RTI Early Check: Voluntary, Expanded Screening for Newborns

Holly Peay, PhD MS CGC

Early Check

Expanded health screening for your baby

Disclosures

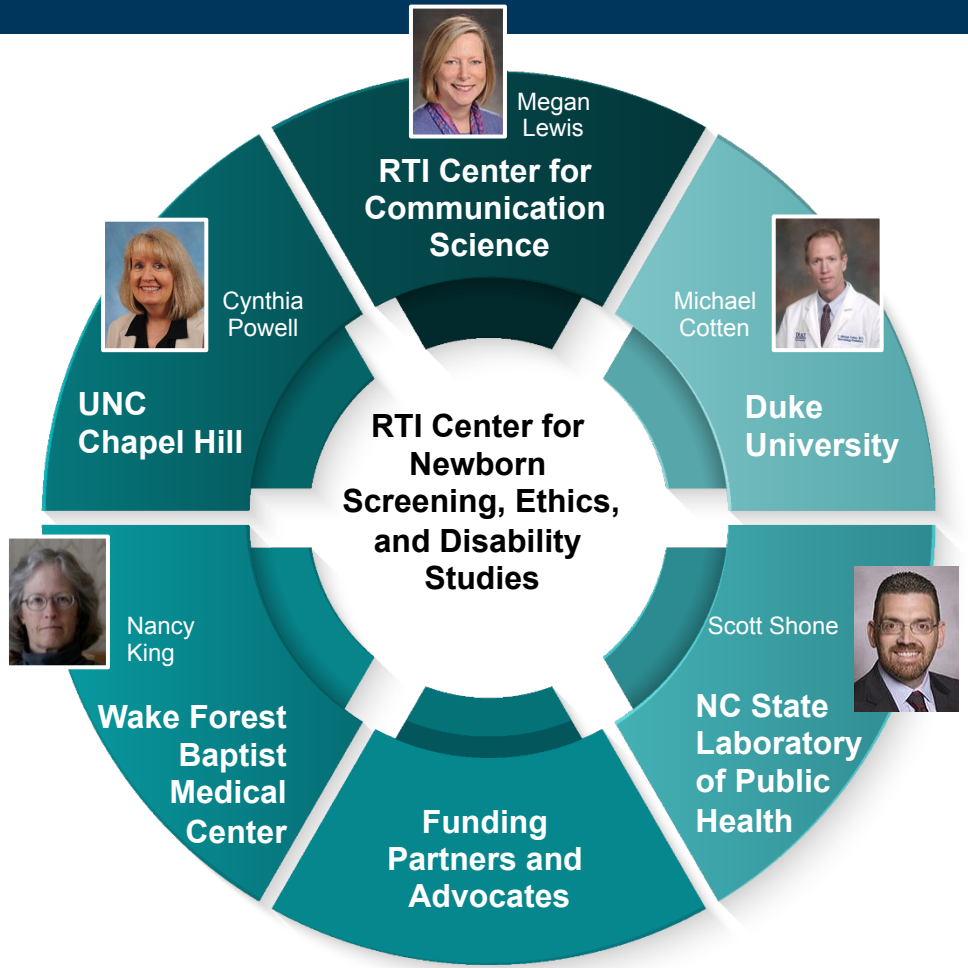
Asuragen provides partial support for Early Check FXS screening.

What is Early Check?

- A research study designed to
  - Develop and evaluate methods to offer free, voluntary screening to 120,000 parents/ year for conditions not currently part of NBS
  - Acquire data to inform NBS policy
    - gauge parents' interests in screening for new conditions
    - develop and test feasibility of the full complement of systems needed to implement screening
    - understand early natural history of "screen positive" infants
    - identify infants who could participate in pre-symptomatic treatment trials
- The foundation for
  - A long-term research resource to which new conditions can be added when ready
  - An envisioned future in which states offer a voluntary panel of "non-RUSP" conditions
- Currently screening for SMA and fragile X syndrome
- Anticipate adding Duchenne screening in 2020

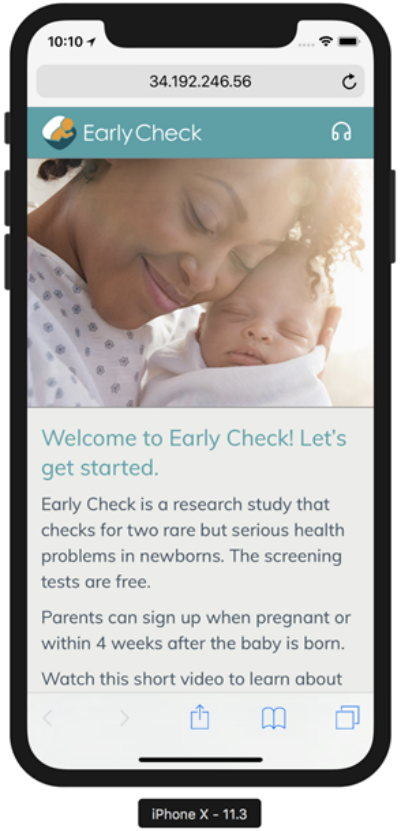
Early Check
Expanded health screening for your baby

Early Check partners



What is unique about Early Check?

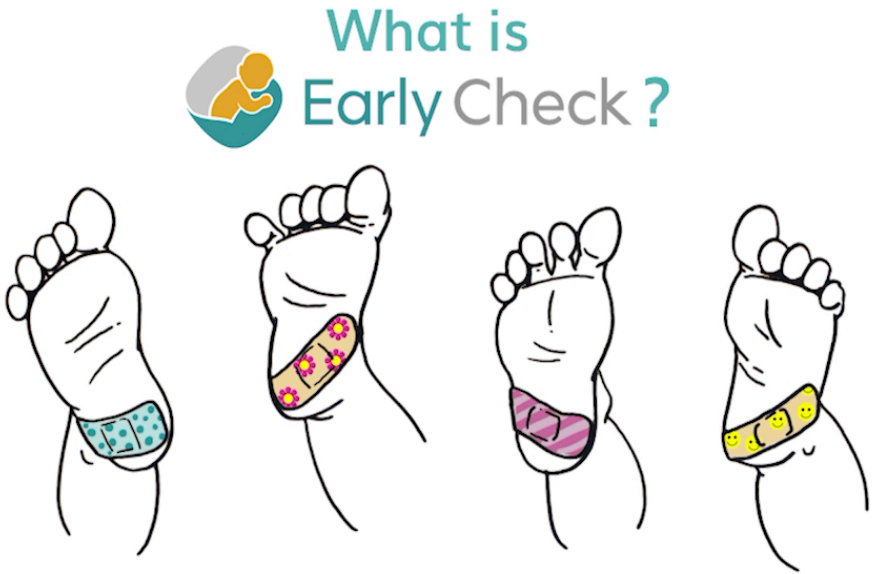
- Collaboration among multiple research partners
- Statewide recruitment
- Use of residual NBS blood spot for screening
- Systematic evaluation of recruitment methods
- Electronic consent (permission)
- Return of negative results on the electronic portal
- Short and long-term follow-up tailored to each disorder
- Tele-genetic counseling and developmental assessment
- Studying the efficacy of interventions



Criteria for disorder inclusion: DBMD example

Criteria for New Early Check Conditions	Duchenne and Becker Muscular Dystrophy (DBMD)
Results in serious problems in health or development	Children and adults with DBMD experience substantial disease-related morbidity and mortality.
Childhood onset and difficult to diagnose early	Average age at which first signs are noted by parents is 2.5 years, and average age at diagnosis of DBMD is 5 years.
Moderate certainty that screening would lead to a net benefit for the child	Two treatments for Duchenne are approved by the Food and Drug Administration, and a range of experimental therapies are in various stages of development.
Low-cost, high-throughput, accurate, and feasible test performed on dried blood spots	PerkinElmer developed an assay to measure elevated creatine kinase MM isoform (CK-MM) levels in dried blood specimens.
Study team could reasonably provide follow-up support	Early Check investigators have considerable neuromuscular expertise and can provide genetic counseling, while the clinical partner, Duke University, has an established neuromuscular center and capacity to perform follow-up for screen-positive newborns.

Introduction to Early Check (Video)



Two options for enrollment

Prenatal Enrollment

Parents will have the opportunity to enroll in Early Check **prior to the birth of their child**.

Information about the Early Check research project will be available through

- health care providers' office
- traditional media
- social media
- other organizations serving expectant parents

Postnatal Enrollment

Parent will have the opportunity to enroll in Early Check within the first month **after the birth of their child**.

- A parent will receive an invitation to participate in the research project by a text and/or email
- A reminder text and/or email will be sent at two weeks after birth
- Enrollment deadline is within **one month** after birth

Engages with Early Check?

