medical care
10. Case-finding should be a continuing process and not "once and for all"

Newborn screening: Four Key Points

Newborn Screening Programs are PUBLIC HEALTH programs

Successful programs require knowledge and coordination from multiple partners.

Newborn screening Programs are STATE-BASED

Variations between Newborn Screening Programs exist from state-to-state.

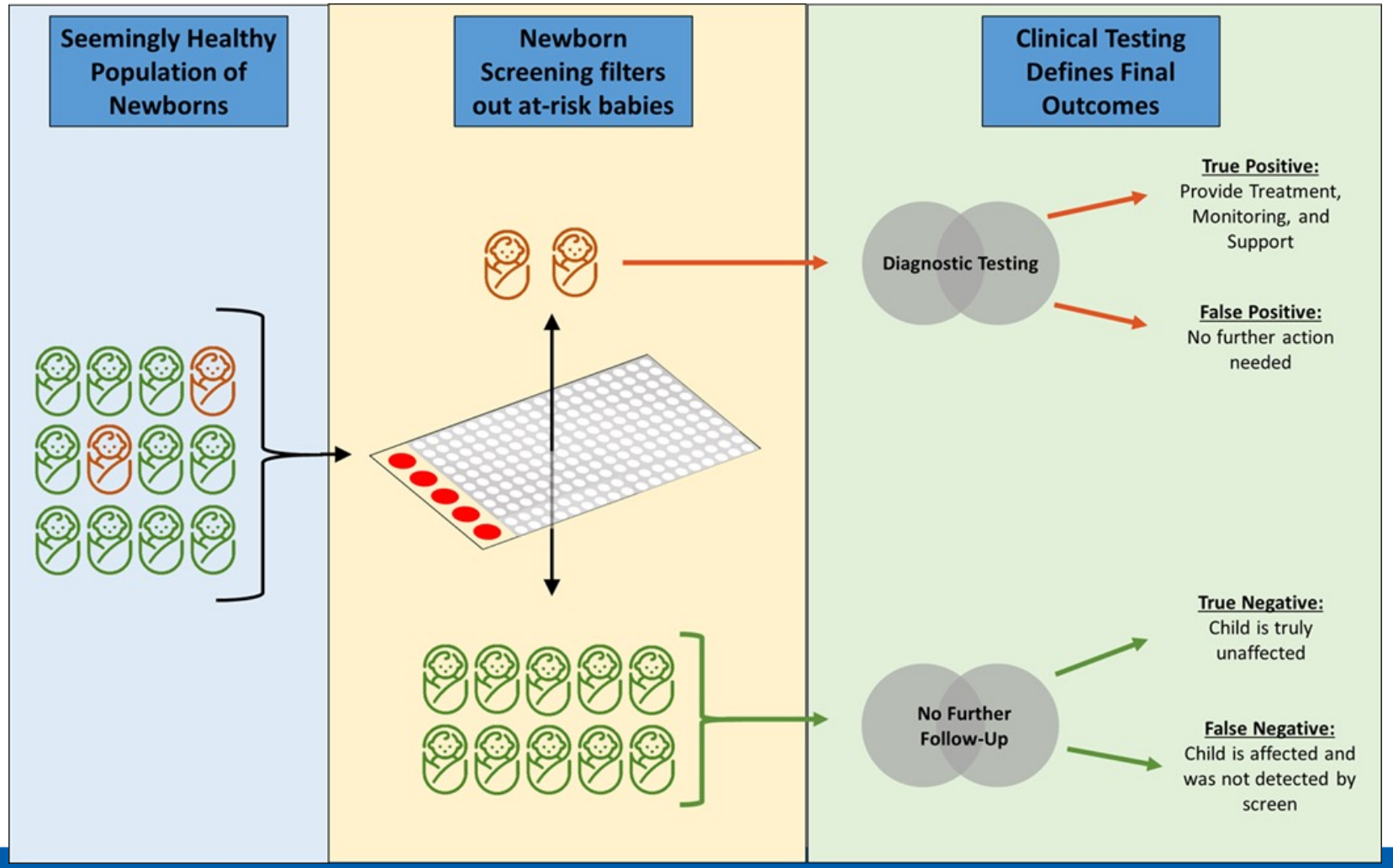
Newborn Screening Programs are OPT-OUT programs

Default is for NBS to occur; relies on legal doctrine known as *parens patriae*.

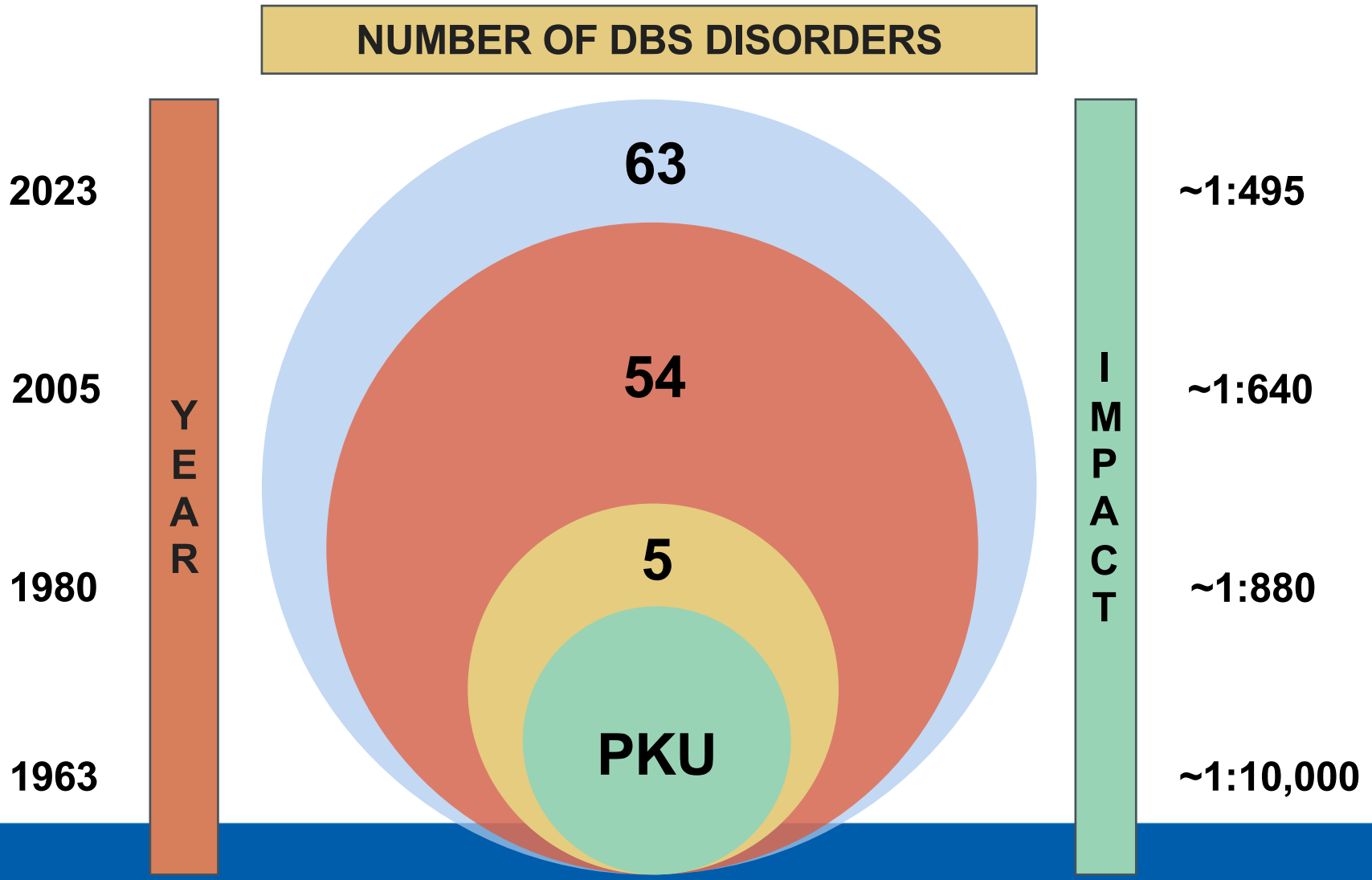
Newborn Screening Programs are designed to detect TREATABLE conditions

