Development of the BEACONS-NBS condition list

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Disclosures

I have been a consultant for RCG Consulting and Guidepoint, LLC.

For the BEACONS study, GeneDx is providing in-kind whole genome sequencing and Illumina is providing sequencing reagents.

The NIH WGSxNBS request

"The overall purpose … is to assess the feasibility of a collaborative, multi-state model for newborn screening that would use whole genome sequencing as a first-tier screening assay for analysis on a ***select group of genetic conditions that are actionable in the first year of life****. … [The] early identification of individuals affected by these conditions holds immense potential for altering disease trajectories by initiating interventions before symptoms emerge or early in the disease course when those interventions are most likely to improve health outcomes."*

Wilson-Jungner criteria

The condition should be an important public health concern
There should be a treatment for the condition
Facilities for diagnosis and treatment should be available
There should be a latent stage of the disease
There should be a test or examination for the condition
The test should be acceptable to the population
The natural history of the disease should be adequately understood
There should be an agreed policy on who to treat
The total cost of finding a case should be economically balanced in relationship to medical expenditure as a whole
Case finding should be a continuous process, not a "once and for all" project

Wilson and Jungner, 1968

HRSA Recommended Uniform Screening Panel

Core

38

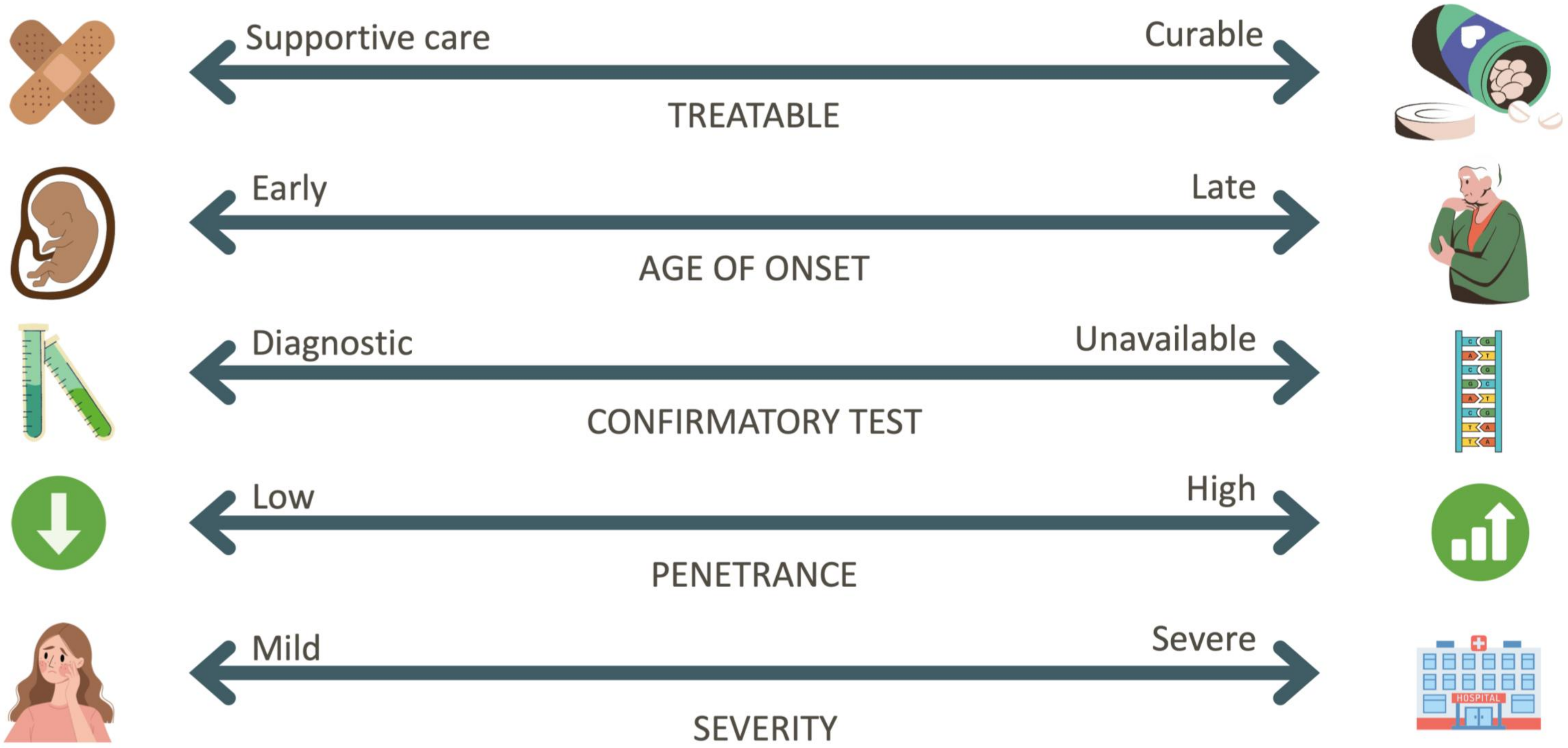
Secondary

26

Other treatable conditions

>1000?

Characteristics of genes and disorders to consider



A scientific *and* an ethical responsibility

What we've tried so far…

- Surveying clinical experts
- Interviewing parents
- Bioinformatically assessing other gNBS studies
- Designing a machine learning model