Permission obtained through use of electronic consent

Parental permission for participation

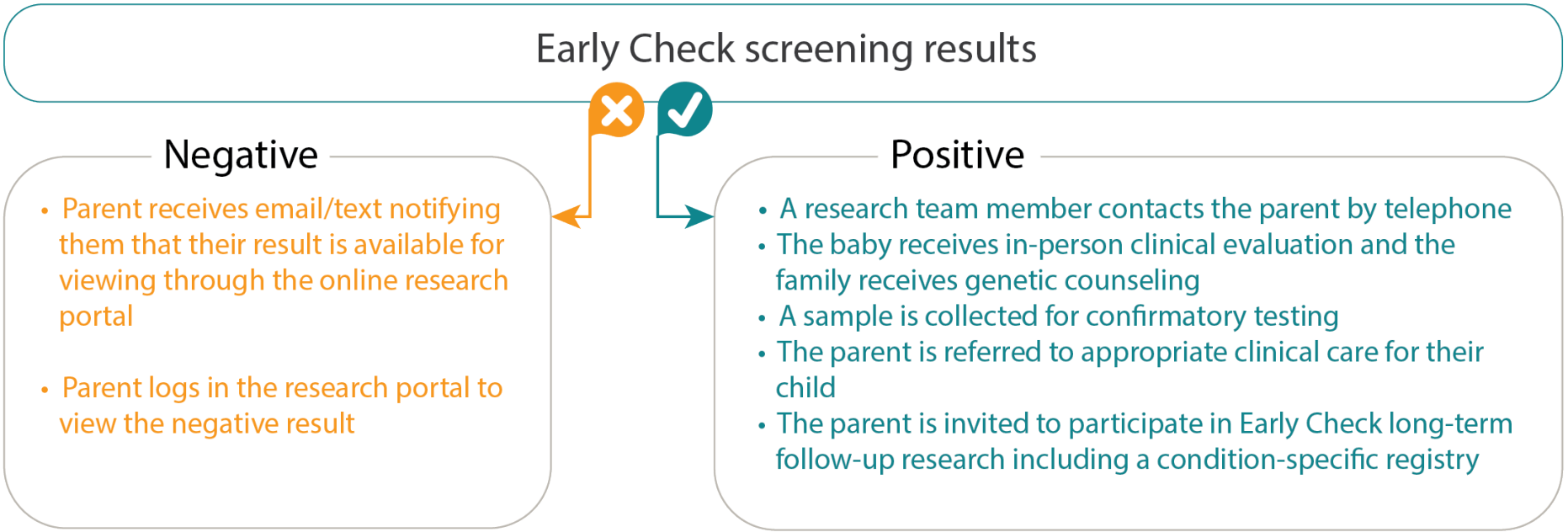
A parent who is interested in Early Check goes to the online Early Check consent module to learn about the project and give permission for their child to participate

PERMISSION?

Early Check Laboratory testing is performed

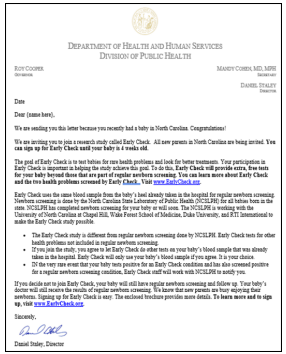
- Newborn screening for the Early Check panel of disorders takes place at the North Carolina State Laboratory of Public Health.
- Early Check screening is performed on the dried blood spot sample already collected for standard newborn screening.

Normal results returned through the Research Portal



Phased studies of targeted outreach strategies

Phase 1: Postnatal (letter, flyer, postcard reminder)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF PUBLIC HEALTH

ROY COOPER
Governor

MANDY COHEN, M.D., MPH
Secretary

DANIEL STALEY
Director

Date

Dear (name here),

We are sending you this letter because you recently had a baby in North Carolina. Congratulations!

We are inviting you to join a research study called Early Check. All new parents in North Carolina are being invited. You can sign up for Early Check until your baby is 4 weeks old.

The goal of Early Check is to test babies for rare health problems and look for better treatments. Your participation in Early Check is important in helping the study achieve this goal. To do this, **Early Check will provide extra, free tests for your baby beyond those that are part of regular newborn screening. You can learn more about Early Check and the two health problems screened by Early Check.** Visit www.EarlyCheck.org.

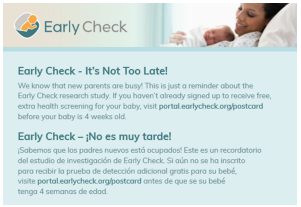
Early Check uses the same blood sample from the baby's heel already taken in the hospital for regular newborn screening. Newborn screening is done by the North Carolina State Laboratory of Public Health (NCSLPH) for all babies born in the state. NCSLPH has completed newborn screening for your baby or will soon. The NCSLPH is working with the University of North Carolina at Chapel Hill, Wake Forest School of Medicine, Duke University, and RTI International to make the Early Check study possible.

- The Early Check study is different from regular newborn screening done by NCSLPH. Early Check tests for other health problems not included in regular newborn screening.
- If you join the study, you agree to let Early Check do other tests on your baby's blood sample that was already taken in the hospital. Early Check will only use your baby's blood sample if you agree. It is your choice.
- In the very rare event that your baby tests positive for an Early Check condition and has also screened positive for a regular newborn screening condition, Early Check staff will work with NCSLPH to notify you.

If you decide not to join Early Check, your baby will still have regular newborn screening and follow up. Your baby's doctor will still receive the results of regular newborn screening. We know that new parents are busy enjoying their newborn. Signing up for Early Check is easy. The enclosed brochure provides more details. **To learn more and to sign up, visit www.EarlyCheck.org.**

Sincerely,

Daniel Staley, Director



Early Check

Early Check - It's Not Too Late!

We know that new parents are busy! This is just a reminder about the Early Check research study. If you haven't already signed up to receive free, extra health screening for your baby, visit **portal.earlycheck.org/postcard** before your baby is 4 weeks old.

Early Check – ¡No es muy tarde!

¡Sabemos que los padres nuevos está ocupados! Este es un recordatorio del estudio de investigación de Early Check. Si aún no se ha inscrito para recibir la prueba de detección adicional gratis para su bebé, visite **portal.earlycheck.org/postcard** antes de que se su bebé tenga 4 semanas de edad.

Phase 2: Pre- & Postnatal (Social media: FB, Instagram)

Early Check
Just now

🌷Spring is in the air and we have free #EarlyCheck health tests to share! Help us spread the word to new and expecting parents: http://ow.ly/G1Br30o5r1Q

Hop to it!
Free #EarlyCheck health tests for new babies

Early Check

Like Comment Share

Phase 3: Multiple hospital, community, and state strategies

EarlyCheck

You Can Make a Difference

You can help your family and other families in North Carolina by joining Early Check, a newborn screening research study. By joining, you'll help advance science, help doctors find treatments for rare disorders, and improve the lives of babies affected by rare disorders.

RTI

NC eWIC

myUNCChart™

Over 4300 consents (4% response rate based on letters mailed)

107731
letters sent
(107731 total)

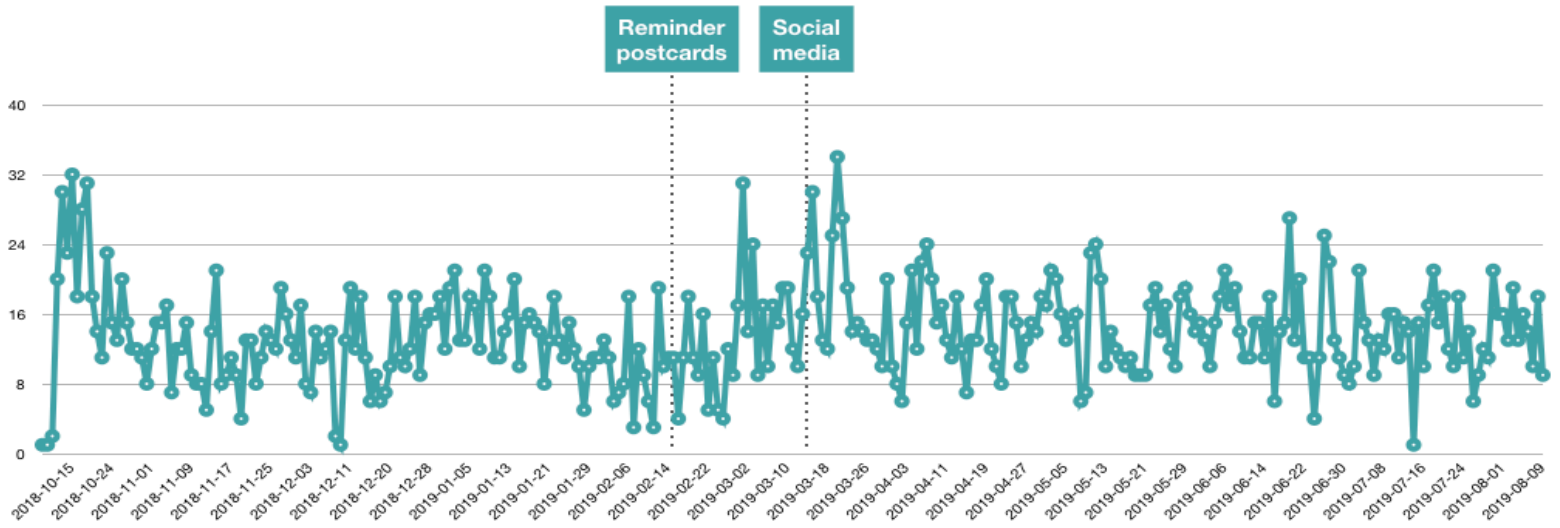
7108
emails sent
(7108 total)

4375
consents
(4375 total)

