



# Baby Badger Network ECHO

## Coordinating and Organizing Workflows in Your NICU

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# Learning Objectives:

1. Describe a clinical workflow for implementation of Exome Sequencing (ES) / Genome Sequencing (GS) in a NICU setting
2. Identify provider roles in the NICU ES/GS workflow
3. Discuss importance of effective communication between providers and family when performing ES/GS in critically ill neonates
4. Discuss challenges and solutions to implementing genomic medicine in a NICU setting

# Children's WI current workflow

- **Primary team consults Genetics**
  - Timing: same day as consult, next day
  - Genetics provider team (MD/APP) reviews patient history and completes physical exam
  - Genetic counselor takes family history
- **Genetics team determines best testing for patient**
  - Timing: ideally same day as consult, next day
  - Genetic counselor meets with family to review testing options
    - Most families are offered a modified exome (secondary findings are automatically not reported)
    - Parents are offered an opportunity to provide samples
- **Genetic counselor orders testing once parents consents to testing**
  - Timing: heavily depends on family's decision-making process; same day to a week later
  - Genetic counselor coordinate parental samples submission with CW send outs lab
- **Test results available**
  - Timing: dependent on testing, could be 2-3days or 8 weeks after testing is ordered
  - Patient still admitted – GC coordinates with primary team to find time to review results with parents
  - Patient is discharged – GC coordinates with genetics team to identify follow up appt and calls out results

# Your theoretical rapid genome workflow

- **Primary team ~~consults Genetics~~**
  - Timing: same day as consult, next day
  - ~~Genetics provider team (MD/APP) reviews patient history and completes physical exam~~
  - ~~Genetic counselor takes family history~~
- **Primary (genetics) team determines (that rapid genome is) best testing for patient where is your institution sending rapid genome?**
  - Timing: ideally same day as consult, next day
  - ~~Genetic counselor meets with family to review testing options~~ Who is tracking family down? Can it be a phone consent?
    - Most families are offered a ~~modified exome~~ (what is your institutional policy about secondaries?)
    - Parents are offered an opportunity to provide samples – who is coordinating parental sample collection? Who is labeling the tubes? Bedside RN?
- **~~Genetic counselor WHO orders testing once parents consents to testing – dot phrase? Who is checking sample requirements for lab, etc? Who is obtaining any needed signatures of TRF for lab?~~**
  - Timing: heavily depends on family's decision-making process; same day to a week later the sooner the better
  - ~~Genetic counselor WHO coordinates parental samples submission with send outs lab –who is completing parental TRFs? Is your send outs lab comfortable handling samples of unregistered parents?~~
- **Test results available –**
  - Timing: dependent which lab is running the rapid genome? Do they provide prelim verbal results? Does your institution disclose prelim results??
  - Patient still admitted – who owns results disclosure? Team that ordered the testing? Team that's caring for the baby when results come back?
  - Patient is discharged – who owns results disclosure?

# Workflow questions to have asked when considering a rapid genome

- **Primary team determines that rapid genome is best testing for patient**
  - Where is your institution sending rapid genomes? Do you have contracts in place or can you just pick a lab?
  - Who is tracking family down to obtain consent? Can it be a phone consent?
  - Are you offering every family a trio? Or does your institution limit testing to just the proband (singleton)?
- **Primary team orders testing once parents consents to testing**
  - Who is ordering the testing for the patient? Do you have an order set/dotphrase to ensure that important details aren't lost/missed?
    - Who is checking sample requirements for lab, etc?
  - What is your policy about secondary findings?
  - Who is obtaining any needed signatures (dependent on TRF from lab performing genome)?
  - Parental samples
    - Who is coordinating parental sample collection? What kind of sample are you collecting?
      - Buccal: Where are the collection tubes kept? Who is labeling the tubes? Who is passing them off to send outs?
    - Who is completing parental test requisition forms (TRFs?)
      - Is your send outs lab comfortable handling samples of unregistered parents?
- **Test results available**
  - Timing: dependent which lab is running the rapid genome
  - Does lab running testing provide prelim verbal results?
    - Does your institution disclose those verbal prelim results? Or do you wait for the finalized report?
  - Patient still admitted – who owns the results disclosure?
    - Team that ordered the testing? Team that's caring for the baby when results come back?
  - Patient has transferred – how do you share the verbal results with OSH? How do you share the written results with OSH?
  - Patient is discharged – who owns the results disclosure?
    - Does family need to come back in for a follow up visit to formally review results?
  - Patient is deceased – who owns the results disclose?
    - Are you documenting results disclose in deceased pt's chart? Are you requiring the results disclosure to happen under a family member's name?

