Returning Genome Sequence Results in SouthSeq

Provider Training Session

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Introductions

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During this training we will discuss:

- An overview of the SouthSeq study
- Logistics of returning SouthSeq results
- Logistics of the trial aspect of SouthSeq
- How to use the online Genome Gateway system
- What whole genome sequencing is, and what it is not
- How to prepare for and give back genome results
- Psychosocial considerations in genetics

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Overview of the SouthSeq Study

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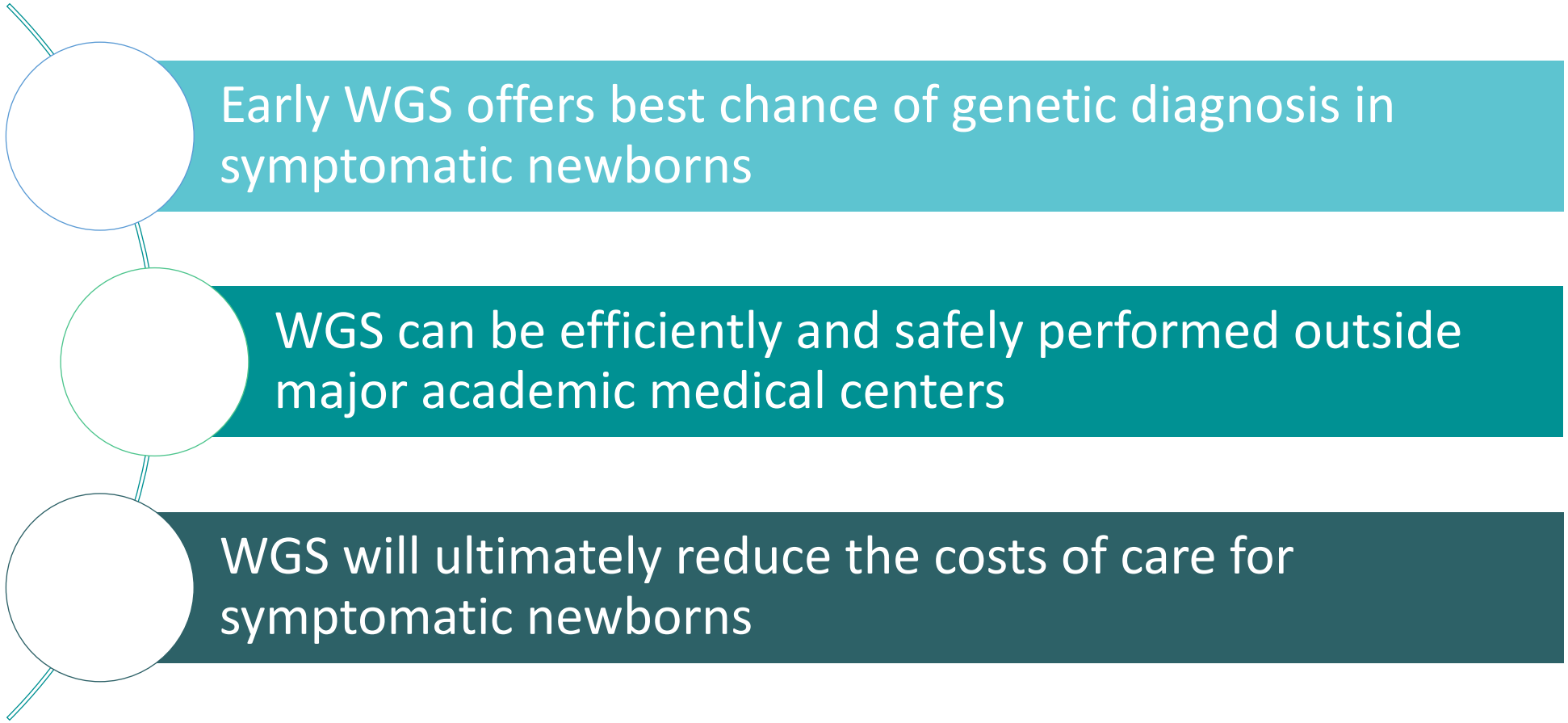
Primary Goal/Hypothesis