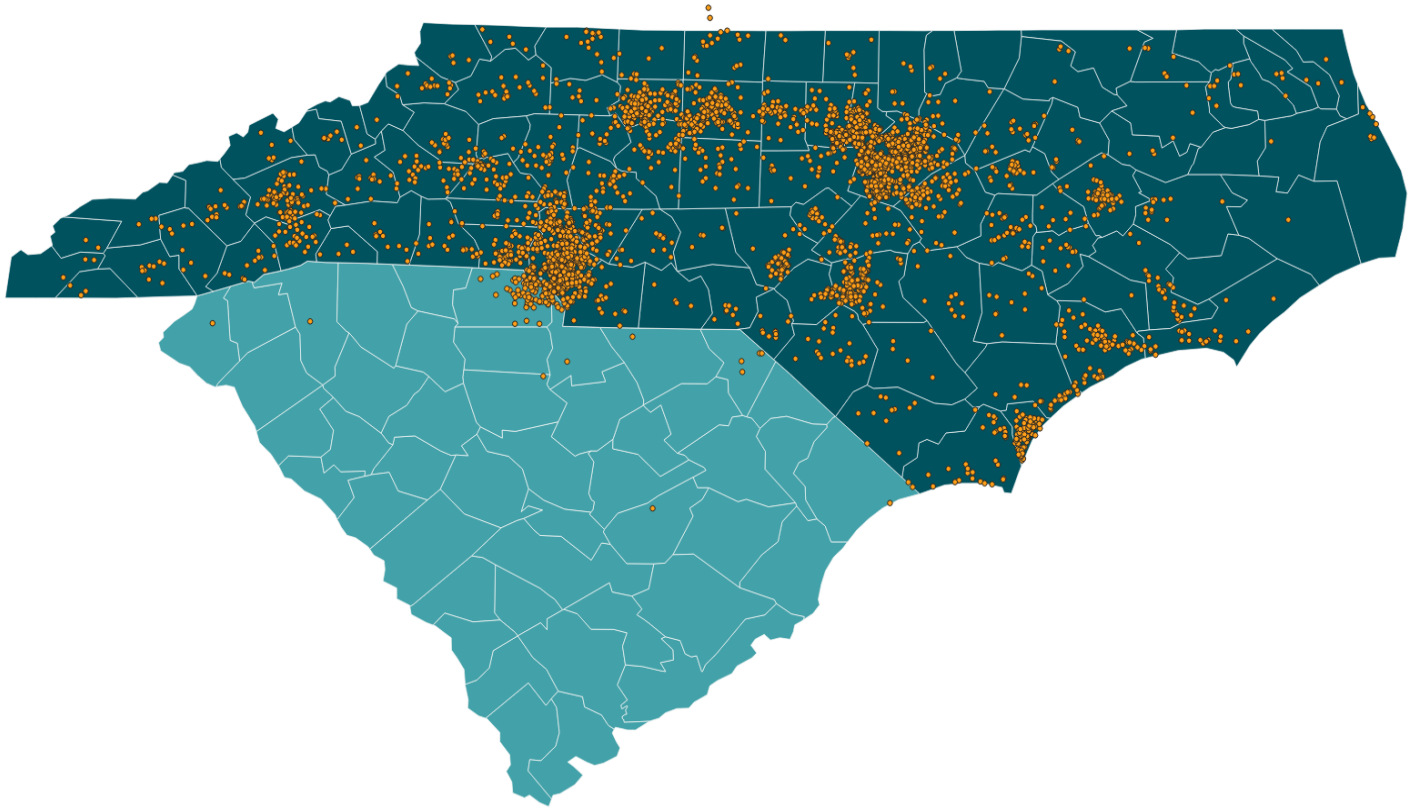
- **Cost per enrollee (letter only) - $20.00**

42% also consent to receive fragile X premutation results

Current enrollment – about 100 consents per week



Enrollees from 95% of counties and 100% of birthing hospitals



Race/ethnicity of consented babies as reported on the NBS card

Race/Ethnicity	Number	%	NC vital stats
White, non-Hispanic	2732	63%	64%
White, Hispanic	178	4%	9%
Black/African American	297	7%	22%
Asian	280	6%	--
More than one race	73	2%	--
Other	33	1%	--
Unknown	741	17%	--
Total	4,334		

Screening results thus far (out of over 4000 tests)

- No SMA screen positive cases
- 18 fragile X premutation carriers
  - 11 in families who chose not to receive these results
  - 7 families received premutation carrier results
- 2 FXS full mutation

Timing of permissions and screening (# of days)

Birth to…	Minimum	Mean	Median	Maximum
Outreach[1]	2	5.5	5	17
Postnatal consent	4	16.3	15	40
Import to lab	5	17.5	16	41
Report out[2]	9	21.3	20	45

[1]Excluding early October dates
[2]Lab is getting results out 3-4 days after getting the list from the portal

Early Check Research Portal

Primary objectives of Early Check Research Portal

- Feasible, ethical, and reproducible approach to facilitate ***large-scale informed choice***
- ***Standardization*** of the consent (permissions) approach
- Provide a mechanism for ***ongoing participant communication***
- ***Participant-oriented results*** provision
- Creation and implementation of a ***responsive "learning" system*** that integrates evaluation and quality improvement efforts

Challenges

- Inviting more than 120,000 birthing parents a year to Early Check
- Providing sufficient information for informed choice
- Managing literacy challenges
- Achieving sufficient participation to make Early Check viable
- Implementing sufficient and feasible communication mechanisms
- Providing a feasible approach to return of results
- Meeting regulatory and ethical requirements

Early Check Research Portal platform

- Web application: anyone with an internet connected device can access the portal (no need to install anything)
- Fully responsive so pages will render properly on a variety of devices and window or screen sizes (phones, tablets, laptops and desktop computers)
- Runs on a CMS (Content Management System) so content can be easily created and modified
- Multiple media incorporated, including voice over of all content
- Spanish-language version available

Let’s get started!

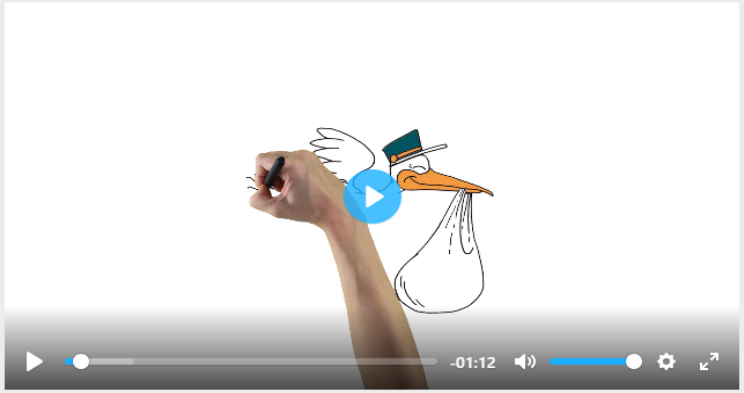
Welcome to Early Check! Let’s get started.

Welcome to Early Check! Let’s get started.

Early Check is a research study that checks for two rare but serious health problems in newborns, fragile X syndrome and spinal muscular atrophy (SMA). The screening tests are free.

Parents can sign up when pregnant or within 4 weeks after the baby is born.

Watch this short video to learn about Early Check. You can read the text instead of watching the video by clicking the “Read” link.



Read

Early Check

Welcome to Early Check! Let's get started.

What do babies have to do?

Nothing!

Babies have a heel prick in the hospital for regular North Carolina newborn screening. We don't need any more blood. Early Check simply does extra screening tests on the same drops of blood.

What do parents have to do?

Sign up your baby. That's all!

Parents go through this site to learn more. Then the mother can decide to sign up her baby. Even though the mother has to give permission, we ask that both parents decide when possible.

Click "Next" to learn about Early Check. Signing up is easy, and it is all done on this site.

- Watch 2 videos
- Learn about the health problems tested in Early Check
- Read through 8 screens of important study information
- Look at 3 review questions
- Fill out the permission form

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Early Check

Ready to find out if your baby can join Early Check?

Play voice over

Find out if you're eligible for Early Check

Has your baby been born yet?

NOT YET

YES

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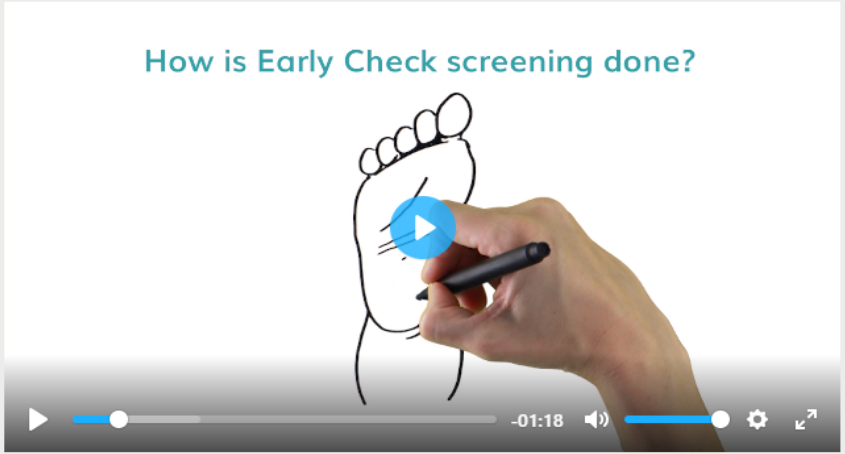
Early Check

How is Early Check done?

Watch this second short video about Early Check.

Click “Play” to begin. You can read the text instead of watching the video by clicking the "Read" icon.



Read

Early Check

What health problems does Early Check look for in newborns?

Early Check looks for two rare health problems.

1. **Spinal muscular atrophy (SMA)** causes muscle weakness that gets worse over time. There is a new treatment and ongoing research, but SMA could still cause early death for some babies.
2. **Fragile X syndrome** causes learning and behavior problems. Fragile X syndrome does not cause early death.