Disorders on the newborn screening panel must meet certain criteria

Newborn screening as a risk assessment



Expansion of newborn screening panels



Technological and Therapeutic Advances

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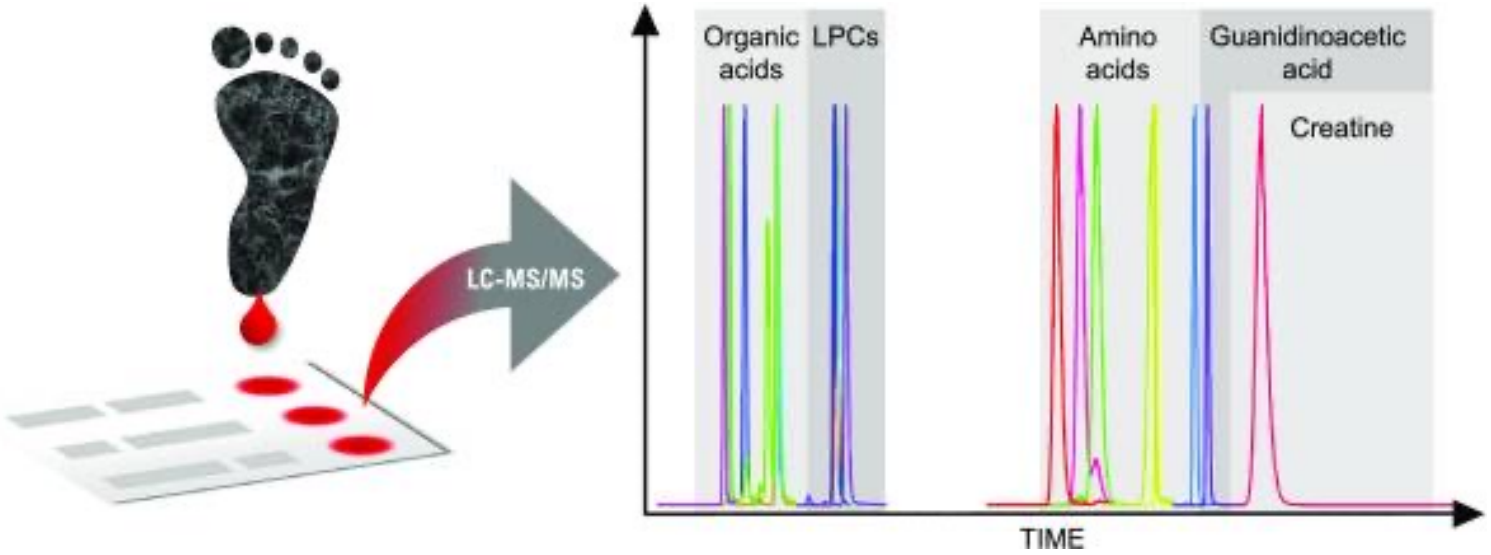
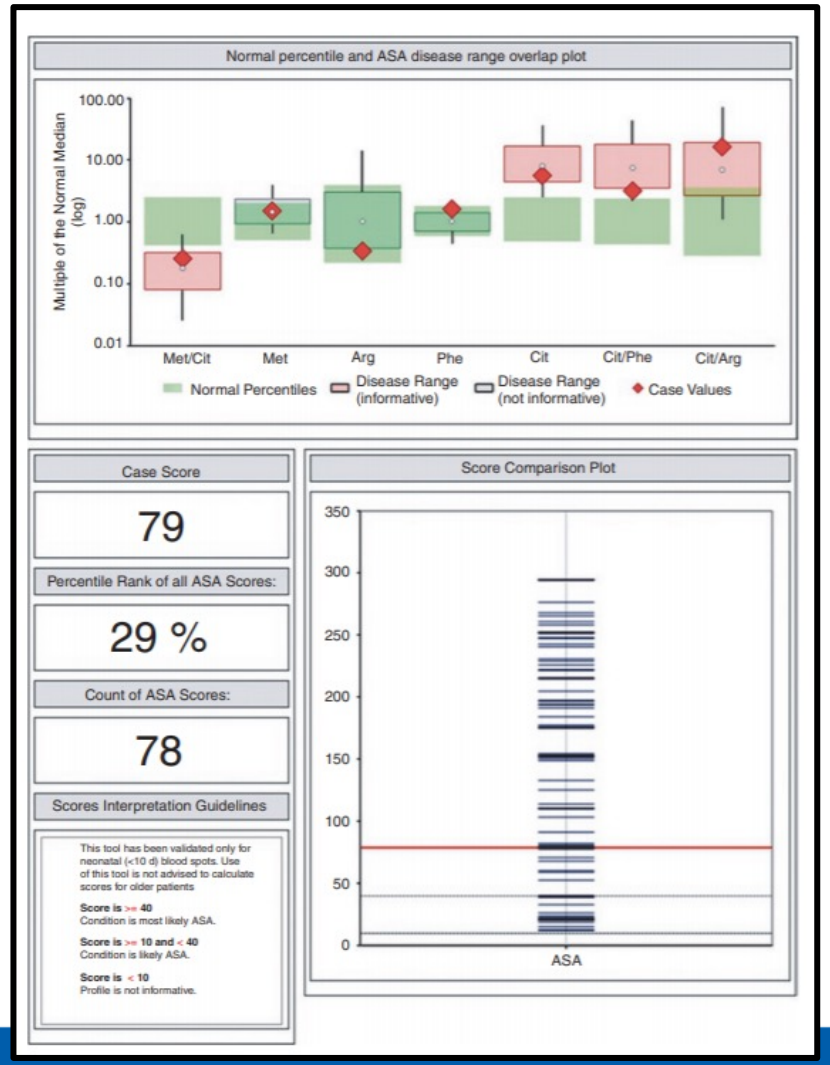
Biochemical Advancements: LC-MS/MS

