Next-Generation Screening:
The Promise and Perils of DNA Sequencing of Newborns at Birth

Noura Abul-Husn, MD, PhD

Vice President of Genomic Health, 23andMe
Associate Professor of Medicine, Icahn School of Medicine at Mount Sinai

Disclosures

- 23andMe: Employee and equity holder
- Allelica: Scientific advisory board member

How will genomic data be used across the lifespan?

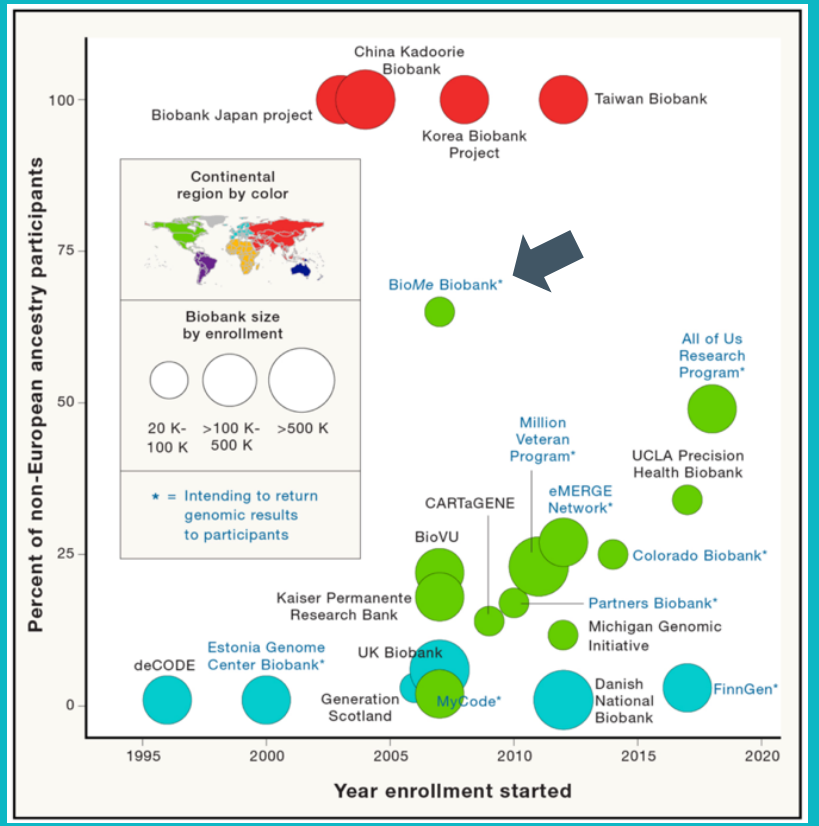
1. Equity: How do we ensure that everyone will benefit?

2. Implementation: How do we achieve genomics-informed healthcare at scale?

DNA Sequencing of Newborns at Birth

How do we ensure that everyone will benefit?

Genomic screening can help address existing disparities in genomic medicine.