# St. Vincent Hospital – Rapid Whole Genome Sequencing (rWGS) or Whole Exome Sequencing (rWES) - Implementation

- rWGS projects in Boston, California and Michigan proved that among high-risk infants meeting specific criteria, rWGS helped identify a final diagnosis in about two weeks for 38% to 58% of babies, resulting in faster, more accurate diagnoses, reducing unnecessary testing, procedures with reductions in healthcare spending.
- After learning about the success of these projects, we talked to one of our NICU docs who was very interested in moving forward with learning more about rWGS for babies in our hospital.
- We asked one of the labs that did rWGS at that time, GeneDx, to present to us so that we could understand more about this testing.
- Our first meeting was in 08/2021.
- Our first patient tested with rWGS was in 09/2021.
- Since we are a multispecialty genetics clinic and have a great NICU team, we had a lot of experience with logistics of this testing and pretty good idea of how to go about implementing this testing and we had a NICU CHAMPION who was pro genetics and pro rWGS – this was key!
- Prior to seeing our first patient, our genetics team worked together with the GeneDx team, and Dr. Rock (neonatologist) to create our workflow, including deciding on
  - rWGS mostly with exception of rWES (if UHC commercial)
  - Our selection criteria
  - Importance of getting parents samples – trio testing
  - Logistics of billing, order sets
  - Ordering
  - Who is responsible for various duties, who are the key team members, educating the team regarding the process to get all involved in the NICU on the same wavelength, informing lab and other departments who may be involved
  - Communication
    - Who starts the process, who talks to parents about rWGS, who contacts genetics
    - How and when are the parents consented, what if both parents can't be there at the same time
    - Once the baby's sample is obtained, where do we keep it until the parents are consented and their sample can be obtained? Who packages and sends out samples and informs the rapid genome lab team? Who informs the lab of new clinical hx?
    - What about parental sample orders, who places those
    - Who gets the results?
    - How are the results communicated between genetics and NICU?
    - Preliminary results are only called out, no written reports until the final results, how do we handle preliminary results – inform the family or not?
    - How will results be handled?
    - What if baby is discharged or transferred by the time the results are back, then how are the results handled?
    - Who can help when questions – who are your support people?

Clinical criteria:

- Neonatal encephalopathy without inciting event
- Multiple congenital anomalies or dysmorphic features not suggestive of aneuploidy or known syndrome
- Concern for metabolic disorder
- Neonatal seizures without HIE
- Hypotonia
- Complex congenital heart disease
- Severe symmetric IUGR without clear etiology
- Hydrops fetalis without clear etiology (added 10/30/2024)
- Hypertonia or muscle weakness of unidentified etiology (added 10/30/2024)

**Genetic counselors:**

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## HSHS St. Vincent Hospital NICU rapid genome/exome process



GeneDx XomeDx Xpress team contact: 888-729-1206; [Xpress@genedx.com](mailto:Xpress@genedx.com)

HSHS St. Vincent Genetics contact: x48559 (920-433-8559)

Genetic counseling assistants:

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12/14/2023  
1<sup>st</sup> case 09/2021

# Order Set for rWGS (or rWES if UHC commercial)

Genetics creates an ambulatory appointment for parents. Genetics can place the miscellaneous order for the blood draw for the parents and route the order to neonatologist who is on that day. The neonatologist then will need to sign the order. This will work as long as genetics is involved and can enter the order.