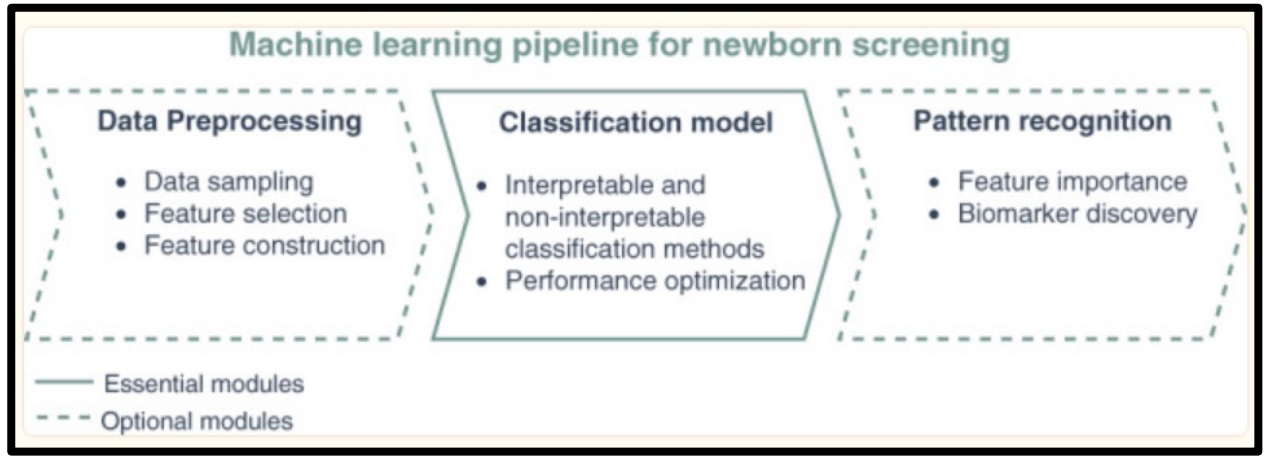
- **More and more programs are utilizing second-tier screening biochemical assays**
  - Often employing separations such as liquid chromatography–mass spectrometry (LC–MS/MS)
- **Use of second-tier assays increases test specificity and drastically reduces false positive results.**

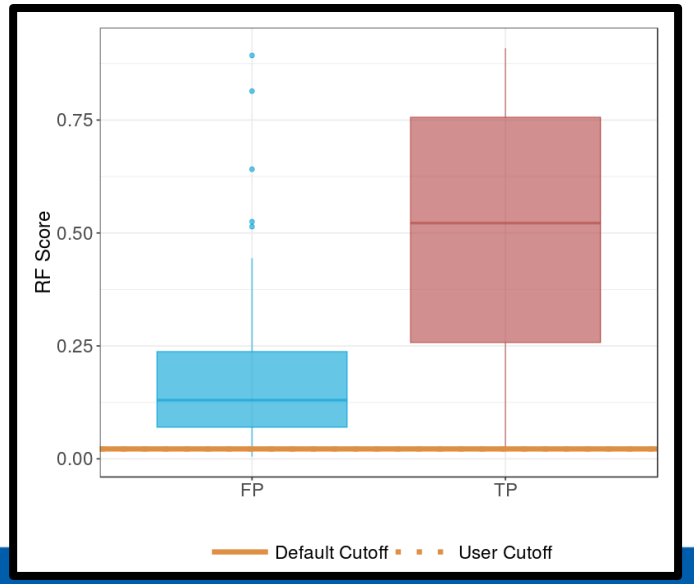


Kilgore, Matthew B et al. "Development of a Universal Second-Tier Newborn Screening LC-MS/MS Method for Amino Acids, Lysophosphatidylcholines, and Organic Acids." *Analytical chemistry* vol. 95,6 (2023): 3187-3194.

Biochemical Advancements: Machine Learning







https://clir.mayo.edu/
https://rusptools.shinyapps.io/RandomForest/

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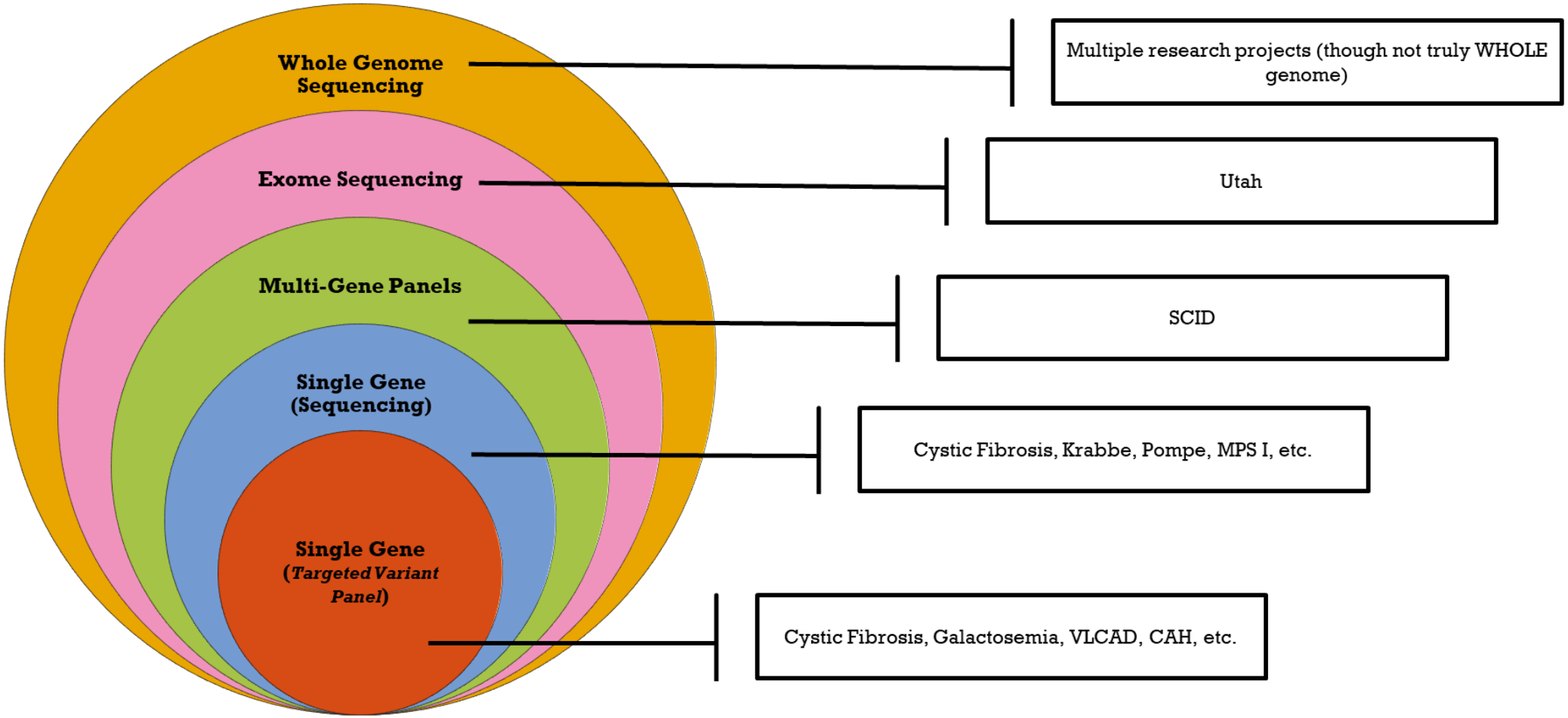
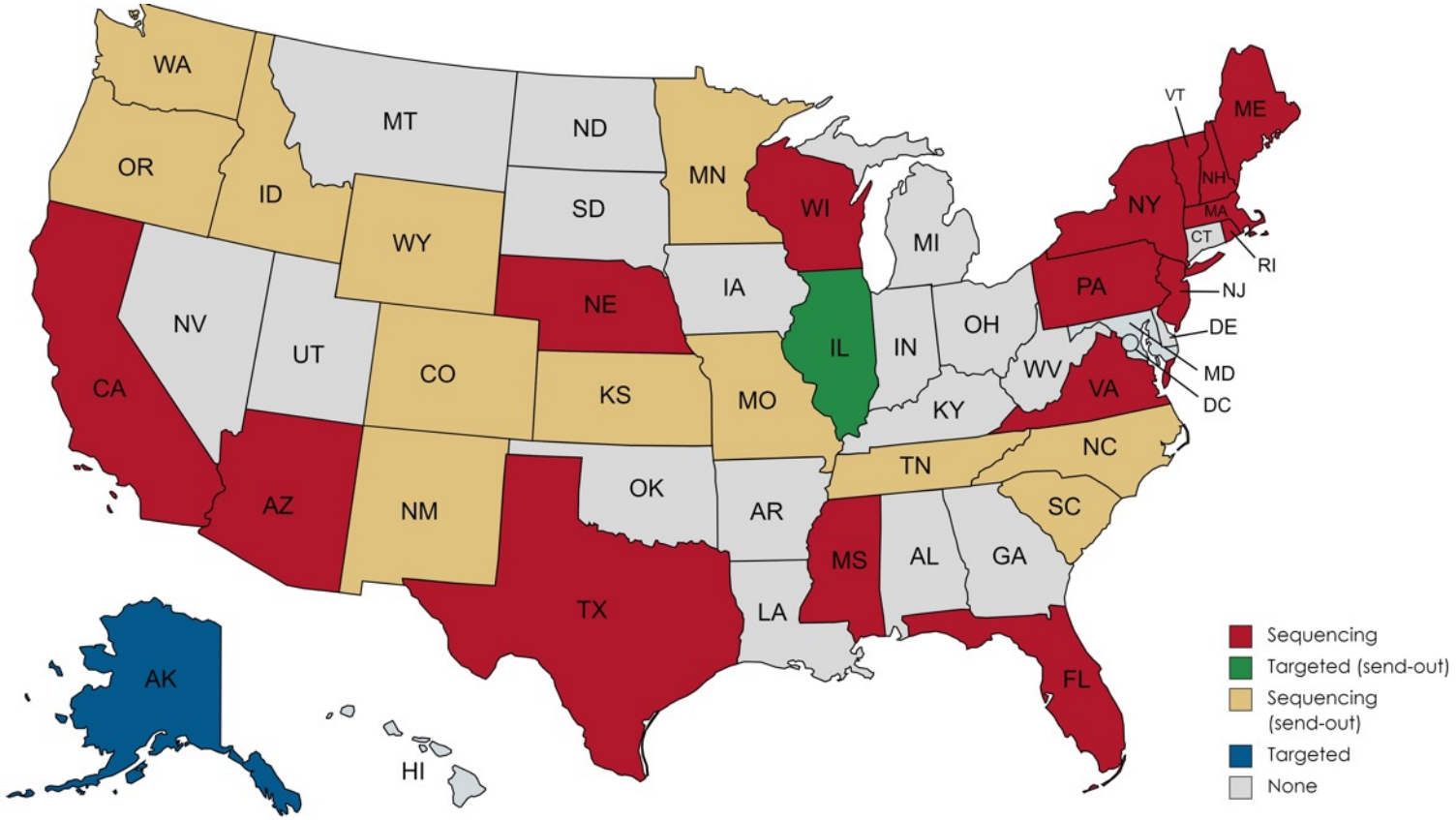
Molecular advancements