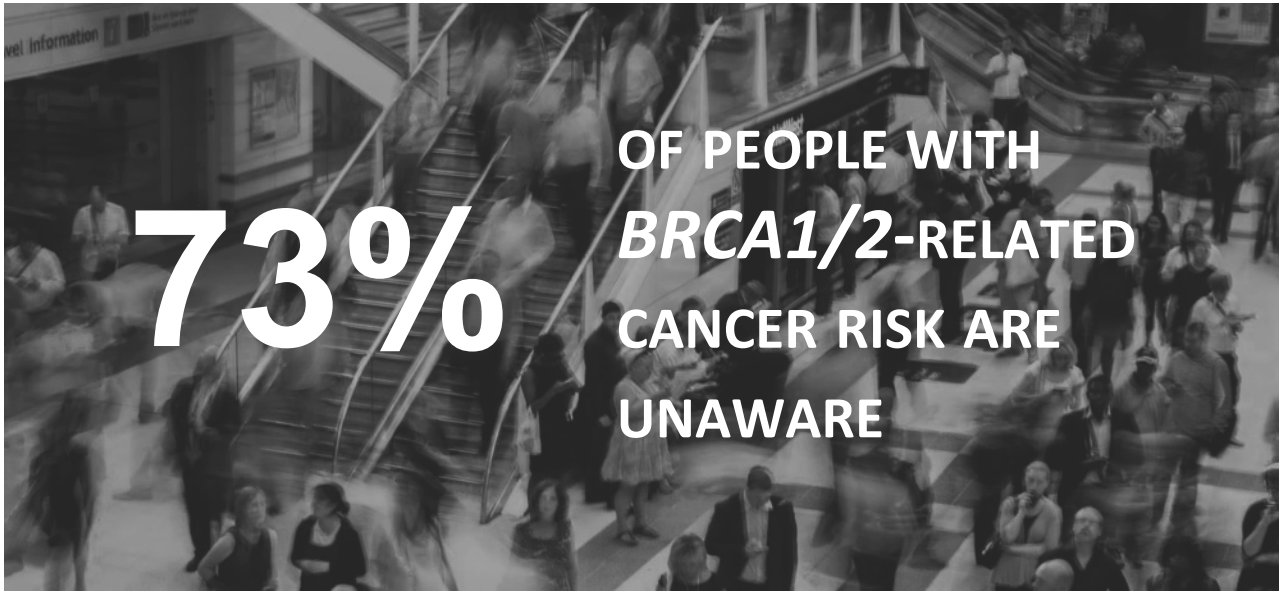


NS Abul-Husn, EE Kenny. *Cell* 2019; 177(1):58-69

Most people are unaware of their genomic risks

39% of participants with AJ founder variants had clinical genetic testing

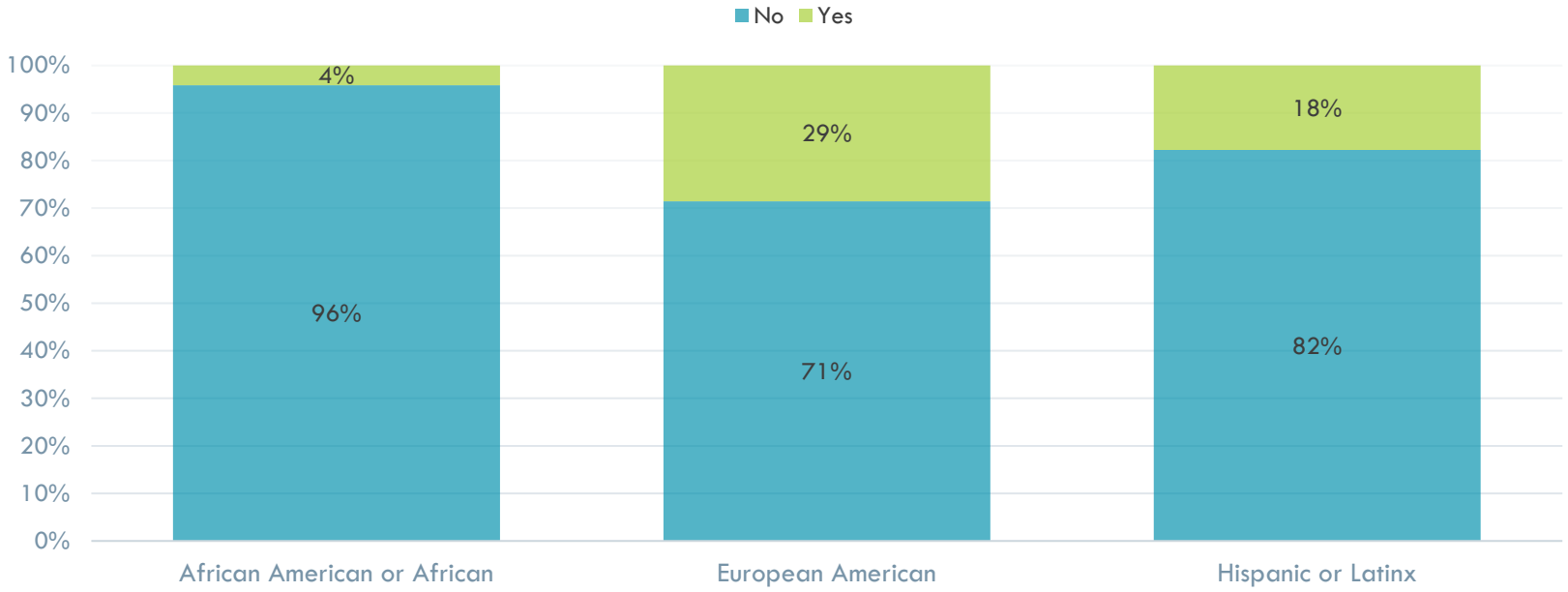
20% of participants with other variants had clinical genetic testing