NICU Rapid WES / WGS Order set (SVG Only) Manage User Versions Remove Order Sets

▼ LABS

▼ Labs

- Whole Exome Sequencing - (Patients with commercial UHC insurance - NOT for patients with medical assistance)  
MISCELLANEOUS LAB TEST (\$)  
Today, today at 1023, For 1 occurrence  
Test Name? GeneDx test code: 896  
Release to patient: System release  
NICU staff will draw 1-2 mL blood into lavender top (EDTA tube). NICU will hold sample (refrigerator) and call Genetics 4-8559 to pick up sample (during business hours). GeneDx will bill patient's insurance directly for testing. When using this procedure, please order ONLY one test per Miscellaneous Lab Test procedure.
- Whole Genome Sequencing (Patient with insurance OTHER THAN commercial UHC insurance)  
MISCELLANEOUS LAB TEST (\$)  
Today, today at 1023, For 1 occurrence  
Test Name? GeneDx test code: TH78  
Release to patient: System release  
NICU staff will draw 1-2 mL blood into lavender (EDTA tube). NICU to hold sample (refrigerator) and call Genetics 4-8559 to pick up sample (business hours). GeneDx to bill SVG and SVG to bill patient's insurance. When using this procedure, please order ONLY one test per Miscellaneous Lab Test procedure.

▼ CONSULTS

▼ Ancillary Consults

NICU staff, please call Genetics at 4-8559 to refer patient.

Ambulatory referral to Genetics

# Resources Created for NICU staff – NOT intended for you to actually read this, just examples

## Provider sheet – how to order rapid whole exome sequencing or whole genome sequencing

- Baby meets clinical criteria? Positive for at least one of the clinical characteristics below?
  - Neonatal encephalopathy without inciting event
  - Multiple congenital anomalies not suggestive of aneuploidy or known syndrome
  - Concern for metabolic disorder
  - Neonatal seizures without HIE
  - Hypotonia
  - Complex congenital heart disease
  - Severe symmetric IUGR without clear etiology
- If baby has commercial UHC insurance, to qualify for UHC's NICU WES program:
  - Baby must be born at greater than 32 weeks gestation
  - AND NICU notes should document "A genetic etiology is suspected."
- Has the baby had transfusion of any blood products?** Please inform genetics team if yes **PRIOR to ordering testing for baby.**
- Initial discussion with parents about testing, if parents would like to proceed, please inform genetics team (4-8559) so they can coordinate time to meet with family for discussion of testing and informed consent
  - Trio testing to include samples from both parents is recommended and most informative. Are both parents available?
- Epic Order Set – includes specimen collection + referral to genetics
  - Rapid WES – NICU (for patients with commercial UHC), or
  - Rapid WGS – NICU (for patients with any other insurance)
- Please inform genetic counseling team at SVH about upcoming WES / WGS test by calling **920-433-8559**
- Arrange for blood draw, **1-2 ml whole blood (MINIMUM is 1 ml) in EDTA tube**; call genetics (48559) to pick up sample (we will pick up Monday-Friday)
  - If sample drawn after hours, leave phone message for genetics, store at room temperature, genetics will pick up M-F
- Put all pertinent phenotypic information into Other section of progress notes and document "A genetic etiology is suspected."
- GOOD COMMUNICATION with the lab send outs person (when lab is involved in sample collection) is important so they are aware of whose blood is being drawn when and that samples will be sent out by genetics.
- If any new phenotypic history emerges after testing is ordered, immediately email GC involved and [Xpress@genedx.com](mailto:Xpress@genedx.com)

### Medical Genetics – 920-433-8559

#### Genetic Counselors

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### NICU rapid Exome/Genome reporting

- Negative preliminary results will be sent to Dr. Rock and GCs via email. Dr. Rock will relay the negative results to the rest of the NICU team.
- GeneDX will be calling any positive prelim results to the NICU. Once a final report is faxed to genetics, we will upload the report in the patient's EMR and let the NICU know it has been uploaded.

## PROVIDER SHEET: Rapid whole genome/exome sequencing overview

- **What it is:** Some of the most comprehensive genetic tests available that look across all known genes (exome) or all DNA (genome)
- **Purpose:** Rather than ordering multiple genetic and biochemical tests sequentially, the time (and cost) to diagnosis can be shortened for many patients by starting with a comprehensive genetic test. The diagnostic yield of at GeneDx for critically ill babies is 38-58% when parental samples are included. Other testing may still be needed after the WES/WGS test (see limitations below).
- **Method:** A blood sample is collected from the patient and both parents. The WES/WGS test is performed on the patient's sample and any plausible genetic variants will be tested for in parental samples to determine if inherited versus de novo.
- **Results:** Will be called to the NICU in ≤7 days of sample receipt at the lab with a formal written report to follow within ~14 days.

