Early Advantage Panel

An Innovative Approach to Panel Design

NxGen MDx

Give Your Patients An Early Advantage

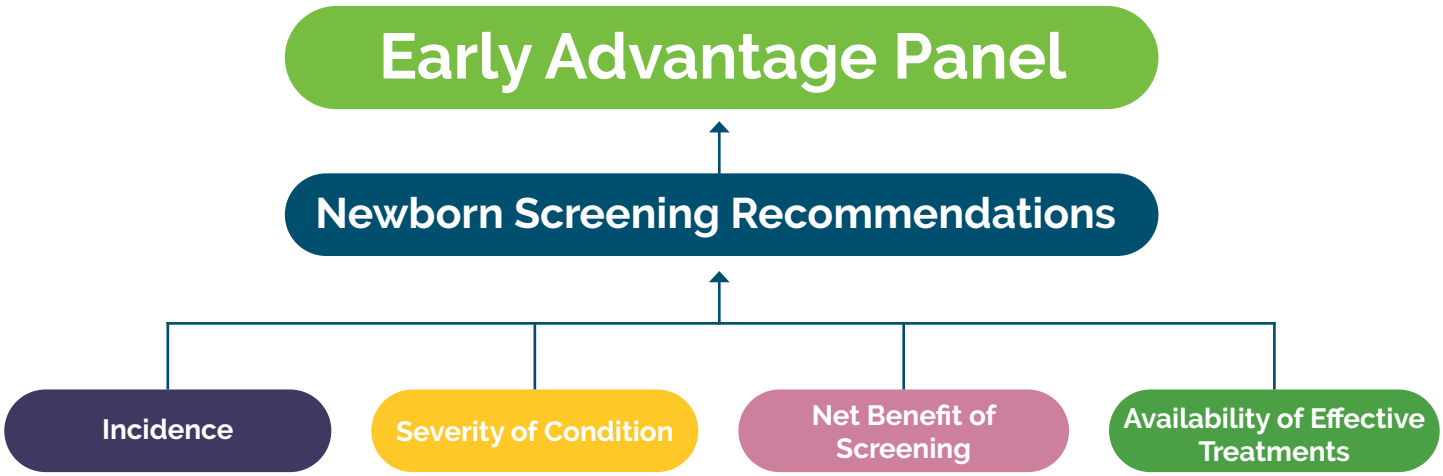
Early Advantage Panel

68 Genetic Conditions

The Early Advantage Panel from NxGen MDx is an innovative approach to carrier screening panel design. It is the first of its size to incorporate conditions that the U.S. Department of Health and Human Services (HHS) recommends be included in newborn screening (NBS) in addition to The American College of Obstetricians and Gynecologists (ACOG) guidelines on carrier screening.

Conditions that HHS recommends for NBS programs are chosen based on their incidence, the severity of the condition, the net benefit of screening, and if there are effective treatments available.

We believe that identifying couples at risk for these conditions before or during pregnancy provides patients with a superior test, better reproductive options, and more timely information to manage their pregnancy and childbirth than relying on NBS alone.



The Foundation of the Early Advantage Panel

The genetic conditions in the Early Advantage Panel were chosen based upon guidelines from leading medical organizations and HHS. Thirty-five of those conditions come from HHS's Recommended Uniform Screening Panel (RUSP). RUSP is the list of conditions that HHS recommends all states use in their NBS programs. **This foundation makes the Early Advantage Panel a powerful tool that can give your patients more pregnancy and birthing options, shorten the diagnostic odyssey, and be ready to begin any necessary treatment right after birth.**

What is NatalCare?

NatalCare is NxGen's curation philosophy for our carrier screening, NIPS, vaginosis, and urinary tract infection products which focuses on improving pregnancy and newborn outcomes.

Our innovative approach in designing the Early Advantage Panel lets us detect more at-risk pregnancies, increase prenatal and birth team choices, and facilitate faster diagnoses and earlier treatments for genetic conditions. We put the focus on the newborn by curating our tests with recommendations from ACOG and HHS.

Strengthening Newborn Screening

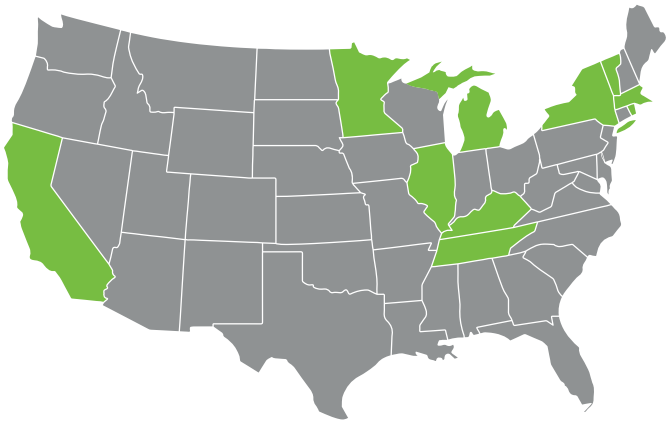
NBS is one of the most successful public health initiatives in the U.S. It is the nation's largest genetic screening program and screens approximately 4 million infants every year.