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Specific Aims

Aim 1: Perform WGS on 1,500 infants in nurseries with symptoms that prompt a genetics referral

Aim 2: Enable non-geneticist clinicians to return WGS results

Aim 3: Conduct trial to compare return of WGS results by non-geneticist providers vs genetic counselors

Aim 4: Conduct facilitated deliberative process with key stakeholders to develop guidelines for future implementation

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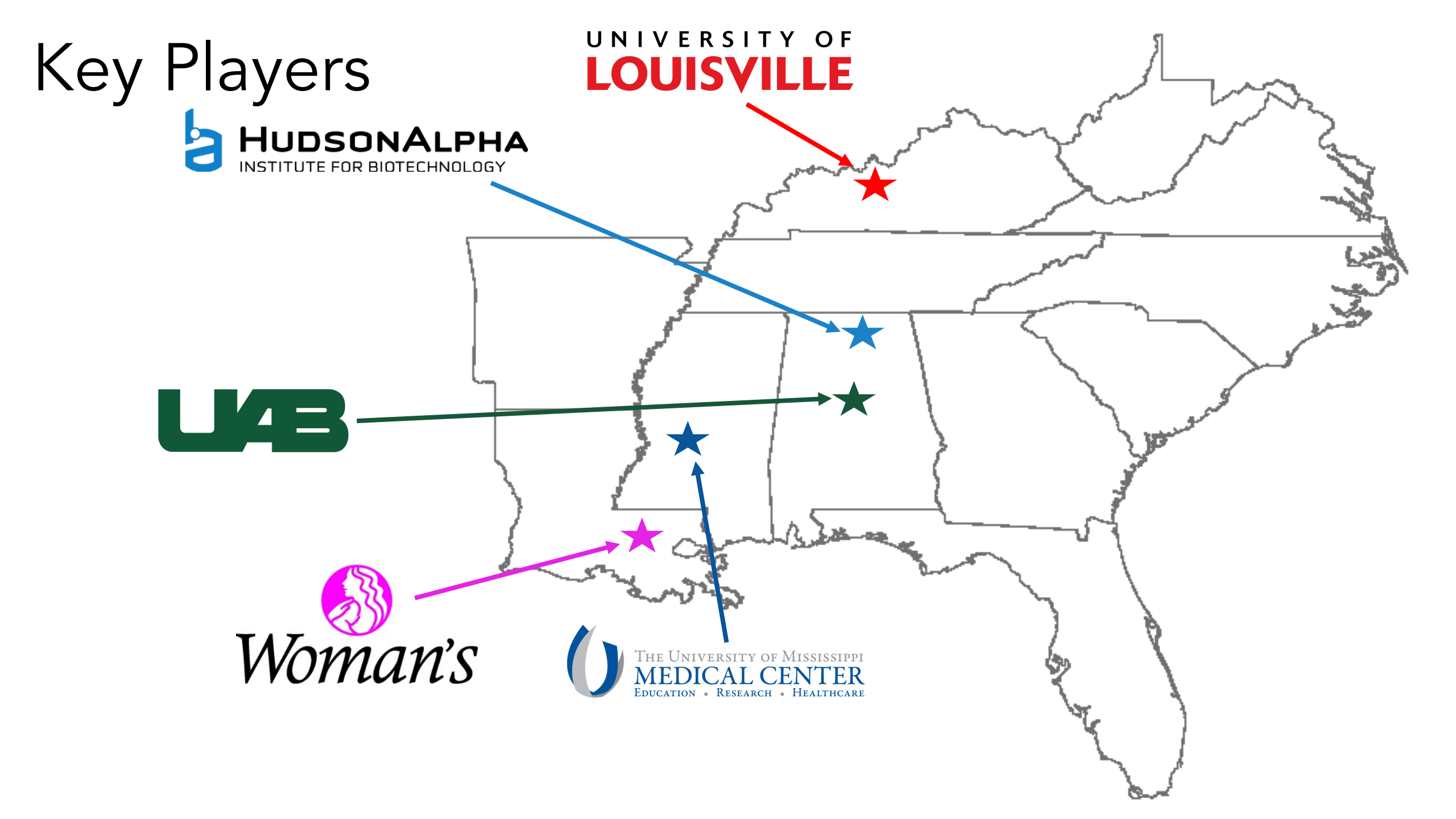
Key Players