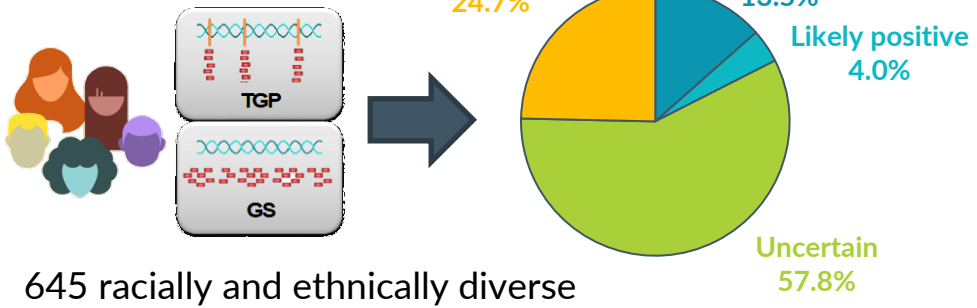
NS Abul-Husn *et al. Genome Med* 2019; 12(1):2

Existing disparities in disease risk awareness

Among unselected individuals with pathogenic variants in BRCA1/2, *those of European descent (by self-report) are more likely to have obtained clinical genetic testing*



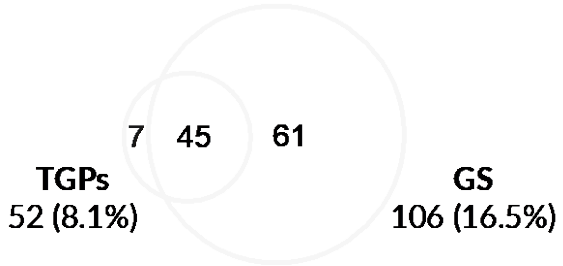
Genome sequencing improves the diagnostic yield for children with suspected genetic conditions



645 racially and ethnically diverse children with neurologic, cardiac, or immunologic conditions

Diagnostic Yield

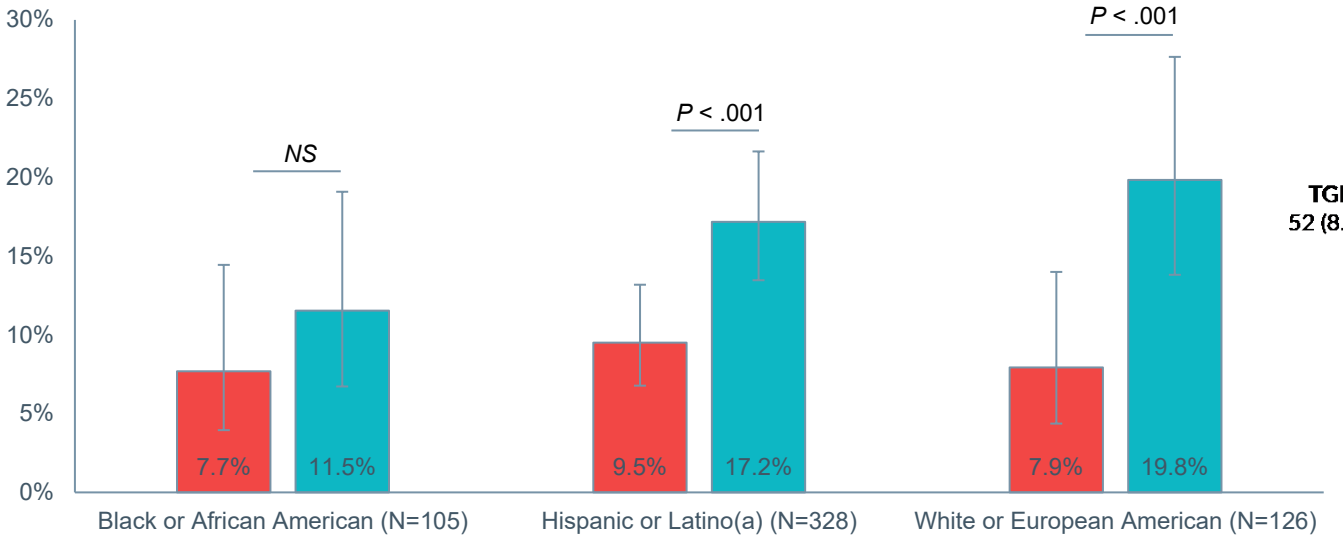
113 of 645 (17.5%)