While NBS is an important part of neonatal care, it does have some limitations.

- The number of conditions screened for is inconsistent from state to state.
- NBS can be negatively impacted by several different factors such as birth weight, ethnicity, and time of sample collection that can lead to more false positives & false negatives.
- Results may be returned too late to begin treatments that are critical in the first few days of life.

The Early Advantage Panel addresses gaps like these in NBS programs by providing a very sensitive test **before birth** that screens for all conditions on RUSP as well as several other conditions recommended by ACOG.

Most states screen for only some of the 35 conditions on the RUSP



States that do screen for all RUSP conditions[1]

States that don't screen for all RUSP conditions[1]

Carrier Screening Addresses Gaps in NBS

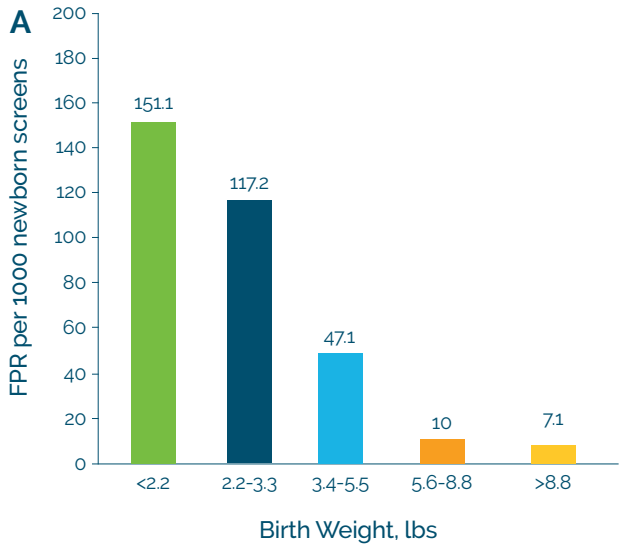
Benefits	NBS	CS
Identifies at-risk children early in life	✓	✓
Provides more reproductive options for parents		✓
Provides more diagnosis options during pregnancy or at delivery		✓
Allows for birth and delivery options		✓
Treatment immediately after birth		✓
Lower false-negatives		✓
Lower false-positives		✓
Health equity regardless of state of residence		✓

1. "Newborn Screening." NORD (National Organization for Rare Disorders). 26 Jan. 2021. https://rarediseases.org/policy-issues/newborn-screening/

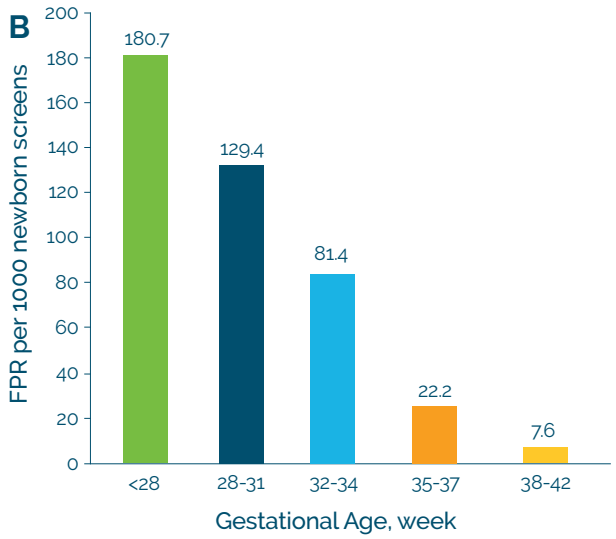
Newborn Screening and False Positive Results

- Children from different ethnic backgrounds have higher NBS false-positive rates across certain conditions.[1]
  - **Carrier screening is 99% accurate across all ethnicities.**
- Infants with very low birth weight have disproportionately more false positive results on NBS.[2]
  - **Carrier screening is not dependent on any characteristics of the infant.**
- Blood collected at 12 hours or less postnatally alters performance of NBS. For low birth weight infants, collection under 48 hours postnatally leads to higher false positive rates.[3]
  - **Carrier screening collects blood from the baby's parents and is therefore not dependent on timing.**
- Conservative thresholds for biochemical assays used in NBS are designed to avoid false negative results. As many as 9 out of 10 positive results are false for one type of NBS assay that detects multiple conditions.[4]