Important facts about the Early Check health problems:

- Babies who have these health problems may not have any signs or symptoms at birth. The signs and symptoms can start later.
- Babies who have these health problems can have mild or serious symptoms.
- There are no cures for these health problems but there are things that may help. Researchers are looking for better treatments.
- The Early Check team will connect parents of babies with these health problems to more information and help them find doctors and support for their child.

+ **Learn more about spinal muscular atrophy from our experts.**

+ **Learn more about fragile X syndrome from our experts.**

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– Learn more about spinal muscular atrophy from our experts

Zheng (Jane) Fan, MD

Associate Professor of Neurology and Pediatrics
University of North Carolina at Chapel Hill

Spinal muscular atrophy (SMA) is a rare condition that affects about 1 in 10,000 new babies in the United States. People with SMA start showing signs at different ages. Most people have signs as babies or young children, but some don't have signs until they are teens or adults.

Over time, the muscles of people with SMA get smaller and weaker. This can affect their ability to walk, eat, and breathe. SMA can cause death in early childhood or later in life depending on the type of SMA a person has.

SMA is a genetic condition, meaning that it can run in families. SMA is caused by a change in a gene called the survival motor neuron gene 1 (SMN1). Some pregnant women have prenatal testing for SMA (a test done during the pregnancy). Parents with one child with SMA could have another child who also has it.

Currently, there is no cure for SMA, but there is one new treatment and researchers are looking for other ways to help. This includes a variety of services to help with breathing, eating, getting around, and other symptoms and che

– Learn more about fragile X syndrome from our experts

Don Bailey, PhD

Director of the Center for Newborn Screening, Ethics, and Disability Studies
Distinguished Fellow
RTI International

Cynthia M. Powell, MD

Professor of Pediatrics and Genetics
Director, Medical Genetics Residency Program
University of North Carolina at Chapel Hill

Fragile X syndrome is a rare condition that is more common in males than females. About 1 in 4,000 boys and about 1 in 6,000 girls has fragile X syndrome. A child with fragile X syndrome might have developmental delays, such as walking and talking later than is usual for their age, and learning disabilities. They might also have anxiety, hyperactivity and a short attention span. Some children with fragile X syndrome also have autism. Girls often have milder symptoms than boys.

Fragile X syndrome is a genetic condition, meaning that it can run in families. Fragile X syndrome is caused by a change in a gene called FMR1. Some pregnant women have prenatal testing for fragile X syndrome (a test done during the pregnancy). Parents with one child with fragile X syndrome could have another child who also has it.

There is no cure for fragile X syndrome, but there are early intervention services that can help with learning, behavior, and social relationships.

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Early Check

Are the screening tests perfect?

A screening test is a good, quick way to check lots of babies, but here are some things to know.

- The screening test may miss some babies with the health problems.
- The first screening test could come back not normal even though the baby is fine. That's why Early Check uses a second test to tell for sure.

Early Check screens for only two rare health problems, SMA and fragile X syndrome. Early Check will not give you information about any other health problems.

In rare cases, we cannot do the screening test because there is not enough blood left over after newborn screening. If this happens, the Early Check team will let the parent know and talk about options.

In rare cases, the screening test may accidentally show information that Early Check tests do not mean to test for. We will not give out the result if this happens.

+ **Click here if you are having twins or multiple babies.**

+ **Learn more about screening tests.**

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Next

− **Learn more about screening tests from our experts**

Scott Shone, PhD
Senior Research Public Health Analyst
RTI International

1. Screening tests may not find all babies.

Early Check screening tests will catch most, but not all, babies with these health problems. A few babies who have a normal screening test may really have the health problem and may develop symptoms later. **Parents should always share any concerns about their baby's development with the doctor.**

A screening result that comes back as not normal could be wrong. That's why we use the second test to tell for sure. Most babies with a result that is not normal have the health problem. A few do not, because screening tests are not perfect.

2. Screening tests are targeted to specific health problems.

Early Check screens for only two rare health problems, SMA and fragile X syndrome. In rare cases, the screening test may accidentally show information that Early Check tests do not mean to test for. We will not give out the result if this happens.

3. There may not be enough blood spot left to do the Early Check screening.

In rare cases, we cannot do Early Check screening because there is not enough blood left over after regular newborn screening. We expect this to happen in less than 1 in 100 babies. If this happens, the Early Check team will let the mother know. The parent can decide whether to have another drop of blood taken from the baby so that the Early Check screening can be done.

4. When second testing is needed, it is done at a different laboratory.

- **Most of the time** the second test will have the same result. Those babies **do** have the health problem.
- **Some of the time** the second test will have a normal result. Those babies **do not** have the health problem.

Either way, the Early Check team will carefully explain the results to the family.

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Why might you say yes to Early Check? And why might you say no?

Play voice over

It's OK to decide yes or no to Early Check. All research has benefits and risks. You should make the best decision for your family.

Watch this last short video about Early Check. Click "play" to begin. You can read the text instead of watching the video by clicking the 'Read' icon.

Read

Here is a checklist to help you decide:

- Would you want to know if your newborn has one of the health problems screened in Early Check?
- Are you okay knowing that right now there is no cure for the health problems?
- Do you have the information you need to make the decision?
- Do you feel ready to learn the answer of the screening tests?
- If your baby has a screening test that is not normal are you okay with your baby having a second test to tell for sure?

If you checked most of these questions, maybe you are ready to sign up your baby. If you did not check most of these questions, maybe you are not ready or it is not the right decision for you.

Parents can **contact** the Early Check team to answer questions.

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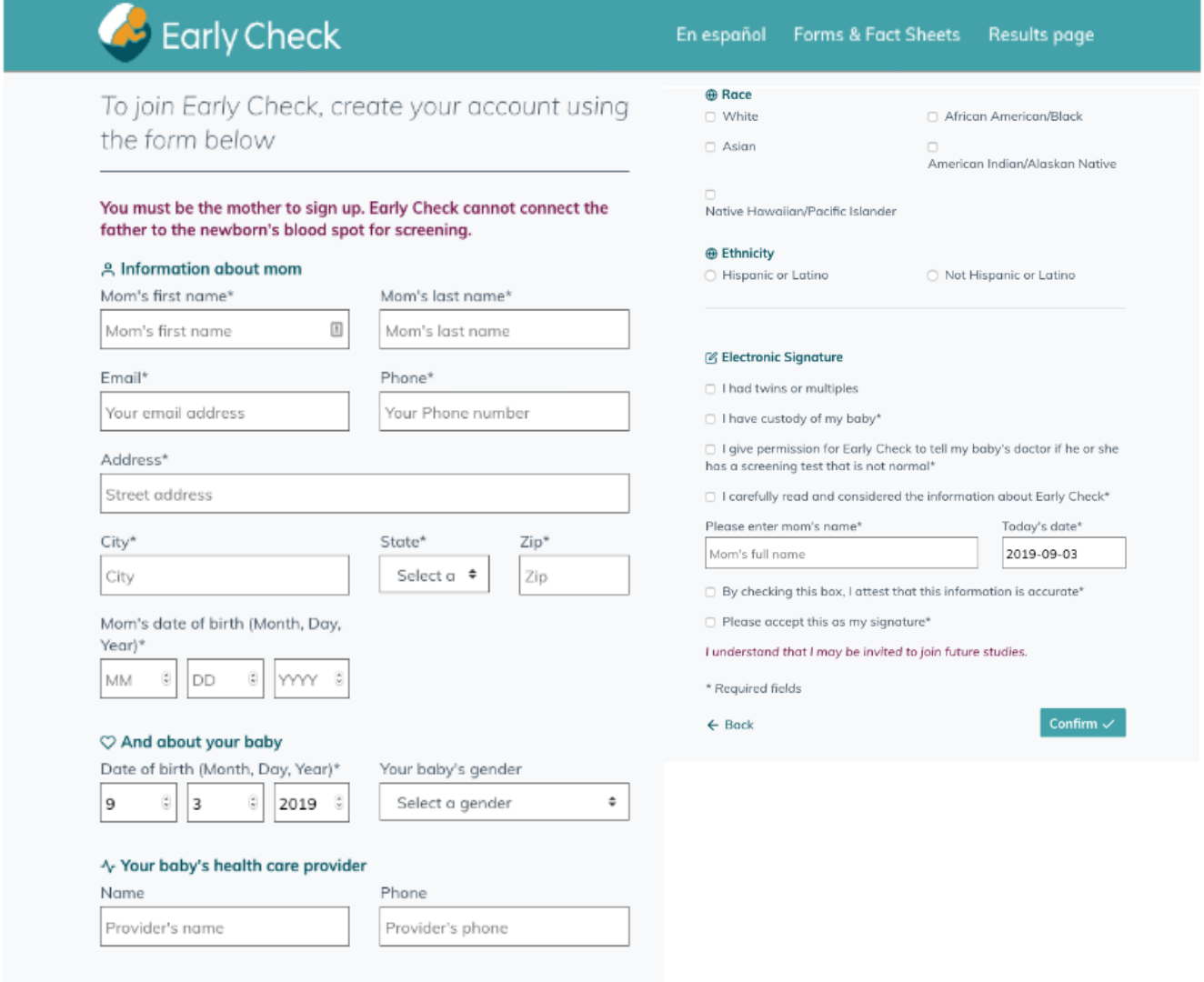
Play voice over



Early Check

En español Forms & Fact Sheets Results page

To join Early Check, create your account using the form below

You must be the mother to sign up. Early Check cannot connect the father to the newborn's blood spot for screening.