UNIVERSITY OF LOUISVILLE
HUDSONALPHA
INSTITUTE FOR BIOTECHNOLOGY
UAB
Woman's
THE UNIVERSITY OF MISSISSIPPI
MEDICAL CENTER
EDUCATION • RESEARCH • HEALTHCARE

Randomization

“Standard of Care” Arm

Informed Consent by Site Research Nurse

Genome Sequencing, Analysis; Results Generated at HudsonAlpha

Results Returned by Site Genetic Counselor

“Experimental” Arm

Informed Consent by Site Research Nurse

Genome Sequencing, Analysis; Results Generated at HudsonAlpha

Results Returned by Site NICU Provider (YOU!)

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Enrollment Criteria

When in doubt, enroll!

Inclusion

- 2 or more major congenital anomalies
- 1 major and 2 or more minor anomalies
- 1 major anomaly and an unexplained major medical condition that is not explained by prematurity
- 1 major anomaly and a first degree relative with the same major anomaly
- **OR, suspicion of a potential underlying genetic condition**

Exclusion

- Known or strong suspicion for a chromosomal aneuploidy (T13, T18, T21, Monosomy X)
- Disorders with established low genetic yield, e.g., gastroschisis, hydronephrosis, isolated congenital heart defects
- confirmed teratogenic exposure
- confirmed congenital infection

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Patient experience

Approached about the study; Decide to enroll

Consent forms signed; blood sample; complete initial surveys; review education

Attend result appointment; get results; complete one survey immediately after results receipt

Complete additional follow-up surveys; review education

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Logistics of return of results

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Return of results is a process by which participant families, and the local clinical team, are notified about the findings of the genome sequencing test.

- Begins when a result report is ready
- Ends when the results have been documented in the medical record and communicated with the clinical team

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From blood sample to result report

- Blood samples sent to HudsonAlpha for sequencing and analysis
- Any findings are confirmed in the lab by a second test
- Any findings are discussed at a Variant Review Committee (VRC) meeting
- HudsonAlpha genetic counselors translate decisions made at the VRC into patient-friendly result report letters

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Where you come in…

Result Ready

- Letter and randomization status sent to site coordinator (in Genome Gateway)
- Will send to you as well, if we know who provider will be
- Will come from HudsonAlpha Genetic Counselor

Result Disclosure

- Appointment scheduled by site coordinator
- Family receives results from either GC or NICU provider (you)
- Family completes first post-result surveys with site coordinator

Documentation and Follow-Up

- You document disclosure in Genome Gateway
- You dcument disclosure at site (varies)
- You communicate result to clinical colleagues for follow-up – ***moving result from research world back to clinical world***

It doesn't end there…

- The lab at HudsonAlpha may learn new information about the results, and issue an updated report
  - Disclosed by the same provider who gave initial results
- The patient may experience new problems/symptoms that could be communicated to the lab
- The patient may have additional questions or concerns that need to be addressed

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The goal of this training is to equip you, the healthcare provider, with information, skills, and confidence to give genome sequencing results back to patients/families in the "experimental arm" of SouthSeq

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Safety Nets

- HudsonAlpha GCs here to be a “just-in-time” resource for you throughout the study
- Specific patient situations that will automatically trigger disclosure by control arm (site genetic counselor)
  - i.e. secondary findings
- Audio recording of result disclosures (all), monitoring and tracking of errors***

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****Not meant to be anxiety inducing.*

Result recording review

High-risk Safety Error

Errors in critical details that are likely to lead to patient harm

Ex. invasive testing recommended based on misinterpreted test result

Notify safety board; Real-time Feedback

Major Errors

Errors in critical details that are likely to have an impact on patient care and decision making