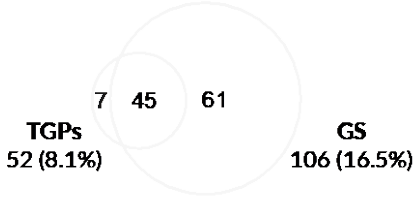


NS Abul-Husn *et al. Genet Med* 2023; In Press

Advances in clinical genomics may not benefit everyone equally

In pediatric patients, diagnostic yield was higher for genome sequencing vs. targeted gene panel testing in Hispanic/Latino and White/European American but not in Black/African American population groups.





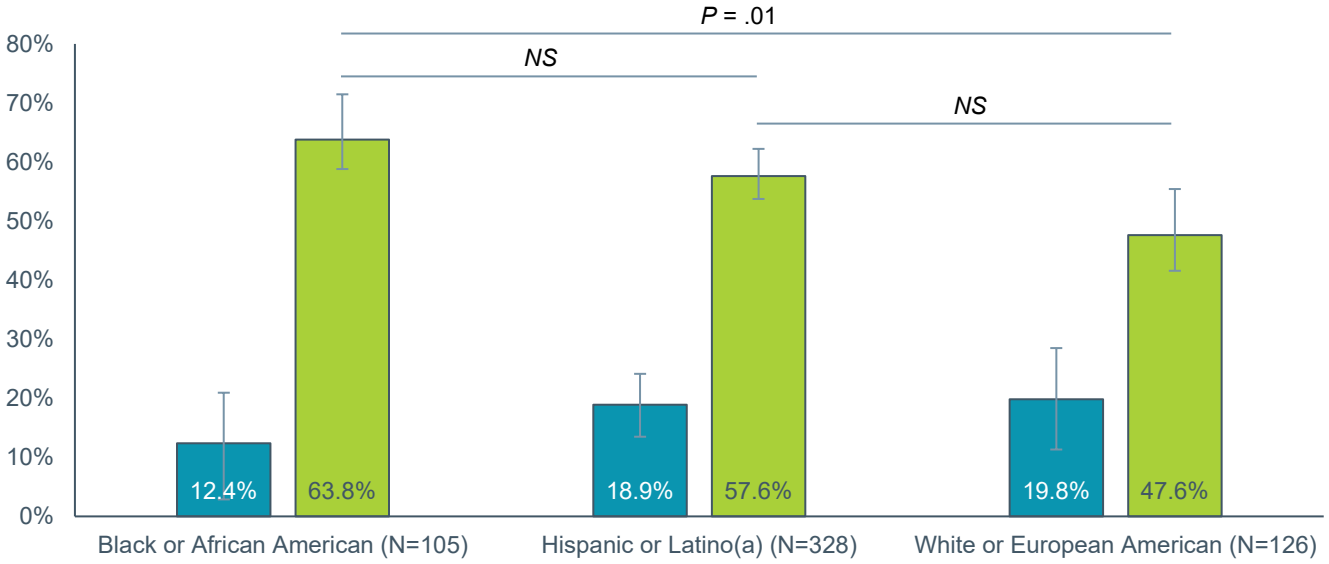
Targeted gene panel

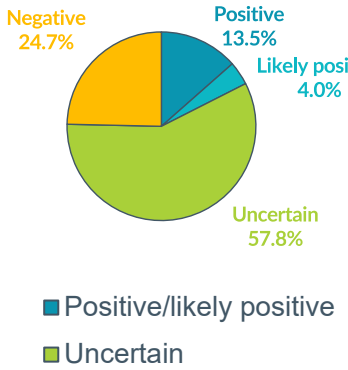
Genome sequencing

NS Abul-Husn *et al. Genet Med* 2023; In Press

Advances in clinical genomics may not benefit everyone equally

Rates of uncertain clinical interpretations were higher in Black/African American than White/European American population groups.



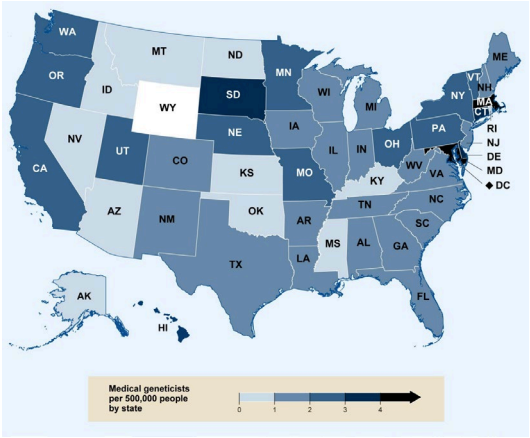


NS Abul-Husn *et al. Genet Med* 2023; In Press

DNA Sequencing of Newborns at Birth

How do we achieve genomics-informed healthcare at scale?

Clinical geneticists cannot keep up with the demand for genomic medicine



US Government Accountability Office (2020). Genetic services: information on genetic counselor and medical geneticist workforces. (GAO-20-593). Report prepared for Congressional Committees. https://www.gao.gov/assets/710/708545.pdf

4 clinical geneticists per 1,000,000 individuals