Note: TREC and *SMN1* analysis not included here owing to use of RT-PCR rather than sequencing

US Programs performing *reflexed* genetic analysis



Includes 'just-in-time' testing; excludes pilot studies

ES: Exome sequencing planned;
GS: Genome sequencing planned (2024)

Adopted from Denise Kay, NYS Program
Source: NewSTEPs repository (2022) and personal communications (2023)

* Not including CF or SMA

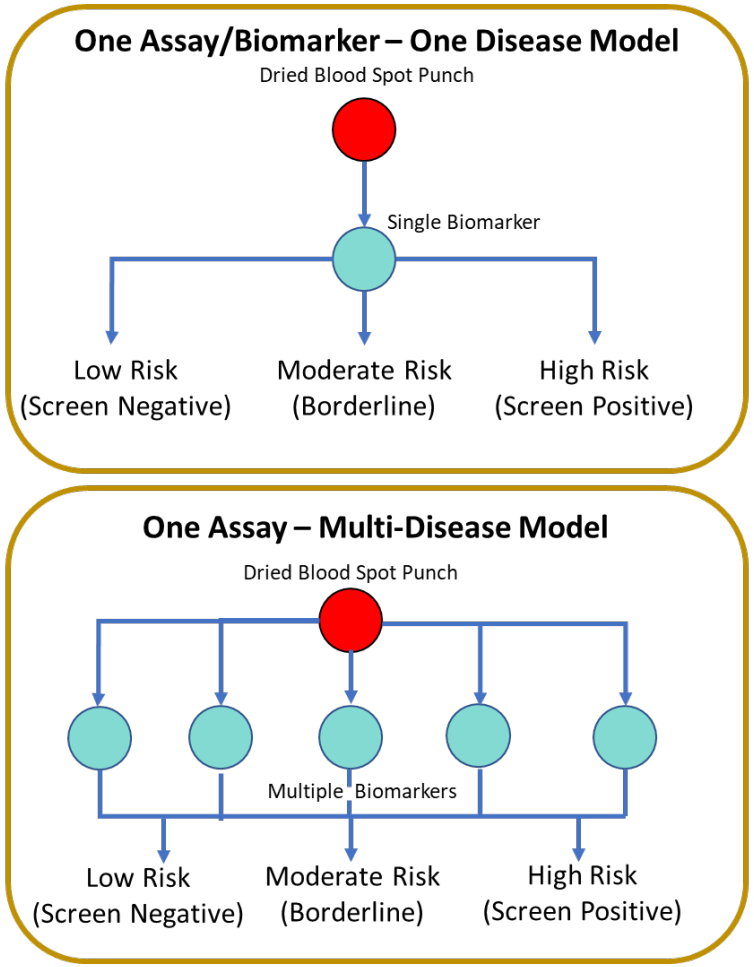
Identified considerations in the use of genetic analysis in newborn screening