Information about mom

Mom's first name*

Mom's first name

Mom's last name*

Mom's last name

Email*

Your email address

Phone*

Your Phone number

Address*

Street address

City*

City

State*

Select a

Zip*

Zip

Mom's date of birth (Month, Day, Year)*

MM DD YYYY

And about your baby

Date of birth (Month, Day, Year)*

9 3 2019

Your baby's gender

Select a gender

Your baby's health care provider

Name

Provider's name

Phone

Provider's phone

Race

White

African American/Black

Asian

American Indian/Alaskan Native

Native Hawaiian/Pacific Islander

Ethnicity

Hispanic or Latino

Not Hispanic or Latino

Electronic Signature

I had twins or multiples

I have custody of my baby*

I give permission for Early Check to tell my baby's doctor if he or she has a screening test that is not normal*

I carefully read and considered the information about Early Check*

Please enter mom's name*

Mom's full name

Today's date*

2019-09-03

By checking this box, I attest that this information is accurate*

Please accept this as my signature*

I understand that I may be invited to join future studies.

* Required fields

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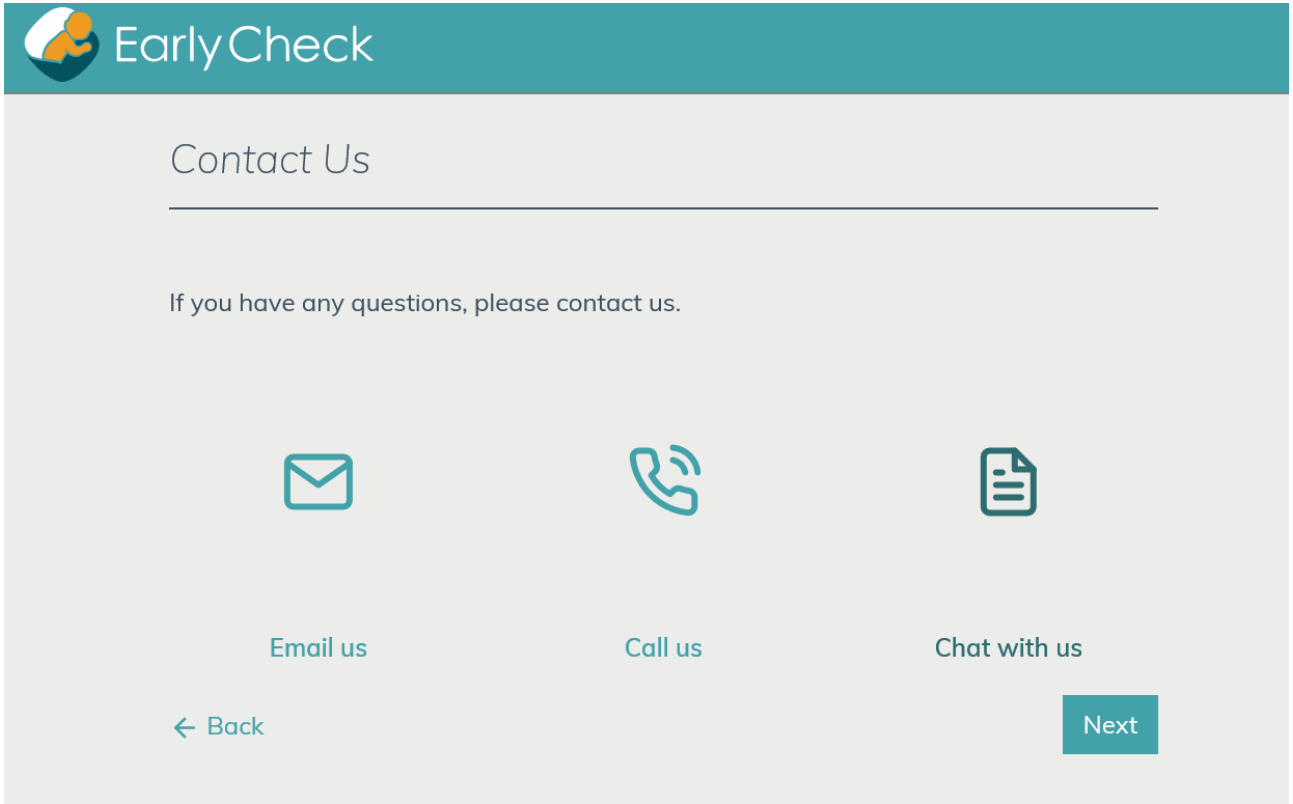
Confirm ✓


EarlyCheck
Contact Us
If you have any questions, please contact us.
Email us
Call us
Chat with us
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Quality Improvement Survey Results

Eligibility Criteria

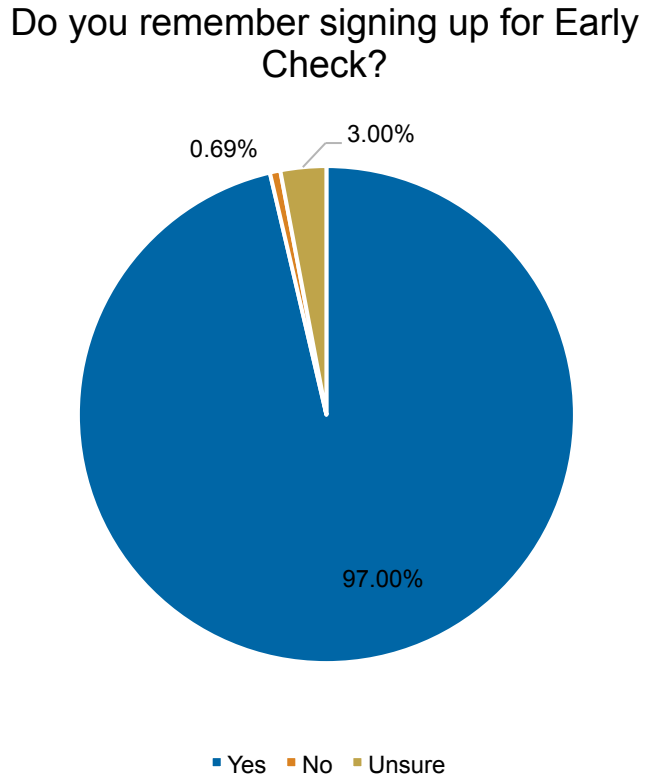
- Mothers at least 18 years old at the time of signing up for Early Check
- Mothers whose babies were born between October 1, 2018 – June 30
- Mothers whose babies received negative screening results

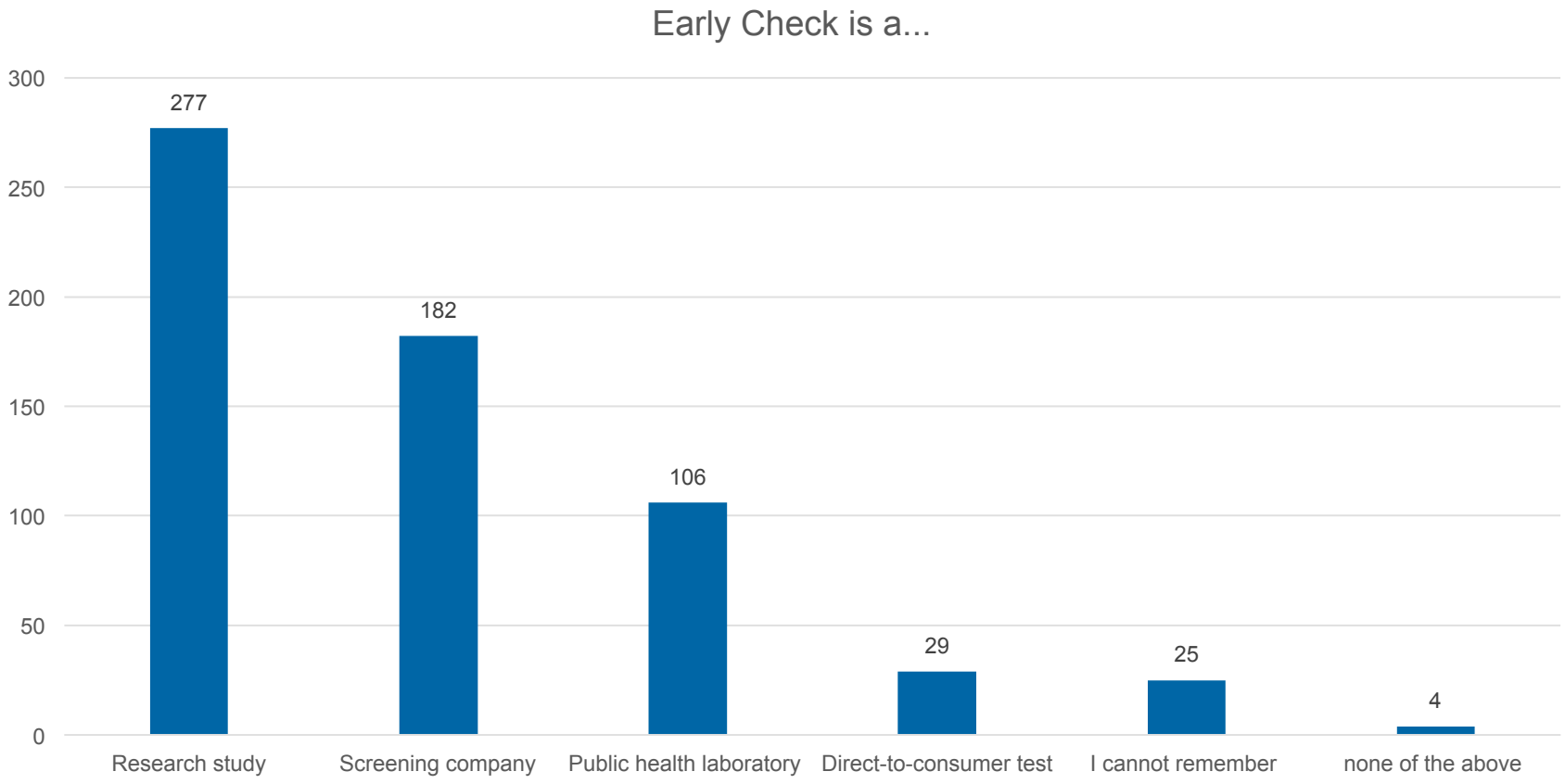
Survey implemented online, English only

Invitation was sent to 3207 participants

Results (n=432)