Ex. the recurrence risk is 25% (instead of <1%)

Real-time Feedback

Minor Errors

Errors in non-critical details that are unlikely to have an impact on patient care or decision making

Ex. this gene is on chromosome 6 (instead of 16)

End-of-study Feedback

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Logistics, and some edge cases

Baby has been discharged prior to results	Come back to NICU to receive results in person
Baby has passed away prior to results	Come back to NICU to receive results in person
Family moves or is unwilling to return to NICU for results	Scheduled phone disclosure by same provider who would have done in-person disclosure, rest of process stays same
Family is completely lost to follow-up	Letter sent to family notifying of available results, results put in medical record

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Questions?

Logistics of the trial

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Study Population and Timeline

- ~1,100 families will be enrolled into the clinical trial
- Start of clinical trial
  - Site-dependent based on provider training
  - Onboarding of new sites
- Trial planned to end 6 months into year 4 (Jan. 2021)

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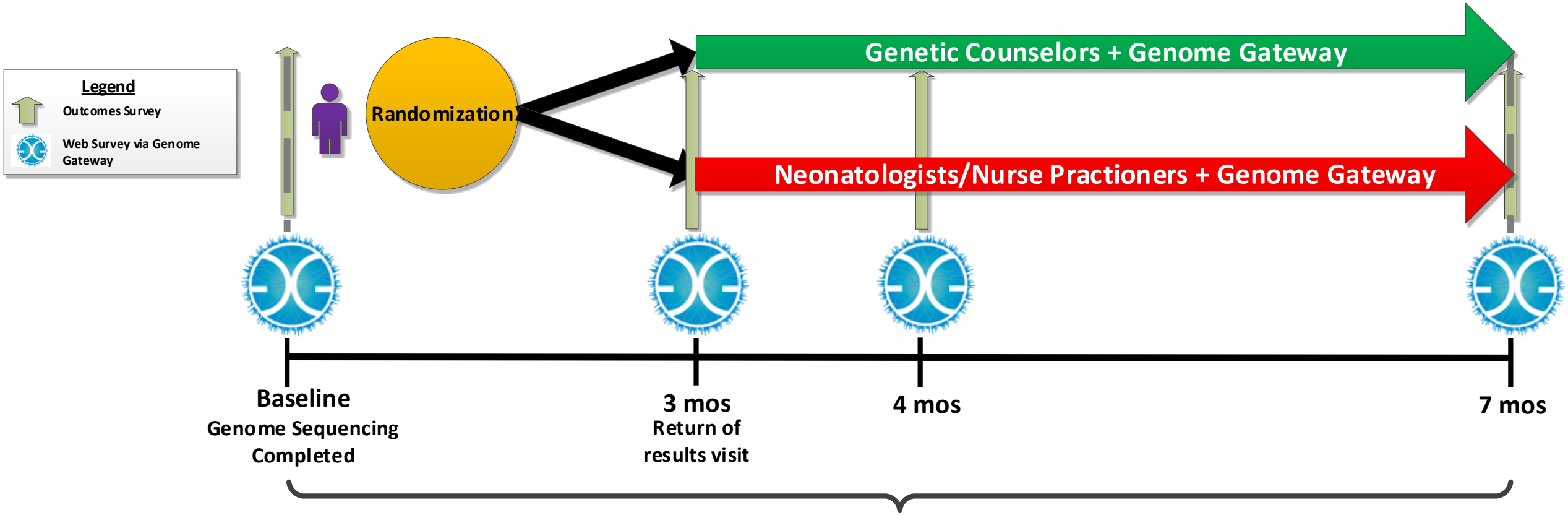
SouthSeq - Workflow