- Creating consensus guidelines

What is actionable?

Actionable is:

- A clinically-available treatment could meaningfully change medical care and substantially improve outcomes, including by avoiding harmful interventions (e.g., ionizing radiation, live vaccines)
- A surveillance strategy in the first year of life

Actionable is not *just*:

- Avoidance of a diagnostic odyssey
- Opportunities to participate in clinical trials
- Opportunities to begin Early Intervention
- Personal, family, psychosocial, and economic utility
- Information used for reproductive decision-making
- Information relevant to medical care for parents

BEACONS inclusion criteria for genetic conditions

1. Clinically-approved treatment or published surveillance guideline that could be initiated before one year of age and is expected to substantially reduce disease severity
2. Laboratory result, imaging finding, or physical sign that is expected to be present prior to the initiation of treatment; for conditions without a biomarker, surveillance or treatment should be considered low risk and potentially high benefit
3. Capacity for short-read whole genome sequencing (WGS) to reliably detect likely pathogenic or pathogenic variants

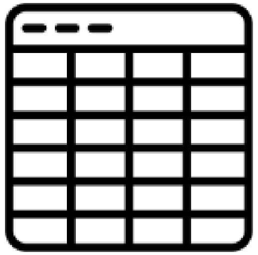
But what about…

- **Prevalence:** Not used to select conditions
- **Penetrance:** Not specifically emphasized, but some variants known to be of low penetrance were excluded
- **Variable age of onset:** Included conditions for which a severe infantile form is known, even if the onset may occur in early childhood or adolescence
- **X-linked variants:** Will report findings in chromosomal females when an actionable phenotype has been described

Where did we start?

1

Genes with treatment in first week of life



Pre-constructed list of treatable genes

Reviewed by clinical experts

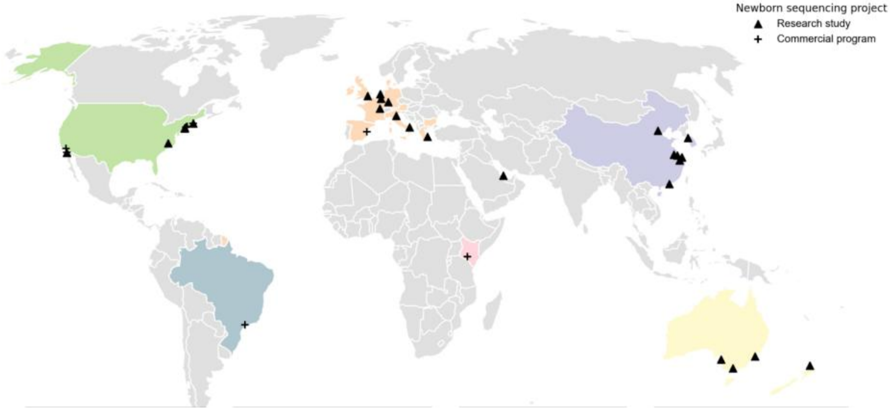
Standard of care therapies that could be applied if genetic diagnosis was known in week 1 of life (n = 267)