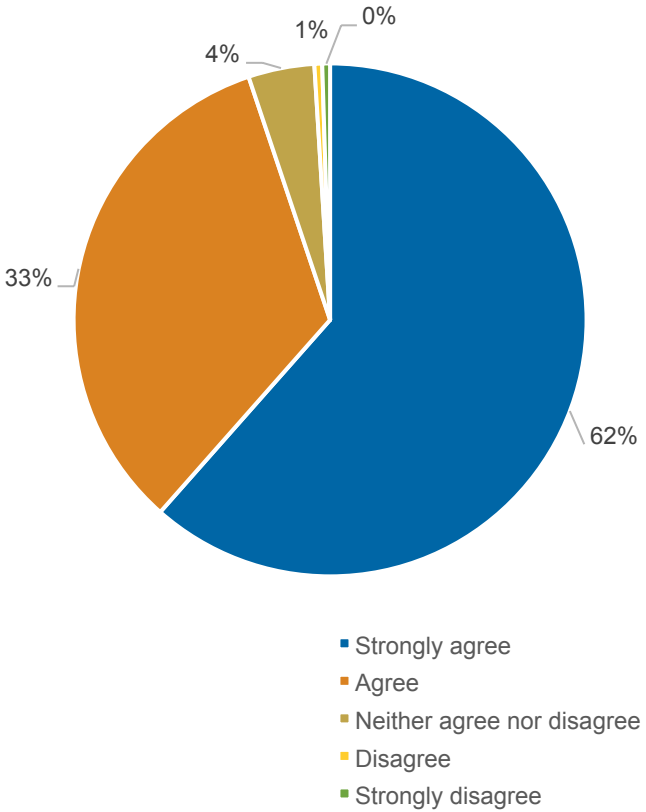
Demographic Characteristics	n	%
Race		
White	361	84.15%
African-American/Black	25	5.83%
Asian	17	3.96%
American Indian/Alaskan Native	4	0.93%
Native Hawaiian/Pacific Islander	0	0.00%
I prefer not to answer	6	1.40%
More than one race	16	3.73%
Total	**429**	100.00%
Ethnicity		
Hispanic or Latino	20	4.65%
Not Hispanic or Latino	403	93.72%
I prefer not to answer	4	0.93%
Total	**430**	99.30%



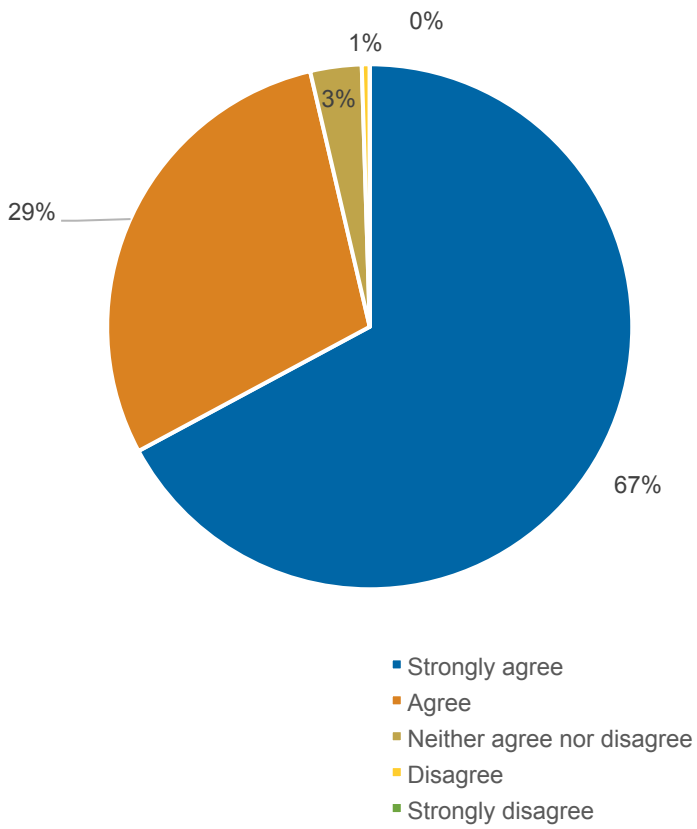


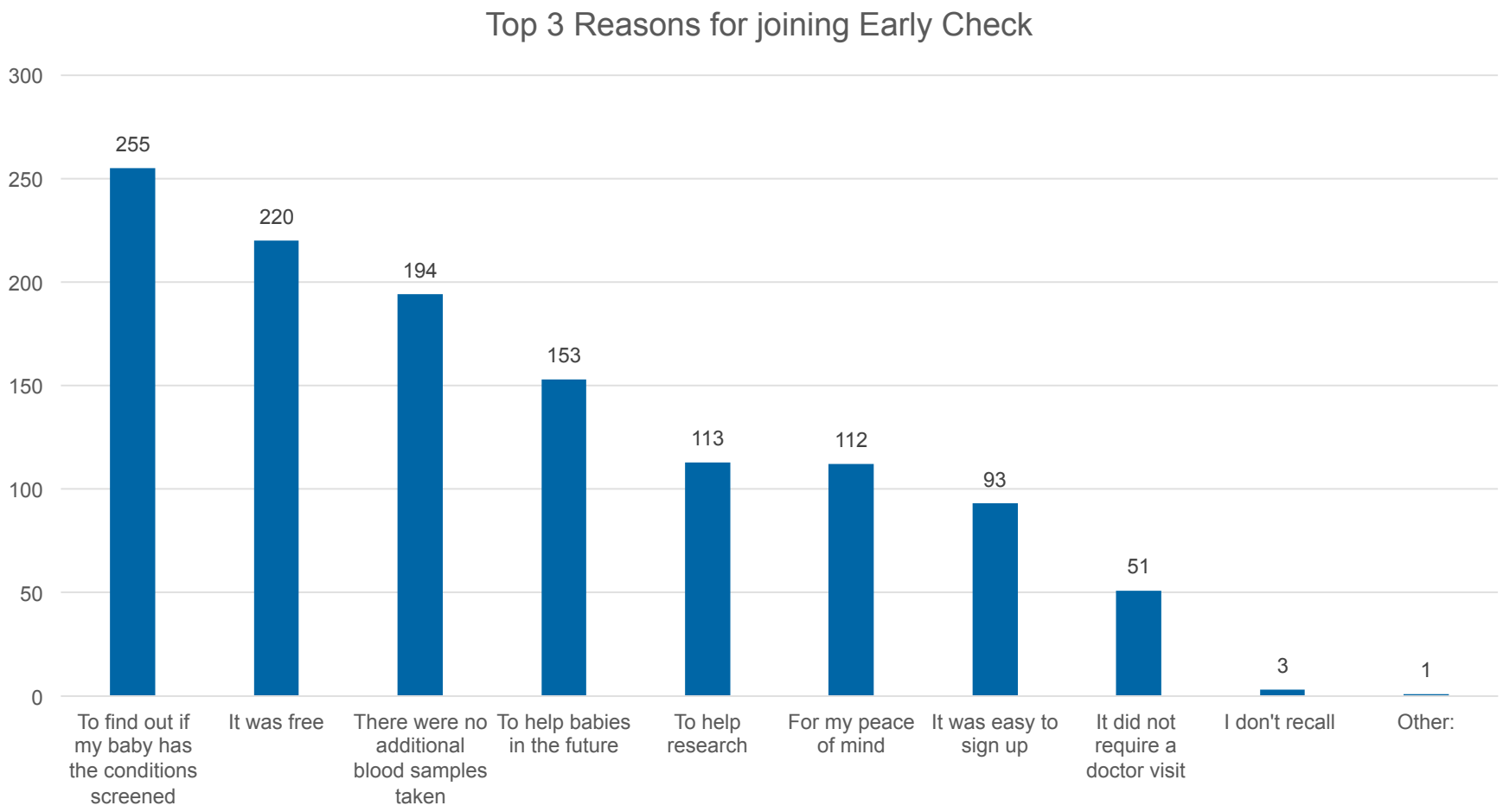
Note: participants could select more than one response