- 40% located in 5 states
- 14 states with ≤ 5 certified clinical geneticists (1 with none)

But other healthcare professionals are not yet prepared to integrate genomics into routine clinical care

- No requirements for non-genetics professionals to have specific knowledge or competencies in genomics
- Few guidelines for non-genetics healthcare professionals

C Eden, *et al. Per Med* 2016; 13(2):129-141
CL Overby, *et al. J Pers Med* 2014; 4(1):35-49
MF Murray, MJ Khoury, NS Abul-Husn. *Genome Med* 2022; 14(1):60

Genomic medicine track in internal medicine residency

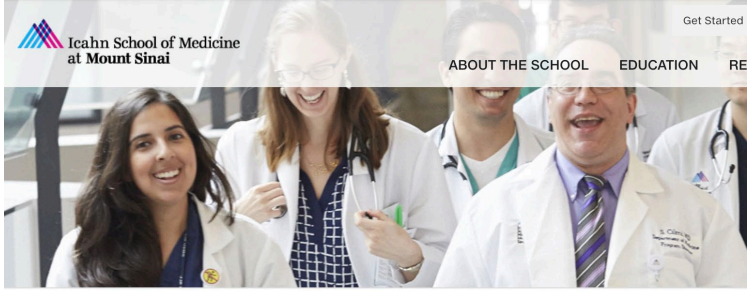
Genomic Medicine Track

Launched in July 2020

The Genomic Medicine Track is a brand-new track designed for residents wanting to deepen their knowledge of genomics and its applicability to patient care. As genomic research and technology continue to scale and permeate routine clinical care, internists have a critical role to play. The Genomic Medicine Track will enable residents to become genomics-ready, providing them with the necessary tools to: identify and care for patients with, or at risk of, genetic conditions; incorporate appropriate genomic testing into clinical practice; and critically assess and communicate genomic test results.