Cohen et al, AJHG, 2025

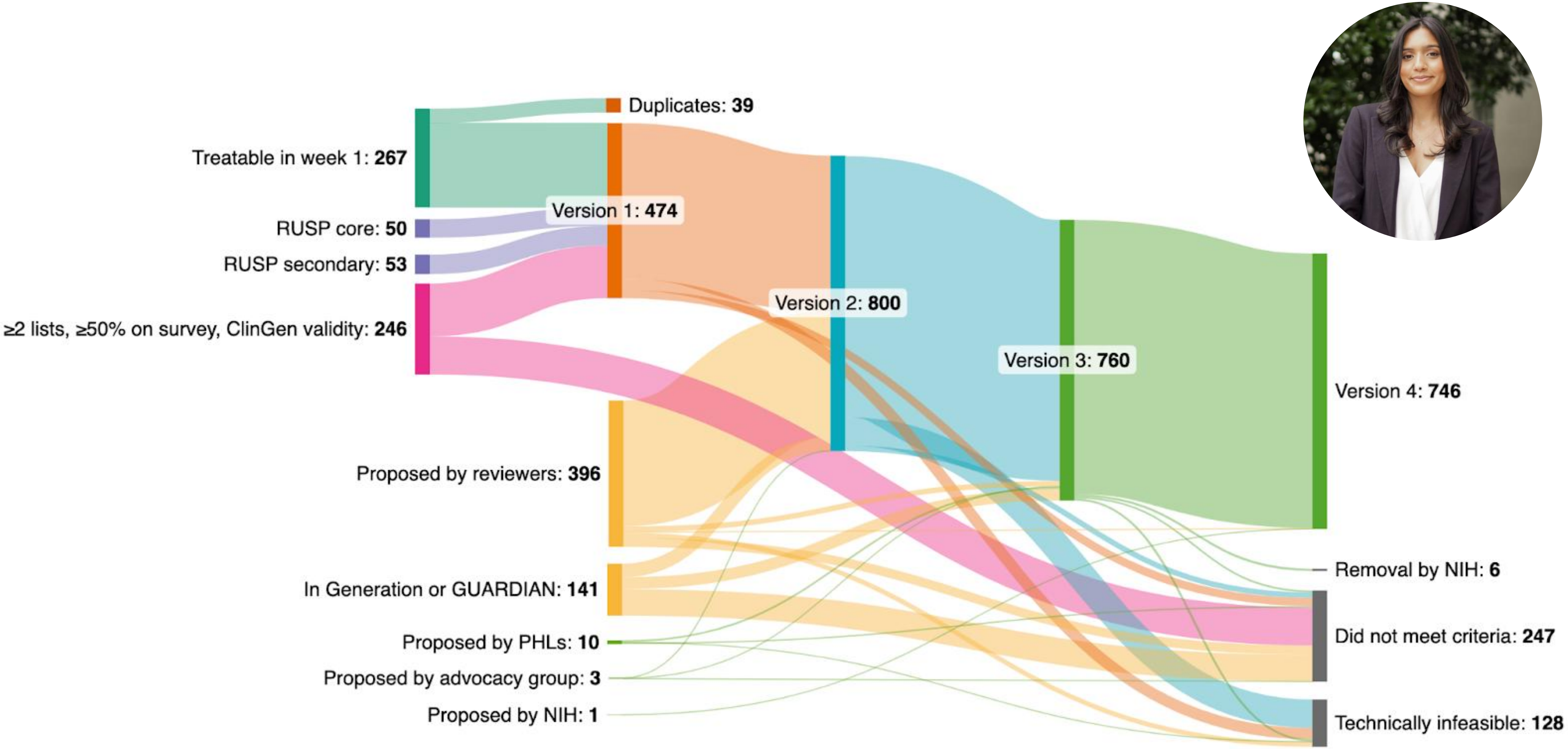
2

Core RUSP

3



ML algorithm based on prior studies & manually reviewed


Duplicates: 39
Treatable in week 1: 267
Version 1: 474
RUSP core: 50
RUSP secondary: 53
≥2 lists, ≥50% on survey, ClinGen validity: 246
Version 2: 800
Version 3: 760
Version 4: 746
Proposed by reviewers: 396
In Generation or GUARDIAN: 141
Proposed by PHLs: 10
Proposed by advocacy group: 3
Proposed by NIH: 1
Removal by NIH: 6
Did not meet criteria: 247
Technically infeasible: 128