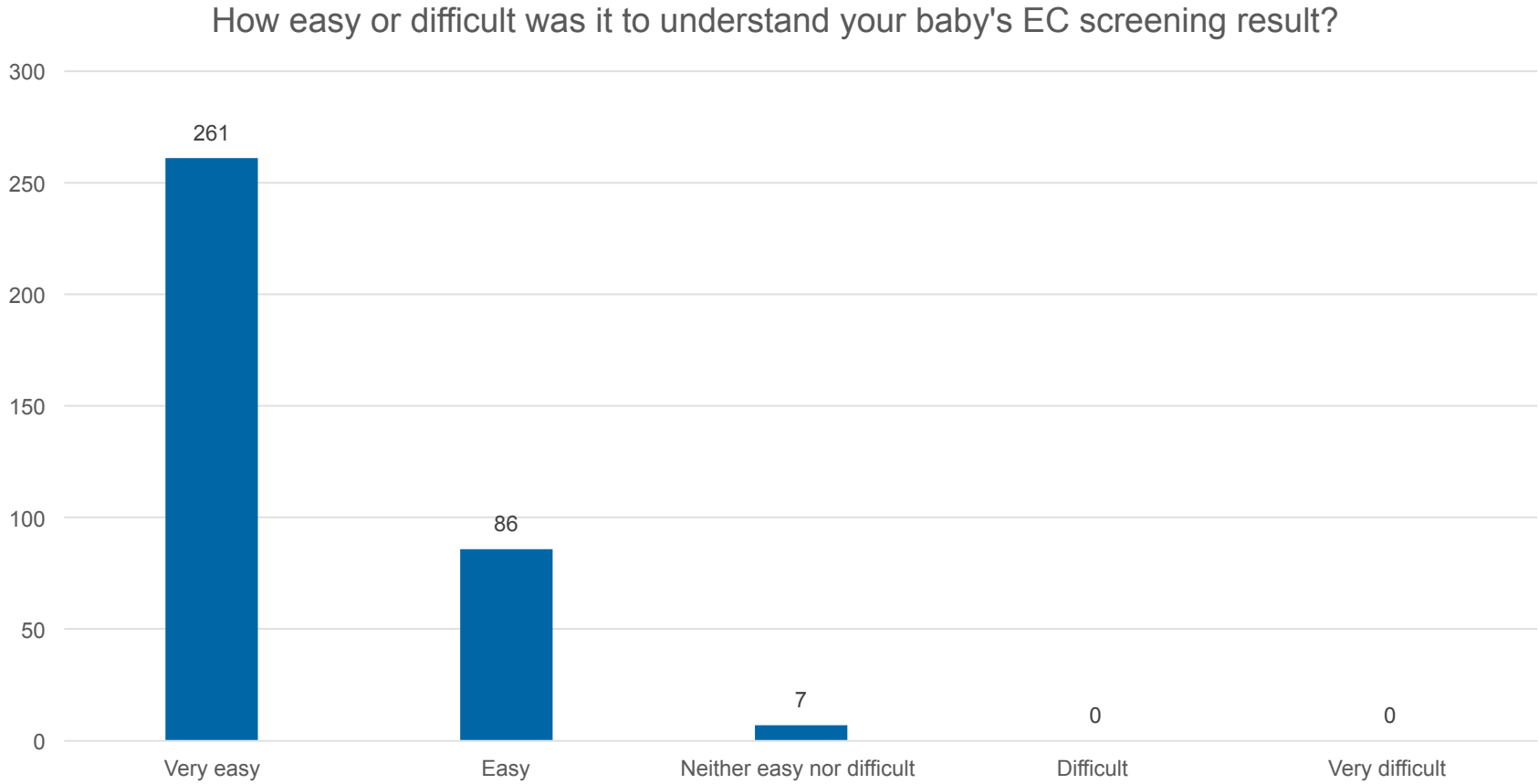
I trust the information on the Early Check website.



Early check gave me enough information to make a decision about signing up.

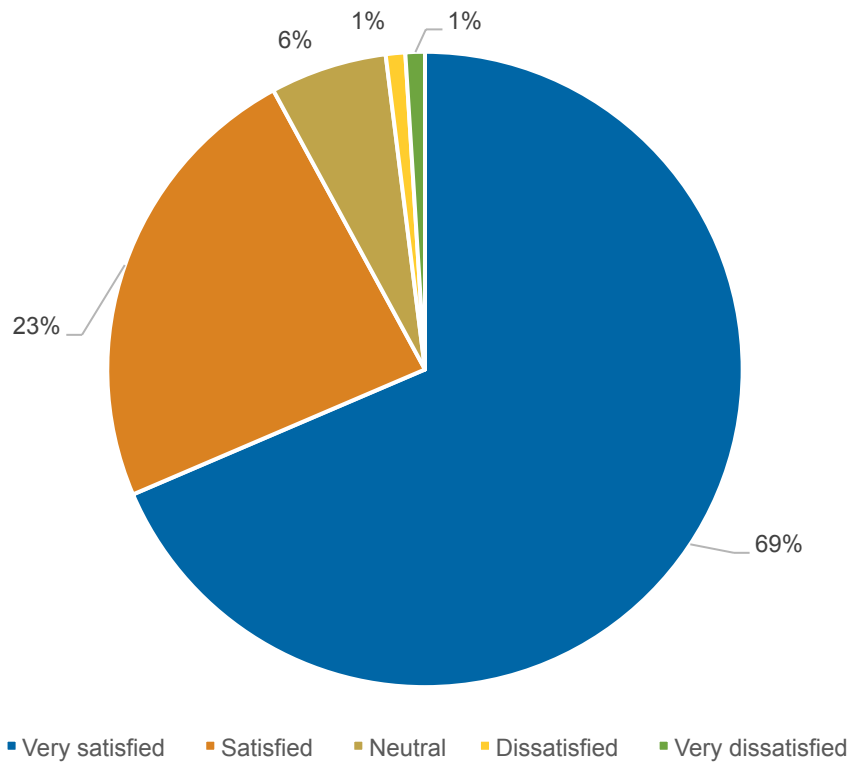



Top 3 Reasons for joining Early Check
300
250
200
150
100
50
0
255
220
194
153
113
112
93
51
3
1
To find out if my baby has the conditions screened
It was free
There were no additional blood samples taken
To help babies in the future
To help research
For my peace of mind
It was easy to sign up
It did not require a doctor visit
I don't recall
Other:



Note: Only asked of participants who indicated “downloaded and saved to my computer,” “shared with my baby’s doctor,” or “shared with family/friend”

Overall, how satisfied are you with Early Check?



Fragile X Premutation Screening Experience

Early Check

If you are 18 or older, you have a choice to get an extra Early Check screening result on your baby.

You signed up for the Early Check research study. You gave permission for your baby to be screened for two rare health problems: spinal muscular atrophy and fragile X syndrome.

The Early Check screening test for fragile X syndrome also gives extra results about fragile X premutation.

- Early Check will know if a baby has fragile X premutation through the same screening test used for fragile X syndrome. You can now choose whether to get this extra screening result for your baby. Every parent who is 18 years or older when they sign up for Early Check is given this choice.
- You have to sign up to get the extra result. You can read the following 6 screens and decide whether you want this extra information on your baby. It is up to you to decide.
- To go through the process, you must be logged in.

You only have 48 hours to sign up for the extra result because the laboratory does all the screening tests together.

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Next

Early Check

Why might you say "Yes" to getting the extra results? Why might you say "No"?

It's OK to decide yes or no. You should make the best decision for your family.

The main benefits are:

- Parents learn more about their baby's health.
- This information may be important to others in the family.
- If we know earlier that the baby could have even mild problems, there may be ways to help.
- For babies with fragile X premutation, Early Check will give information to parents and offer genetic counseling and a check of the baby's development.

Risks:

- Parents may worry about their baby's future.
- Doctors are not sure what the diagnosis of fragile X premutation will mean for a child. If their baby's test is not normal, parents won't know if the baby will show any problems or if the problems will be very mild or more serious.
- Parents may worry about the privacy of their or their baby's information.

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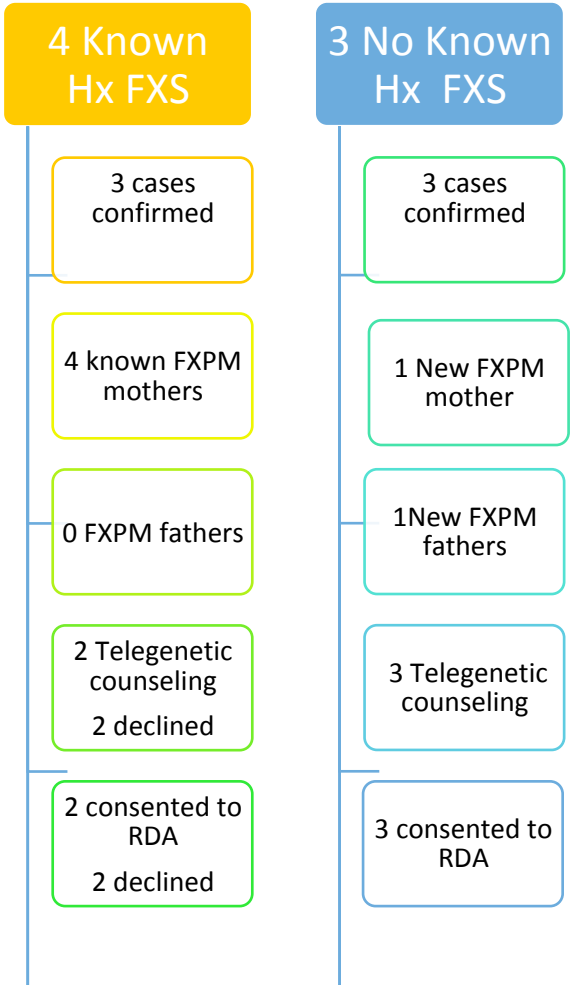
Early Check identification of fragile X premutation

- 18 babies identified with FXPM
  - 11 did not consent to premutation results
  - 7 consented to premutation results