False Positive Rate by Birth Weight[2]



False Positive Rate by Gestational Age[2]



448,766 neonates were analyzed to find that false-positive NBS rates increased with decreasing birth weight (A) and with gestational age (B).[2]

1. Peng, G., Tang, Y., Gandotra, N., Enns, G.M., Cowan, T.M., Zhao, H., and Scharfe, C. (2020). Ethnic variability in newborn metabolic screening markers associated with false positive outcomes. J. Inherit. Metab. Dis. 43, 934–943.
2. Slaughter, J.L., Meinzen-Derr, J., Rose, S.R., Leslie, N.D., Chandrasekar, R., Linard, S.M., and Akinbi, H.T. (2010). The Effects of Gestational Age and Birth Weight on False-Positive Newborn-Screening Rates. Pediatrics 126, 910–916.
3. Peng, G., Tang, Y., Cowan, T.M., Zhao, H., and Scharfe, C. (2021). Timing of Newborn Blood Collection Alters Metabolic Disease Screening Performance. Front. Pediatr. 8, 623184.
4. Kelly, N., Makarem, D.C., and Wasserstein, M.P. (2016). Screening of Newborns for Disorders with High Benefit-Risk Ratios Should Be Mandatory. J. Law Med. Ethics J. Am. Soc. Law Med. Ethics 44, 231–240.

Case Studies in Newborn Screening

Congenital Adrenal Hyperplasia (CAH), *CYP21A2*-Related

Common Recessive Condition	Effective Treatment Available	Technically Challenging Gene
• **1/60 are carriers** • 1/15,000 births • Many carriers have no known family history	• **Early intervention prevents morbidity** • Allows for more options in populations with fertility concerns • Ongoing monitoring and adjustment of treatments for better outcomes	• **Absent from most carrier panels** • Presence of pseudogene • High recombination of gene & pseudogene

Give Your Patients The Early Advantage

All states offer newborn screening for the classic form of congenital adrenal hyperplasia (CAH), *CYP21A2*-related. The rationale for screening is to recognize and promptly treat the potentially life-threatening severe salt-wasting classic form of CAH.

- Each state develops its own NBS independently, leading to disparities in the sensitivity of 21-CAH screens based on state and birth weight.[1]
- 22-32% of 21-CAH results from NBS were identified as false positives.[2,3,4]
- Several states require a second 21-CAH screen to be taken after two weeks of life to combat false negatives due to low positive predictive values, prolonging the wait for answers.

Adding 21-CAH to the Early Advantage Panel gives your patients more options when family planning and improves outcomes by allowing intervention when it matters most, at birth.

Early Advantage Panel Offers Superior Accuracy

	NBS	Early Advantage Panel
Reduces infant mortality	✓	✓
Lessens severe hyponatremia	✓	✓
Early intervention leading to fewer learning disabilities, better growth outcomes, and fewer hospitalizations	✓	✓
High detection rates; low false-negatives		✓
Detects classic and non-classic CAH		✓
Time to make appropriate delivery plans		✓
Time to learn about condition and find healthcare team		✓
Time to connect with support resources		✓

1. Speiser PW, Chawla R, Chen M, Diaz-Thomas A, Finlayson C, Rutter MM, Sandberg DE, Shimy K, Talib R, Cerise J, Vilain E, Délot EC. Newborn Screening Protocols and Positive Predictive Value for Congenital Adrenal Hyperplasia Vary across the United States. Int J Neonatal Screen. 2020 Jun;6(2):37. doi: 10.3390/ijns6020037. Epub 2020 May 8. PMID: 32832708; PMCID: PMC7422998.
2. Sarafoglou K, Banks K, Gaviglio A, Hietala A, McCann M, Thomas W. Comparison of one-tier and two-tier newborn screening metrics for congenital adrenal hyperplasia. Pediatrics. 2012 Nov;130(5):e1261-8. doi: 10.1542/peds.2012-1219. Epub 2012 Oct 15. PMID: 23071209.
3. Sarafoglou K, Banks K, Kyllo J, Pittock S, Thomas W. Cases of congenital adrenal hyperplasia missed by newborn screening in Minnesota. JAMA. 2012 Jun 13;307(22):2371-4. doi: 10.1001/jama.2012.5281. PMID: 22692165.
4. Chan CL, McFann K, Taylor L, Wright D, Zeitler PS, Barker JM. Congenital adrenal hyperplasia and the second newborn screen. J Pediatr. 2013 Jul;163(1):109-13.e1. doi: 10.1016/j.jpeds.2013.01.002. Epub 2013 Feb 12. Erratum in: J Pediatr. 2013 Jul;163(1):308. PMID: 23414665.

Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD)

Common Recessive Condition	Effective Treatment Available	Early Advantage Panel Offers Superior Accuracy
• **1/66 are carriers** • Most common fatty acid oxidation disorder with an incidence of 1 in 15,000 • Affected individuals are unable to break down medium-chain fatty acids	• **Early intervention prevents mortality and morbidity** • The mainstay is avoidance of fasting: infants require frequent and supplemental feedings	• Detection rate for MCADD is >99% across all ethnicities

Give Your Patients The Early Advantage

All states offer newborn screening for medium-chain acyl-CoA dehydrogenase deficiency (MCADD). Clinically, MCADD is characterized by hypoketotic hypoglycemia, and it can result in sudden death when the body is not able to effectively mobilize fatty acids in response to fasting. Treatment revolves around preventing these episodes of fasting with frequent feedings.

- Screening identifies affected infants and allows implementation of appropriate dietary interventions before an acute episode.
- 11-24% of babies with MCADD will show signs of metabolic decomposition before NBS results are back.[1,2]
- Unfortunately, 5-9% of babies with MCADD will pass away during that waiting period.[2,3,4,5,6]

Screening for MCADD using the Early Advantage Panel allows treatment to begin at birth which improves neonatal outcomes and prevents death from this disease.

Early Advantage Panel Offers Superior Accuracy

	NBS	Early Advantage Panel
Reduces infant mortality	✓	✓
Prevents hypoketotic hypoglycemia	✓	✓
Early intervention leading to better growth outcomes	✓	✓
Detects mild and classic forms of MCADD		✓
Prevents metabolic crisis before NBS results are back		✓
High detection rates; low false-negatives		✓
Time to make appropriate delivery plans		✓
Time to learn about condition and find healthcare team		✓
Time to connect with support resources		✓

1. Hsu HW. et al. Spectrum of medium-chain acyl-CoA dehydrogenase deficiency detected by newborn screening. Pediatrics. 2008 May;121(5):e1108-14. doi: 10.1542/peds.2007-1993. PMID: 18450854.
2. Ahrens-Nicklas RC, Pyle LC, Ficicioglu C. Morbidity and mortality among exclusively breastfed neonates with medium-chain acyl-CoA dehydrogenase deficiency. Genet Med. 2016 Dec;18(12):1315-1319. doi: 10.1038/gim.2016.49. Epub 2016 May 5. PMID: 27148938; PMCID: PMC5538896.
3. Ensenauer R, Winters JL, Parton PA, Kronn DF, Kim JW, Matern D, Rinaldo P, Hahn SH. Genotypic differences of MCAD deficiency in the Asian population: novel genotype and clinical symptoms preceding newborn screening notification. Genet Med. 2005;7:339–43.
4. Wilcken B, Haas M, Joy P, Wiley V, Chaplin M, Black C, Fletcher J, McGill J, Boneh A. Outcome of neonatal screening for medium-chain acyl-CoA dehydrogenase deficiency in Australia: a cohort study. Lancet. 2007;369:37–42.
5. Lovera C, Porta F, Caciotti A, Catarzi S, Cassanello M, Caruso U, Gallina MR, Morrone A, Spada M. Sudden unexpected infant death (SUDI) in a newborn due to medium chain acyl CoA dehydrogenase (MCAD) deficiency with an unusual severe genotype. Ital J Pediatr. 2012;38:59.
6. Andresen BS, Lund AM, Hougaard DM, Christensen E, Gahrn B, Christensen M, Bross P, Vested A, Simonsen H, Skogstrand K, Olpin S, Brandt NJ, Skovby F, Nørgaard-Pedersen B, Gregersen N. MCAD deficiency in Denmark. Mol Genet Metab. 2012;106:175–88.

Personalized Patient Support

Personalized customer service that streamlines testing for both you and your patients. You can reach our team by calling **855-776-9436.**

In-depth materials to help educate patients and make integrating testing easier for your practice

Intelligently curated tests that provide clear, actionable results you can use to guide patient care

Accessible genetic counseling support for your patients to explain results and help bring clarity to decision making

Testing that is affordable for everyone through our Access for All Program. You can learn more about the Access for All program by visiting **nxgenmdx.com/access-for-all**.

NxGen MDx LLC is a leading women's health company delivering highly accurate genetic testing. NxGen MDx offers preconception and pregnancy testing as well as screening and diagnostic tests for health & wellness.

801 Broadway Ave NW, Suite 203, Grand Rapids, MI 49504

Phone: (855) 776-9436

Fax: (616) 710-4667

info@nxgenmdx.com

nxgenmdx.com