The BEACONS list of genetic conditions

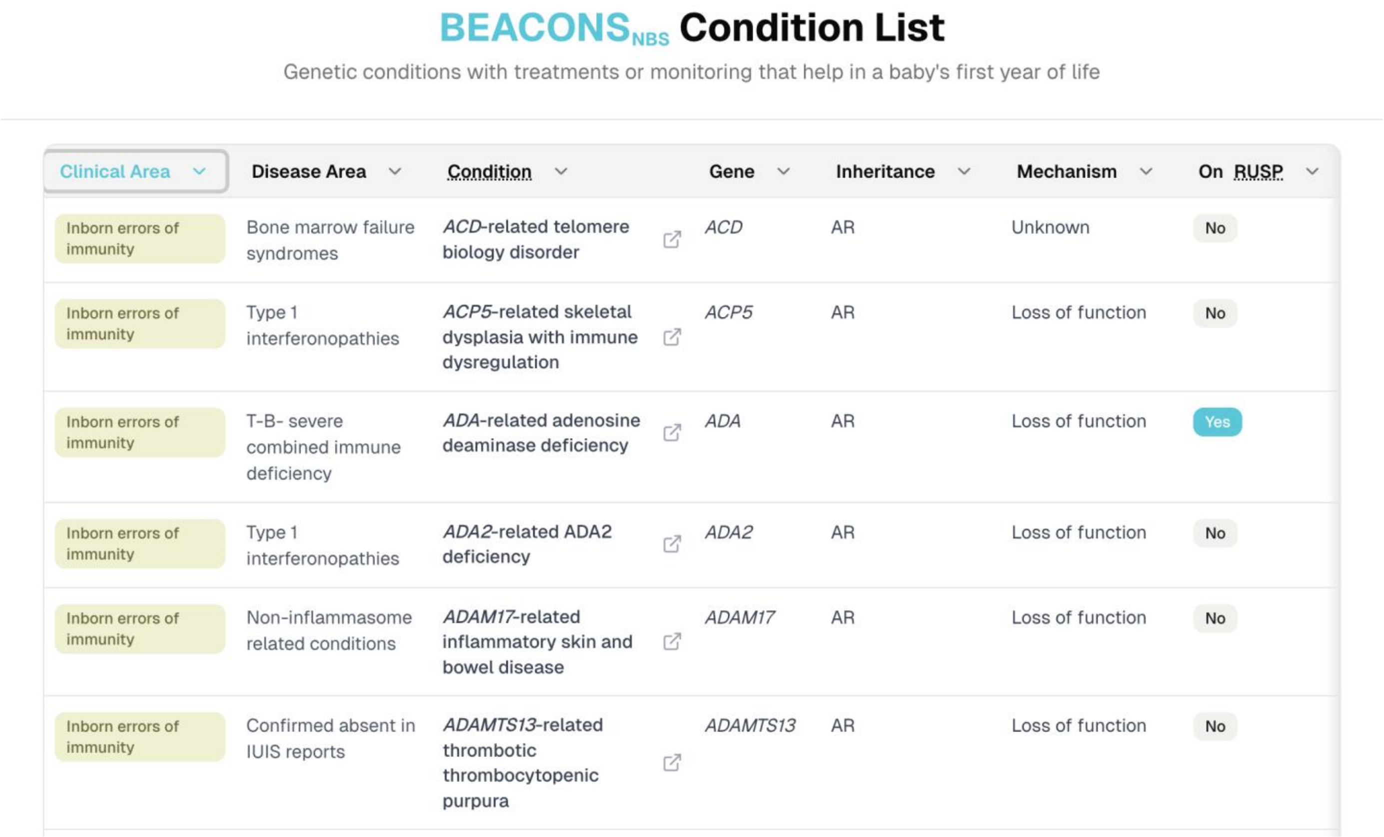
777 conditions

**743 genes, 1 CNV,
1 aneuploidy**

Organizing the data

- Core conditions on the RUSP
- Cardiac Disorders
- Endocrine Disorders
- Gastrointestinal Disorders
- Hematologic Disorders
- Hereditary Cancer Predisposition Syndromes
- Inborn Errors of Immunity
- Inherited Metabolic Disorders
- Neurologic Disorders
- Ophthalmologic Disorders
- Pulmonary Disorders
- Renal Disorders

Displaying and interacting with the data



BEACONS NBS Condition List

Genetic conditions with treatments or monitoring that help in a baby's first year of life

Clinical Area	Disease Area	Condition	Gene	Inheritance	Mechanism	On RUSP
Inborn errors of immunity	Bone marrow failure syndromes	*ACD*-related telomere biology disorder	*ACD*	AR	Unknown	No
Inborn errors of immunity	Type 1 interferonopathies	*ACP5*-related skeletal dysplasia with immune dysregulation	*ACP5*	AR	Loss of function	No
Inborn errors of immunity	T-B- severe combined immune deficiency	*ADA*-related adenosine deaminase deficiency	*ADA*	AR	Loss of function	Yes
Inborn errors of immunity	Type 1 interferonopathies	*ADA2*-related ADA2 deficiency	*ADA2*	AR	Loss of function	No
Inborn errors of immunity	Non-inflammasome related conditions	*ADAM17*-related inflammatory skin and bowel disease	*ADAM17*	AR	Loss of function	No
Inborn errors of immunity	Confirmed absent in IUIS reports	*ADAMTS13*-related thrombotic thrombocytopenic purpura	*ADAMTS13*	AR	Loss of function	No