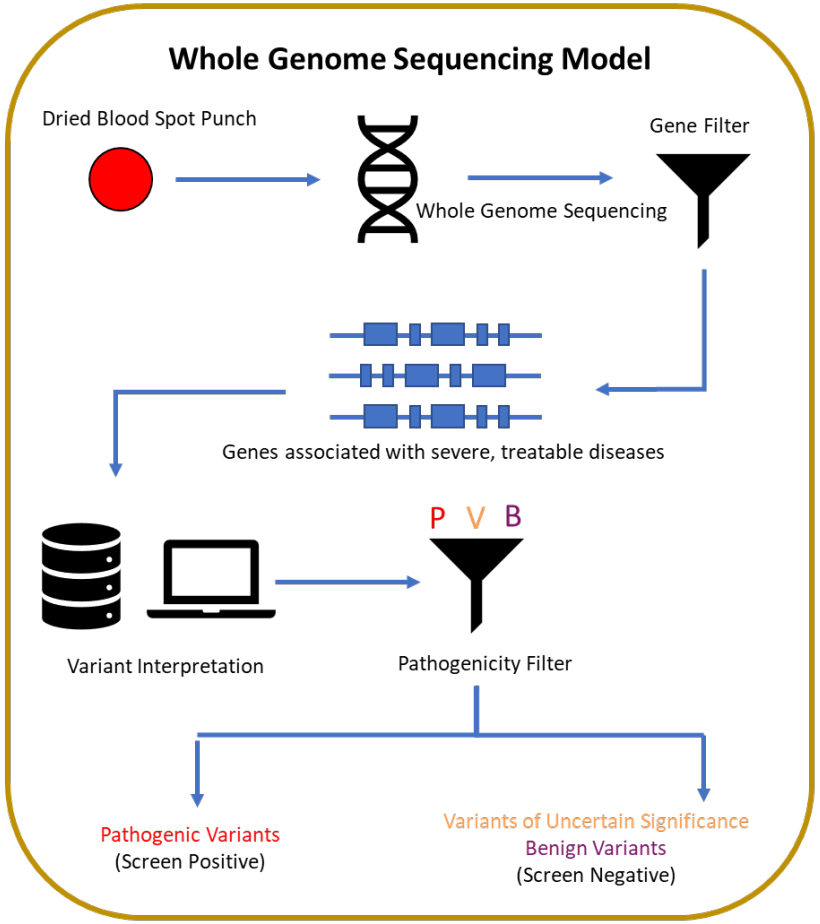
- **Infrastructure**
- **Cost**
- **Test availability**
- **Variants of uncertain significance (VUS), reduced penetrance, variable or age-dependent expressivity**
  - California = 41% VUS findings for XALD
  - New York = CRMS to CF ratio of 2.9:1
- **Delay in results (decision-making vs. just-in-time)**
- **Screening vs. diagnostic testing**

Genomic sequencing in newborns

- **Increased integration of genomics into NBS**
  - Adjunct screen
  - Replacement technology
- **Potential deluge of complex genomic information**
  - Incidental or secondary findings
  - Increased uncertainty
- **Need to revisit consent and educational frameworks**

Is genomic analysis just another disruptive technology?





Vockley J, Defay T, Goldenberg AJ, Gaviglio AM. Scaling genetic resources: New paradigms for diagnosis and treatment of rare genetic disease. *Am J Med Genet C Semin Med Genet*. 2023;193(1):77-86.

Challenges & opportunities in precision public health through newborn screening

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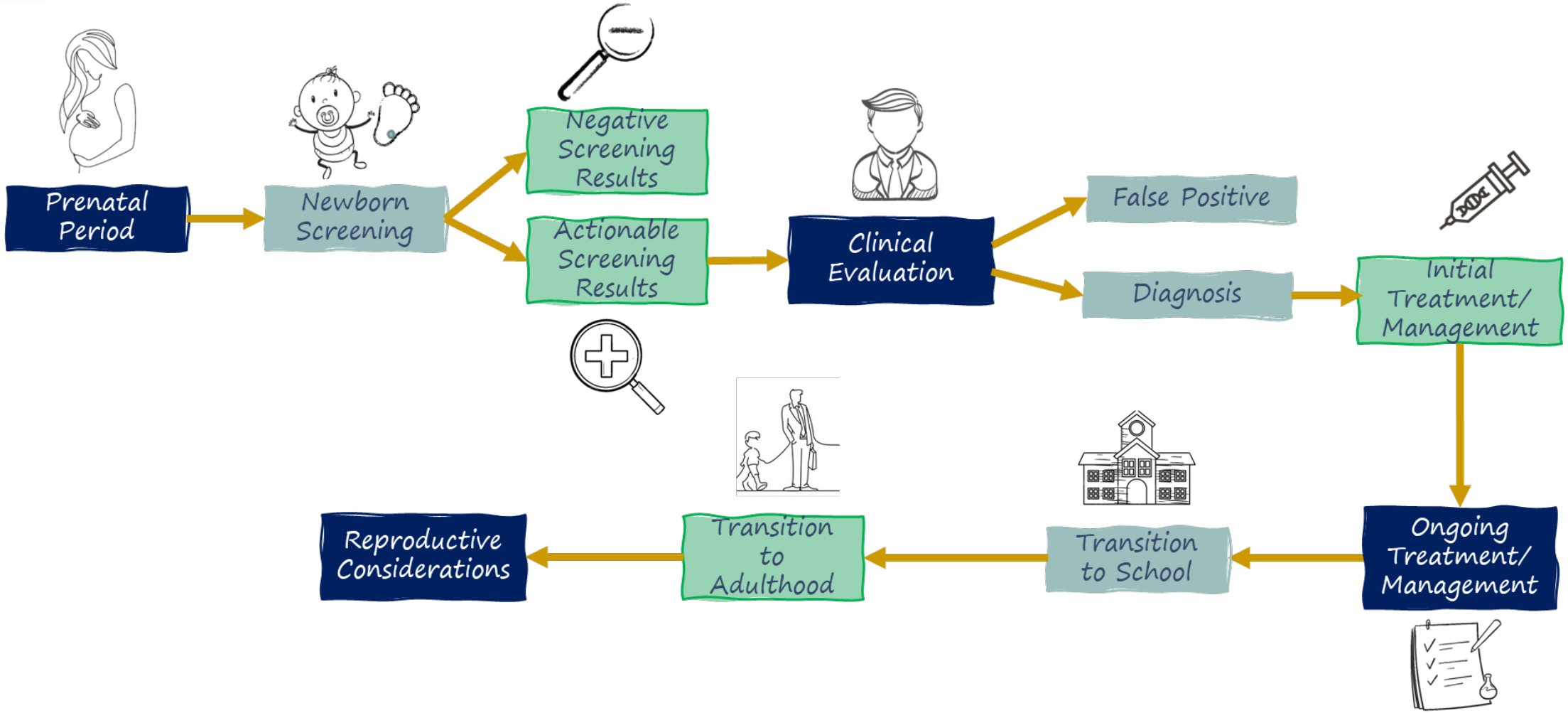
The newborn screening journey



So much more than a test…

"Discovering a condition in the newborn period is not sufficient to eliminate disparities in outcomes…

As NBS programs evolve, we must ensure that they continue to reduce the persistent health disparities among historically underserved populations."

Timeliness by race (cystic fibrosis): birth to diagnosis

Race (median; IQR)	Native American	Islander	Asian	White	Other/Mixed	Black/African American
Native American (22; 18)						
Islander (19; 20)	ns					
Asian (71.5; 176.5)	*	*				
White (29; 42)	ns	ns	*			
Other/Mixed (50; 81)	ns	ns	*	*		
Black/African American (41; 62)	*	ns	*	*	ns	

ns = not significant

TAKE AWAY: BLACK/AFRICAN AMERICAN, OTHER, and ASIAN BABIES HAVE LONGER TIMES TO DIAGNOSIS THAN WHITE BABIES

Asterisks (*) indicate significant differences ($p < 0.05$) between reported racial categories. Conducted by Kruskal-Wallis/post-hoc Dunn.

Timeliness by race (cystic fibrosis): birth to intervention

Race (median; IQR)	Native American	Islander	Asian	White	Other/Mixed	Black/African American
Native American (15; 13)						
Islander (16; 7)	ns					
Asian (36; 27.5)	*	*				
White (17; 18)	ns	ns	*			
Other/Mixed (29; 47)	*	*	ns	*		
Black/African American (21; 24)	ns	ns	*	*	*	

ns = not significant

TAKE AWAY: BLACK/AFRICAN AMERICAN, OTHER, and ASIAN BABIES HAVE LONGER TIMES TO INTERVENTION THAN WHITE BABIES

Asterisks (*) indicate significant differences ($p < 0.05$) between reported racial categories. Conducted by Kruskal-Wallis/post-hoc Dunn.