This track is the first-of-its-kind to offer residents an opportunity to engage in topics ranging from cancer and cardiovascular genomics to direct-to-consumer genetic testing and polygenic risk. The track consists of a dedicated genomics curriculum, including expert faculty-led lectures and workshops in the second year. In addition, all residents will complete a mentored genomics-centered research project in their third year.

Applicants interested in the Genomic Medicine Track should apply to the Categorical Residency Program. Once enrolled at Mount Sinai, residents are encouraged to speak with Noura Abul-Husn, MD, PhD, Director of the Medical Genomics Track, about entering this program. Interested applicants should make note of their interest on their application, so appropriate interviews can be arranged.



Categorical Residency

The Categorical Residency is a three-year program dedicated to producing the finest clinicians and future leaders in Internal Medicine. The program focuses on the clinical skills, knowledge and humanistic qualities of the internist.

The practice of clinical excellence, while utilizing a scientific thought process, is the central theme of our categorical curriculum. An evidence-based approach is emphasized both in the inpatient and the outpatient settings.

Through research projects, mentorship and extra-curricular activities related to three elective tracks, Medical Education, Medical Genomics and Health Care Leadership, participants in the Categorical Residency have numerous opportunities to pursue interests directly related to their specific career plans. The program challenges each resident with progressively increasing responsibility in a setting characterized by close faculty mentoring.

- Year-by-Year Schedule
- Health Care Leadership Track
- Medical Education Track
- Genomic Medicine Track
- Global Health Elective
- Housestaff Stories

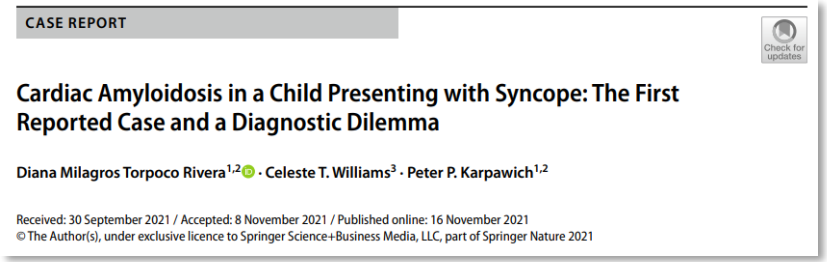
Variant identification ≠ diagnosis

"First known case of pediatric cardiac amyloidosis"

- 12-year-old African American male with frequent PVCs, atrial and ventricular arrhythmias, and LV non-compaction
- Genetic testing revealed *TTR* V142I
- Mother and two adult siblings with same variant and asymptomatic
- Scintigraphy with technetium 99-m pyrophosphate (Tc-99m PYP) showed no cardiac radiotracer update

***TTR* V142I**

- Associated with hereditary transthyretin amyloidosis (hATTR)
- Present in 4% of African Americans
- Incomplete and age-dependent penetrance, with typical onset of cardiac or neurologic disease in individuals ≥ 50 years
- Gold standard testing for presence of cardiac amyloid deposition is Tc-99m PYP



CASE REPORT

Cardiac Amyloidosis in a Child Presenting with Syncope: The First Reported Case and a Diagnostic Dilemma

Diana Milagros Torpoco Rivera[1,2] · Celeste T. Williams[3] · Peter P. Karpawich[1,2]

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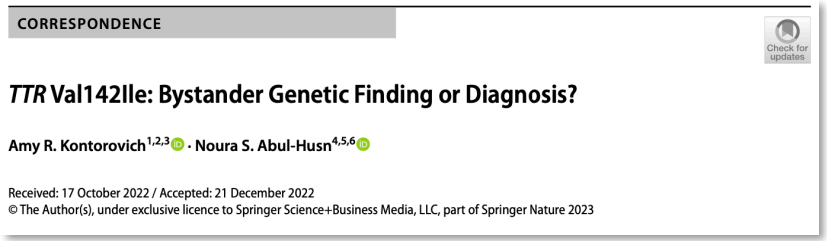

CORRESPONDENCE

TTR Val142Ile: Bystander Genetic Finding or Diagnosis?