www.beaconsnbs.org/condition-list

AIRE-related autoimmune polyendocrinopathy disorder

Gene	Clinical Area	Inheritance
AIRE	Inborn errors of immunity	AR

Mechanism	OMIM Number	On RUSP
Loss of function	240300	No

Disease Area

Autoimmunity with or without lymphoproliferation

Condition Description

Changes in both copies of *AIRE* can cause autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), a condition that commonly includes chronic yeast infections, low calcium from hypoparathyroidism, and adrenal insufficiency. Other autoimmune problems can occur and vary widely, including thyroid disease, diabetes, hepatitis, and skin or hair changes.

Reason for Early Detection

This condition may present with early-onset autoimmunity and immune dysregulation before age 1. Early detection allows for treatment with prophylaxis and hematopoietic stem cell transplantation.

Suggestive Signs, Symptoms, and Biomarkers

CBC with differential, autoantibodies (anti–21-hydroxylase, anti-GAD, anti-IA2, anti-TPO, anti–intrinsic factor, anti–parietal cell), endocrine function tests (calcium, glucose, thyroid function, adrenal function), lymphocyte subsets, immunoglobulins, serum or plasma cytokines (especially CXCL9 and interferon-γ), other anti-cytokine and tissue-specific autoantibody screening (as indicated by clinical presentation), bone density assessment, APECED, chronic mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency, ectodermal dystrophy, autoimmune hepatitis, vitiligo, alopecia