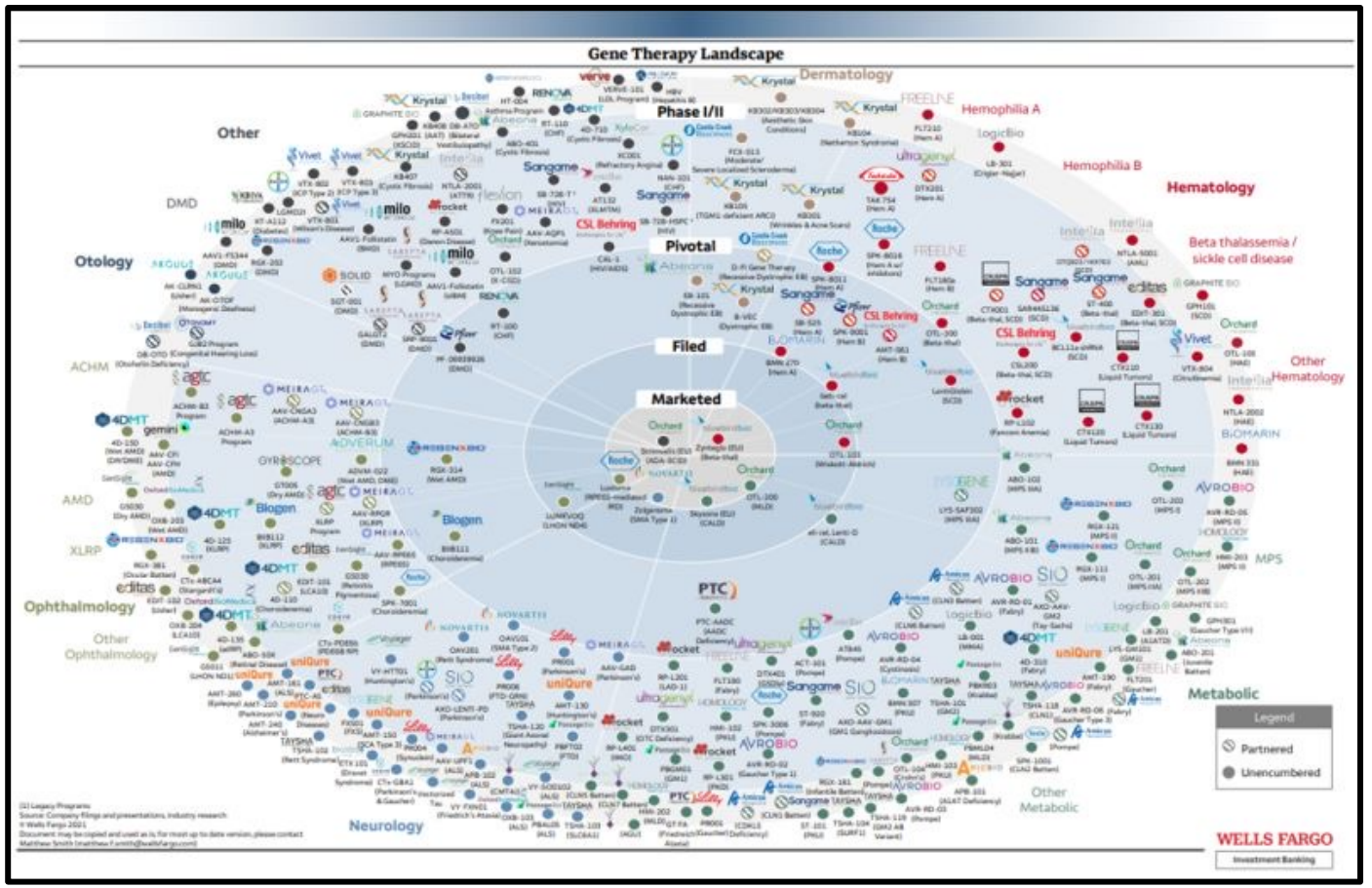
Can newborn screening respond to increased therapeutic availability?

The FDA Predicts…

By 2025

10-20

Gene and cell therapy approvals per year



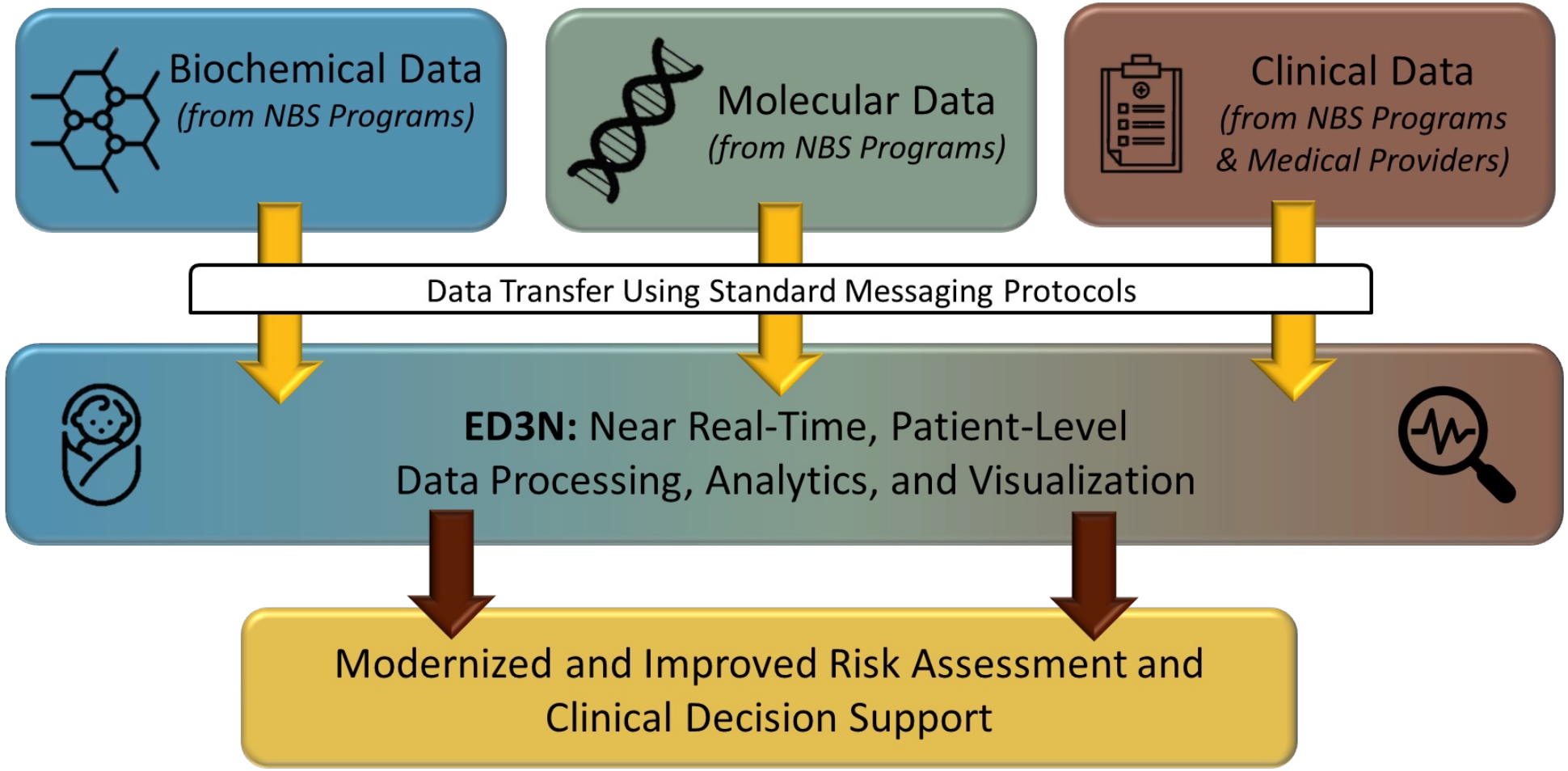
Are we leveraging data to improve understanding and outcomes?