Follow up offered under research protocol

- Flexible, parent-centered genetic counseling
  - Intentional messaging about uncertainty
  - Telegenetic or in-person counseling appointments
  - On-demand interpreter service

- Assessments at 3 and 6m
  - Developmental assessment (Vineland, Bailey, Peabody)
  - Autism Observation Scale for Infants
  - Parent-reported infant behavior, feeding, sleep questionnaires
  - Parent wellbeing (stress, anxiety, depression)
  - Decisional conflict and regret

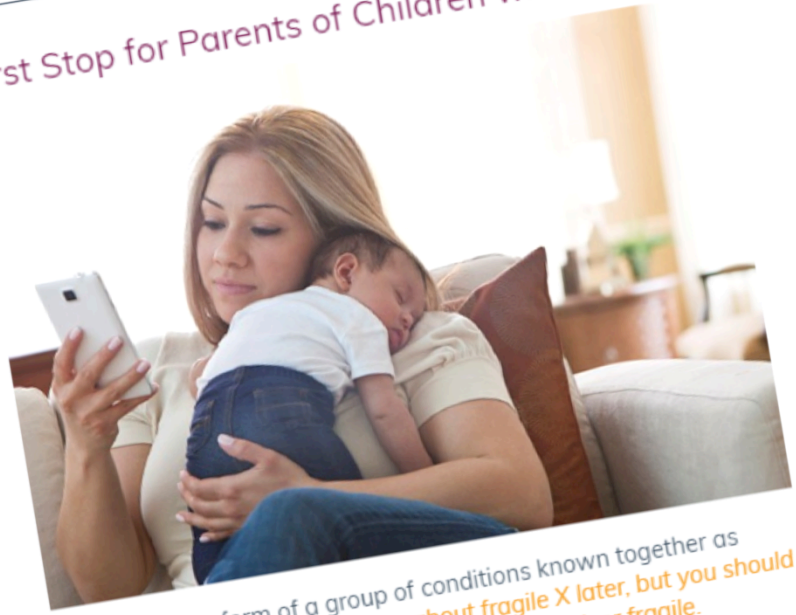
Targeted web content

- Developed by fragile X experts, genetic counselors, and web and data visualization specialists
- Uses plain language/low literacy concepts
- Tested and refined to improve understanding and user experience
  - Identified unexpected barriers to understanding
    - Strong negative images evoked by the terms “fragile X” and “mutation” “premutation” made it difficult for participants to receive reassurance about the actual implications
    - Association of the term “carrier” with infectious disease led to misunderstanding of genetic inheritance
  - Added animations with subtitles and voice-overs for high cognitive demand concepts

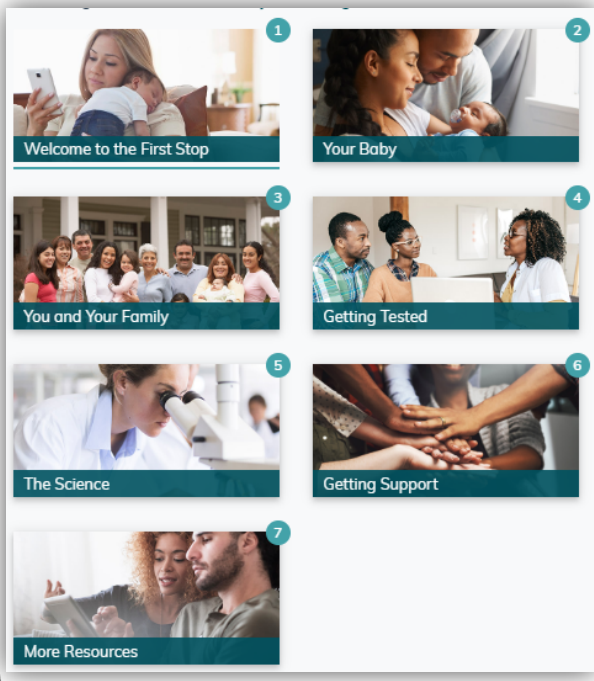
For New Parents

First Stop for parents of babies with the fragile X premutation

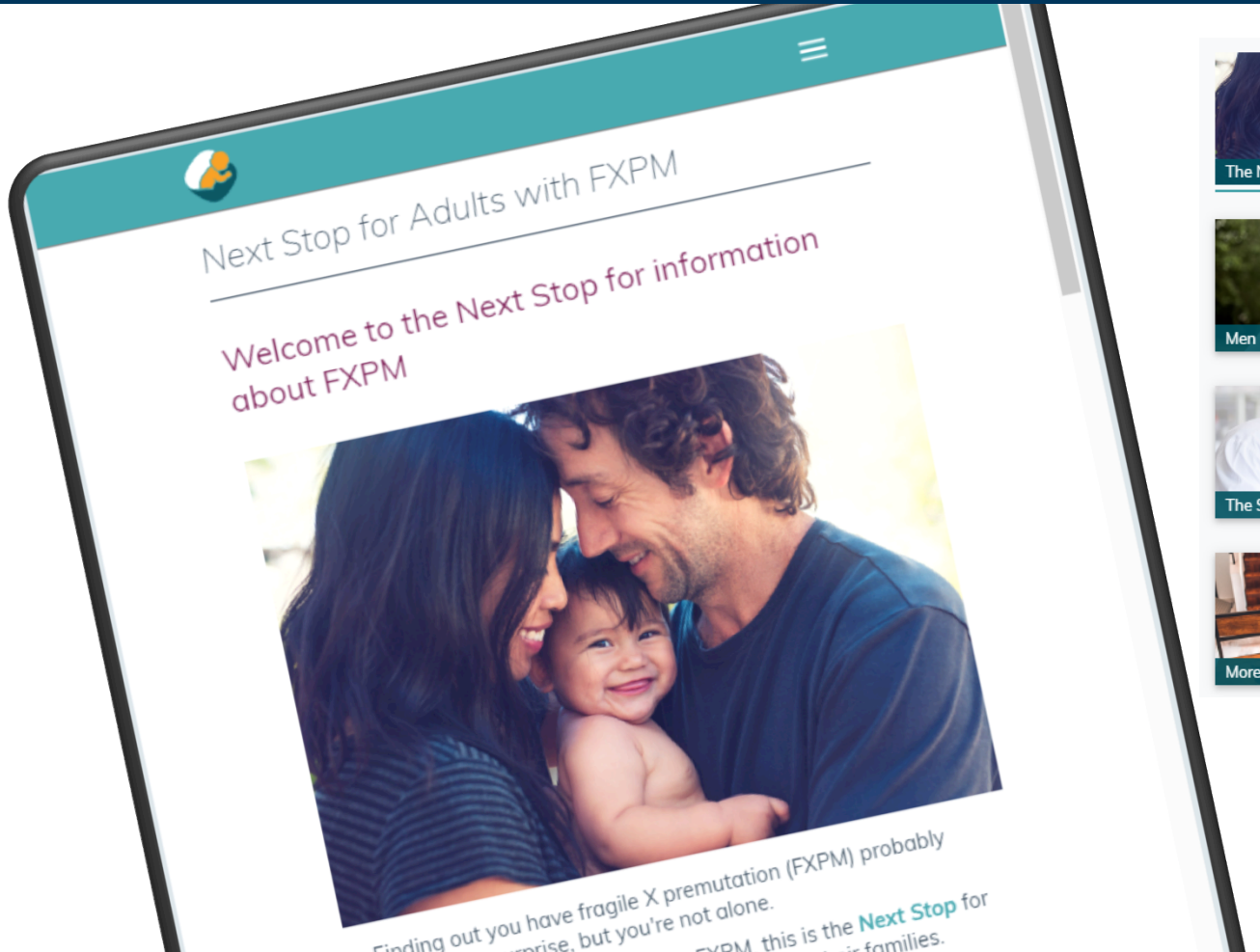
First Stop for Parents of Children with FXPM



- FXPM is one form of a group of conditions known together as "fragile X". We'll tell you more about fragile X later, but you should not cause people to be weak or fragile.



For Newly Identified Adult Carriers



Experience returning premutation NBS results: lessons learned

Initial Protocol

- Abnormal infant screening results are relayed by phone to the mother.
- During the initial phone call, mothers are informed about carrier testing.
- Mothers' testing has been performed at the same time as confirmatory testing for the babies.
- Baby's confirmatory results and mother's carrier testing results are relayed to the mother or parents via a telegenetic counseling session.
- If mother's result is negative *and* baby is a girl, fathers receive pre-test counseling are offered carrier testing.

Experience returning premutation NBS results: lessons learned

Anticipated (and experienced!) challenges

- For those with no prior family history and an apparently healthy newborn, the *unexpected* positive screening result is difficult to comprehend.
- During the initial phone call to relay screening results and arrange confirmatory testing, the implications of parental carrier testing for the mother may not be fully appreciated.
- Mothers may not pass information on to fathers, and fathers have not contacted the genetic counselor.
- When the baby is a girl and the mother's result is negative, the father's carrier status (or non-paternity) can be immediately inferred.
- Implications of fragile X premutation is complex and very different for women, men and babies, each best supported through separate genetic counseling sessions.

Experience returning premuation NBS results: lessons learned

Protocol modifications

- When possible, arrange for both parents to hear screening results simultaneously.
- Offer parental carrier testing at a second session after counseling about the baby's confirmed test result, especially if there is no known family history.
- Approaches to discuss implications for men vs women:
  - reproductive implications (FXS, FXPOI)
  - presymptomatic identification of a genetic condition (FXTAS)
  - potential to infer father's status or non-paternity if mother's result is negative

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