## Frequently asked questions

- **What is the difference between exome and genome sequencing?** Exome sequencing looks at the protein-coding exons of the gene, while genome sequencing also includes introns (non-coding DNA). The genetics field is just beginning to learn about disease caused by intronic mutations. Due to insurance differences, we plan to order WES (XomeDxXpress) for patients with commercial UHC insurance and WGS (GenomeXpress) for patients with any other ins type.
- **Which babies should we consider this for?** If a genetic etiology is suggested and infant meets one or more of the following clinical criteria:
  - Neonatal encephalopathy without inciting event
  - Multiple congenital anomalies not suggestive of aneuploidy or known syndrome
  - Concern for metabolic disorder
  - Neonatal seizures without HIE
  - Hypotonia
  - Complex congenital heart disease
  - Severe symmetric IUGR without clear etiology
- **What if both parents aren't available?** The yield of testing is **significantly** higher when both parents' specimens are sent. If at all possible, please push to have both parents' participation. If there is no possible way, testing can be sent as a duo (patient/one parent) or singleton (pt only).
- **How do I order testing?** See separate document – "NICU provider sheet – how to order"
- **What are the limitations of this testing?** WES/WGS does not detect repeat disorders, imprinting disorders, each test may not detect all types of chromosome abnormalities, some deletions or duplications may be missed. There may be limited coverage of some genes. If a genetic condition is suspected after a normal WES/WGS test, other tests such as microarray, targeted panels, or mitochondrial genome testing may be indicated.
- **Are blood transfusions a problem?** Please contact genetics before proceeding if a baby has received a blood transfusion.

# Comparison of St. Vincent Hospital and BBN selection criteria – process improvement

## HSHS rWGS / rWES selection criteria

- Clinical criteria:
- Neonatal encephalopathy without inciting event
- Multiple congenital anomalies not suggestive of aneuploidy or known syndrome
- Concern for metabolic disorder
- Neonatal seizures without HIE
- Hypotonia
- Complex congenital heart disease
- Severe symmetric IUGR without clear etiology

## BBN rWGS selection criteria

- **Hydrops fetalis without clear etiology**
  - **A systematic review of monogenic etiologies of nonimmune hydrops fetalis 2020 publication**
  - Nonimmune HF has many possible monogenic etiologies, several with treatment implications, but current diagnostic approaches are not exhaustive. Studies are needed to assess if broad sequencing approaches like exome sequencing are useful in clinical management of HF.
- Neonatal encephalopathy without inciting event
- Multiple congenital anomalies not suggestive of aneuploidy
- Suspected inborn error of metabolism
- Seizures
- Abnormal neurologic exam including significant hypotonia/**hypertonia, weakness**
- Growth abnormality including Intrauterine Growth Restriction (IUGR) , Small for Gestational Age (SGA), micro/macrocephaly or overgrowth without clear etiology
- **Dysmorphic features**

# St. Vincent new rWGS clinical criteria – beginning 11/01/2024

## **NEW HSHS rWGS / rWES clinical criteria would be:**

- **Hydrops fetalis without clear etiology – add - yes**
- Neonatal encephalopathy without inciting event
- Multiple congenital anomalies **or dysmorphic features** not suggestive of aneuploidy or known syndrome – **add - yes**
- Concern for metabolic disorder
- Neonatal seizures without HIE
- **Hypotonia, hypertonia, weakness without clear etiology – yes**
- Complex congenital heart disease
- Severe symmetric IUGR without clear etiology

# Our first meeting to review SVH first 10 rWGS cases - Topics for Discussion – can we do better, what are the pain points?

- Labeling tube (baby's tube labeled with mom's label)
- Parental sample snafu
- Any neonate with congenital heart defect should be considered for chromosomal microarray and /or other testing, even if he/she does not meet WGS / WES criteria – don't want to become tunnel visioned and forget about other testing
- GeneDx - Results
  - Currently, they were emailing out NEGATIVE results to GCs and calling out POSITIVE results to NICU
  - We agreed on having negative results emailed to NICU and GCs – will make sure it's working
  - Important to accurately record verbal preliminary results
- We talked about - for kids with seizures should we continue to do WGS vs. seizure panel? Nope – sticking with rWGS.