- **Newborn Screening generates A LOT of data**
  - ~4,000,000 babies each year X 100+ data points = approaching BIG DATA
  - NBS Programs remain largely siloed from other public health programs

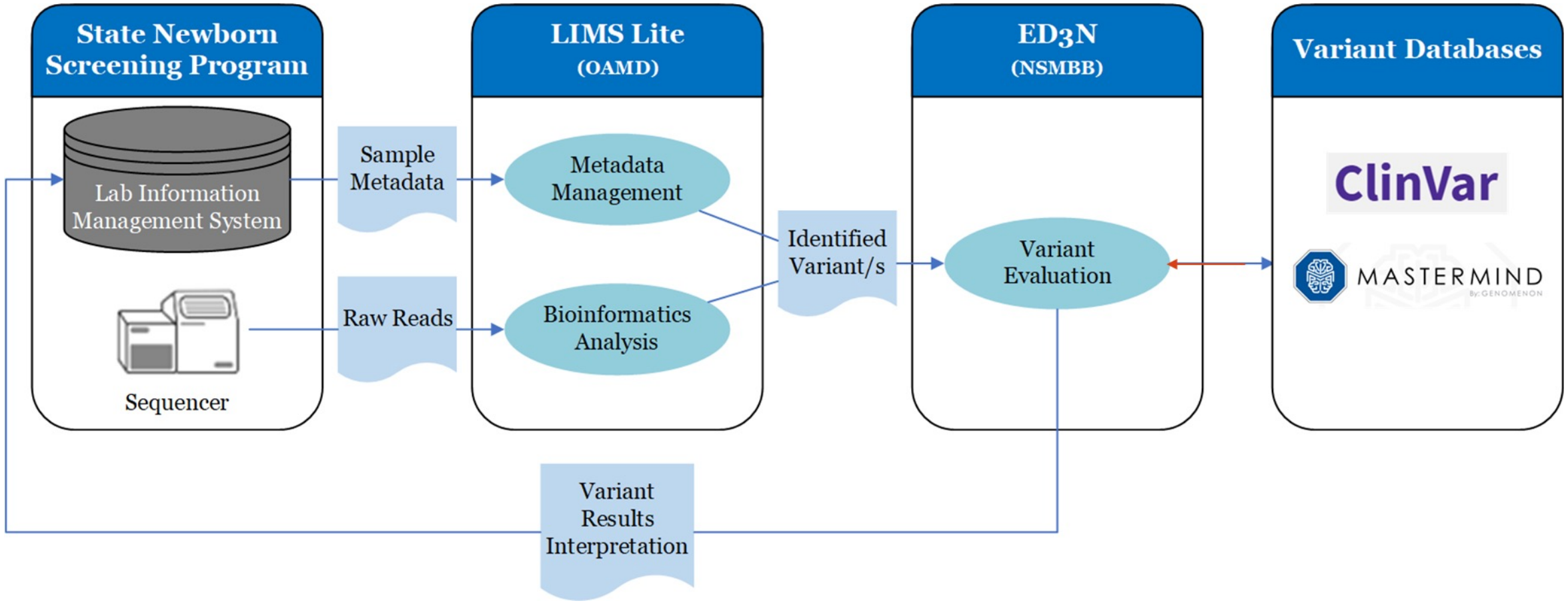
- **These data can be used to:**
  - Assess better ways to detect at-risk newborns through screening
  - Identify novel biomarkers/analyte ratios
  - Assess natural history, outcomes, and disparities

- **BUT** – rarity of many of the diseases within one state necessitates aggregation of data to accomplish the above analyses

CDC NSMBB ED3N Project

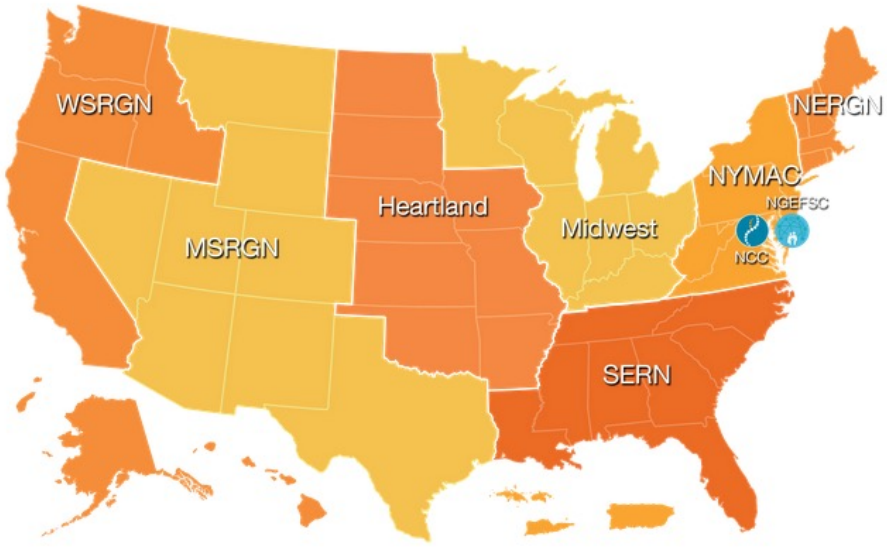


Molecular end-to-end solution within ED3N



Should newborn screening continue to be state-based?

- System of 'Haves' and 'Have Nots' between State Programs
- Despite RUSP, each state still has to go through own approval and implementation process
- Increasingly complexity of testing, and more importantly, interpretation is stretching current resources
- Emergency preparedness and back-up opportunities



Are new criteria needed in a genomic era?