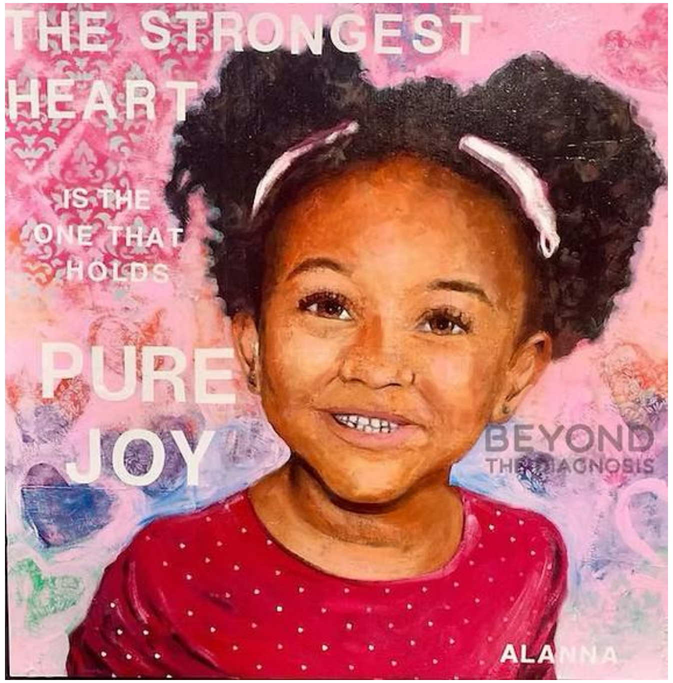
Surveillance or Treatment

HSCT, immunomodulation, antimicrobial prophylaxis

Citations

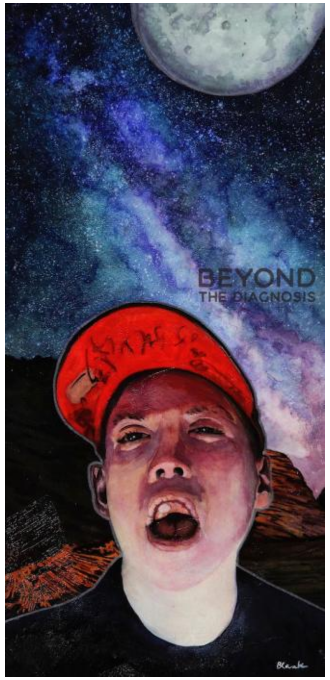
Faiyaz-Ul-Haque et al., Zaidi et al., Kogawa et al., Ponranjini et al., Anderson and Su

Whom might we identify?



Alanna
Law Blanke

Long QT syndrome



Colin
Law Blanke

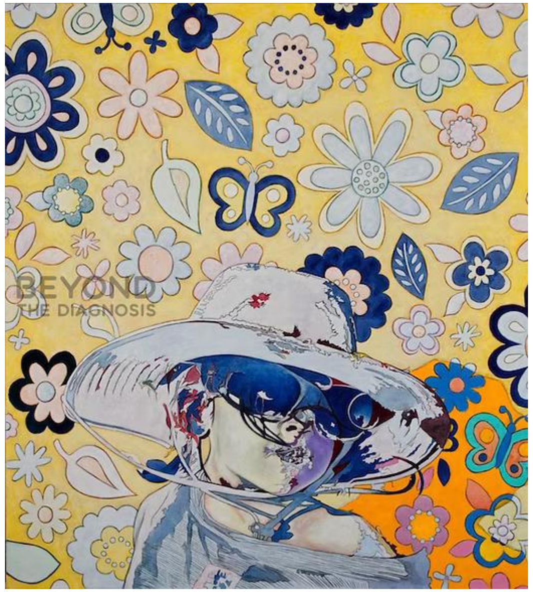
Menkes disease

Brooklyn
Thanaseth Raksuthakarn

22q11 deletion

Limitations: Sensitivity and specificity

No clinical therapies



Eliza
Ian Mohon

Sanfilippo syndrome

Adult-onset conditions

Matthew
Robert Francis Whelan

Neurofibromatosis, type I

Incomplete penetrance

Milaniya
Robert Hurst

Alagille syndrome

How will the list evolve over time?

Plans for revision of the list

- Will collect continuous feedback on the BEACONS website

- One year into study, will collect information from:
  - GeneDx
  - Public health laboratories
  - Clinical experts

- Can revise the list at the halfway point of the study:
  - Adding conditions with newly-approved therapies
  - Removing conditions with poor gene-disease validity

Changing our approach to VUS curation