Amy R. Kontorovich[1,2,3] · Noura S. Abul-Husn[4,5,6]

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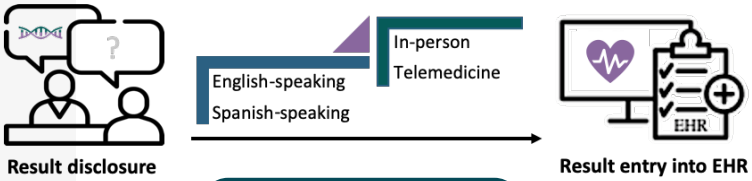
AR Kontorovich & NS Abul-Husn, *Pediatr Cardiol* 2023; 44(2):499

Genome-informed care navigation



TTR
positive result

Referrals

Multi-disciplinary amyloidosis care

Primary care

Evaluation and Surveillance

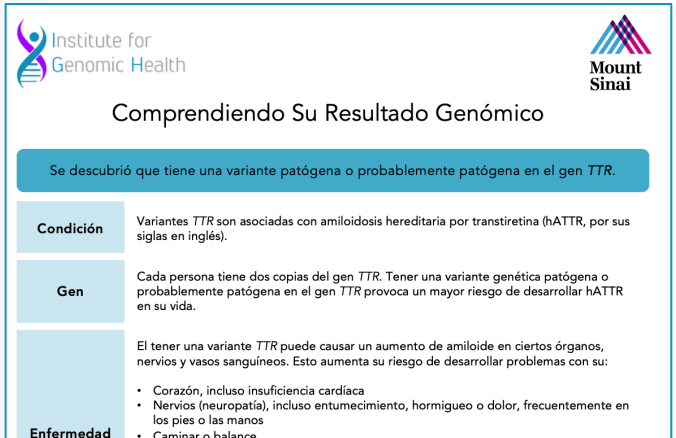
Baseline echocardiogram

Additional cardiac and nerve testing as needed (MRI, nuclear scan)

Referral to additional specialists as needed (GI, renal, eye)

Interventions

Initiation of therapy if amyloidosis confirmed



Institute for Genomic Health

Mount Sinai

Comprendiendo Su Resultado Genómico

Se descubrió que tiene una variante patógena o probablemente patógena en el gen *TTR*.

Condición	Variantes *TTR* son asociadas con amiloidosis hereditaria por transtiretina (hATTR, por sus siglas en inglés).
Gen	Cada persona tiene dos copias del gen *TTR*. Tener una variante genética patógena o probablemente patógena en el gen *TTR* provoca un mayor riesgo de desarrollar hATTR en su vida.
Enfermedad	El tener una variante *TTR* puede causar un aumento de amiloide en ciertos órganos, nervios y vasos sanguíneos. Esto aumenta su riesgo de desarrollar problemas con su: • Corazón, incluso insuficiencia cardíaca • Nervios (neuropatía), incluso entumecimiento, hormigueo o dolor, frecuentemente en los pies o las manos • Caminar o balance

NS Abul-Husn *et al. Genome Med* 2021; 13(1):17
ER Soper *et al. J Pers Med* 2021; 11(1):49

Genomic data obtained at birth will be used to make early diagnoses, predict and prevent disease, and personalize treatment across the lifespan

To ensure that everyone will benefit, we need to:

- Improve our knowledge of genomic variation in diverse populations
- Pilot genomic screening programs that promote health equity
- Educate healthcare professionals in genomic medicine
- Implement genome-informed care in routine clinical practice

Acknowledgements

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Mount Sinai NYCKidSeq Team

Mount Sinai The Charles Bronfman Institute for Personalized Medicine
BioMe Biobank
Your history is our future.

Icahn School of Medicine at Mount Sinai

NIH National Heart, Lung, and Blood Institute

NIH National Human Genome Research Institute

NYCKIDSEQ

cser Clinical Sequencing Evidence-Generating Research

emerge network ELECTRONIC MEDICAL RECORDS & GENOMICS

23andMe