Wilson & Jungner Criteria

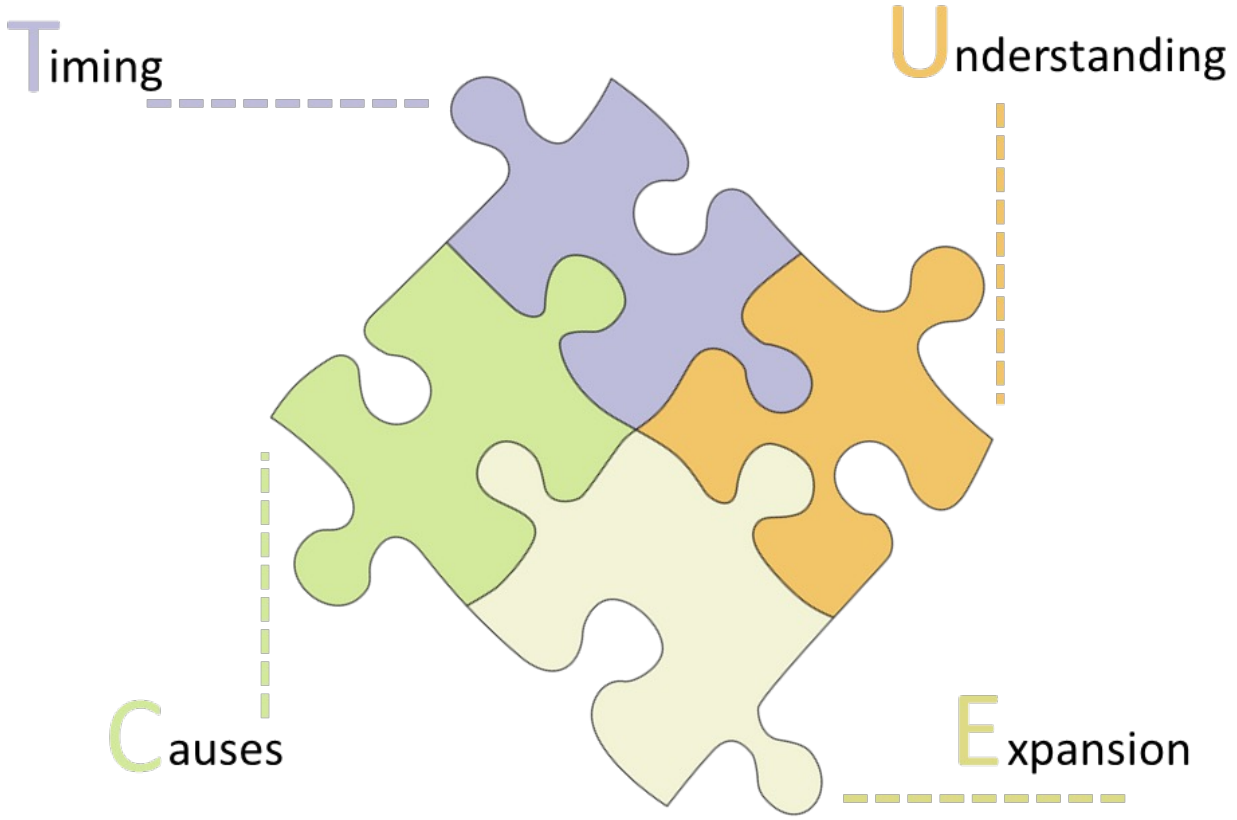
- Treatable illness
- Detectable in newborn period
- Presymptomatic initiation of treatment is beneficial
- Available resources for diagnosis/treatment/follow-up
- Availability of a simple method for sample collection
- Evidence of substantial public benefit & acceptance
- Suitable and simple test methods
- Acceptable costs

Proposed Criteria in Genomics Era

- Responsive to recognized need
- Objectives of screening defined at outset
- Defined target population
- Integration of education, testing, clinical services, and program management
- Quality assurance with mechanisms to minimize risks
- Equity and access should be promoted
- Program evaluation should be planned from the beginning
- Overall benefits should outweigh the harms

Andermann A, Blancquaert I, Beauchamp S, Déry V. Revisiting Wilson and Jungner in the genomic age: a review of screening criteria over the past 40 years. *Bull World Health Organ*. 2008;86(4):317-319.

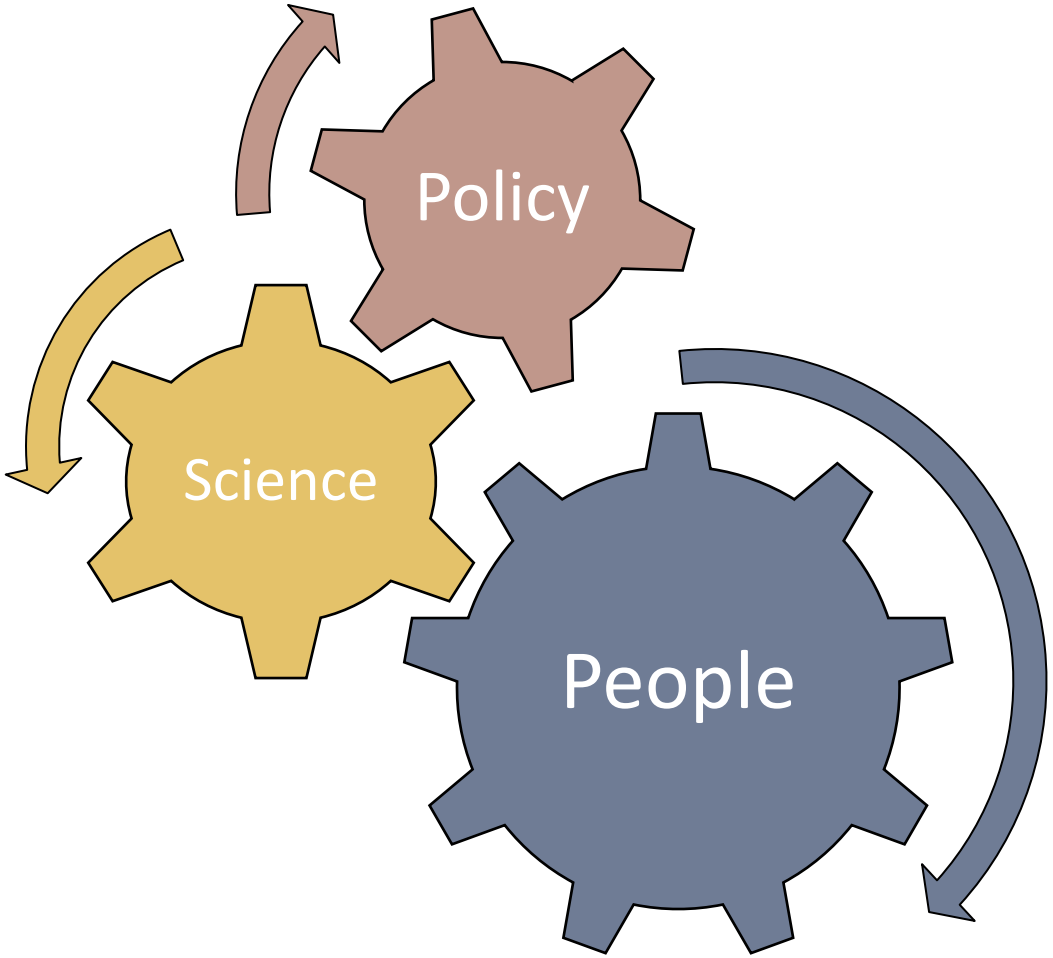
How do public health NBS and newborn sequencing co-exist?



- WGS (and sometimes even NBS) is not fast enough to obtain results prior to symptom onset
- Not all rare diseases are genetic or can be detected through WGS
- Biochemical and Molecular information often required for fuller understanding of disease
- Scope for potential screened diseases is wider with WGS

Foundational Concept: Universality ≠ Equity in Access or Outcomes

The future of newborn screening



- Integration of People, Science, and Policy will continue to be hallmark of NBS
- But… we need to heed past lessons and experiences
- Ongoing evolution and adaptation are critical
  - Must begin to address issues of expansion, variability, equity, and education

THANK YOU!

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