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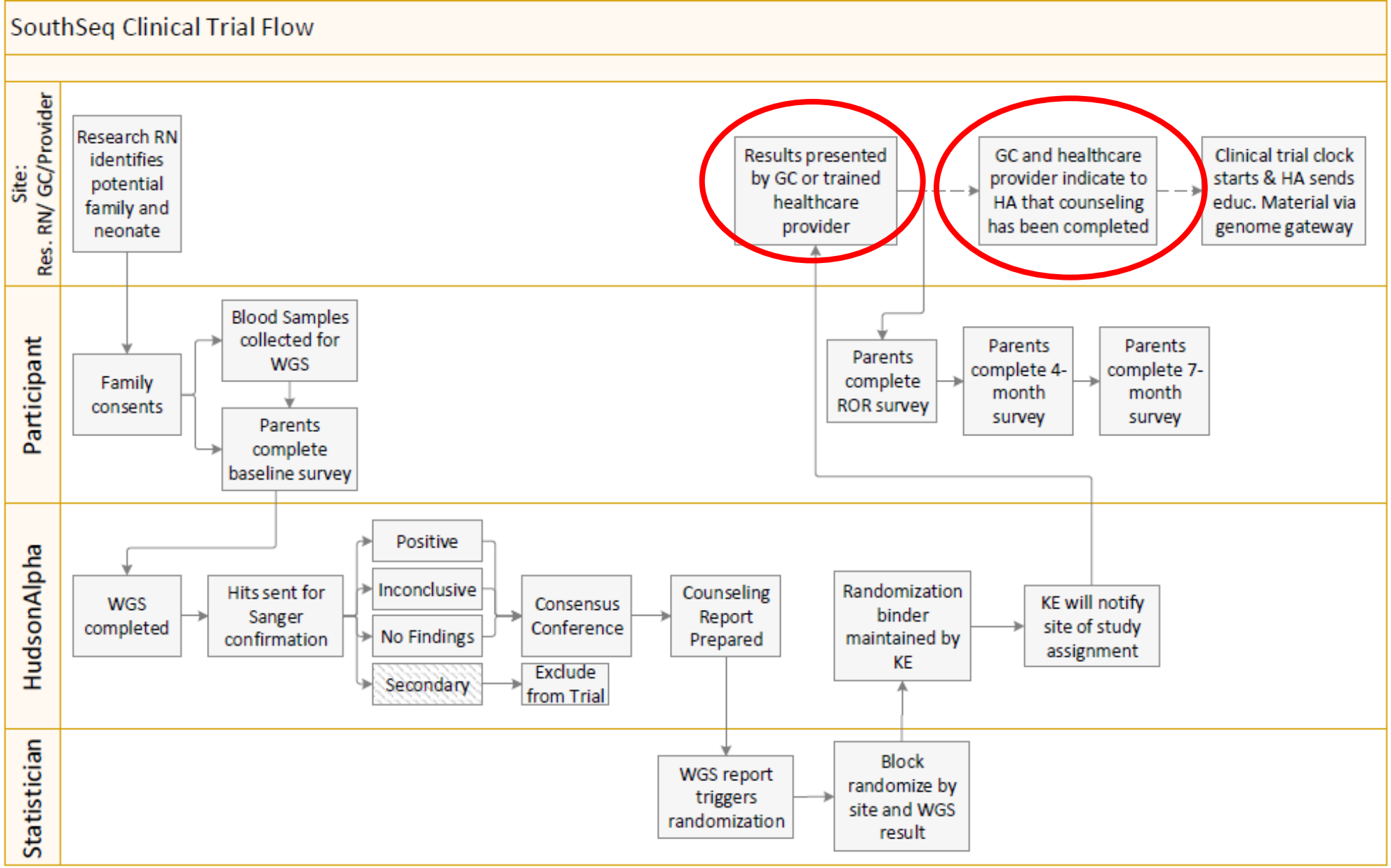

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Hypotheses

Primary Hypothesis: No clinically relevant difference in the **parental empowerment** between the two arms (trained healthcare provider vs. genetic counselor)

Secondary Hypothesis: Trained health care provider arm will be non-inferior to the genetic counselor arm in terms of **personal utility** and **uncertainty**

X = Y

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Take Away Messages

- The healthcare provider delivering results should not be the babies' current NICU attending MD/NP
  - The purpose of return of results does not include care/management of the condition (can discuss likely care changes/guidelines but not trigger that care during disclosure)
- Documentation by the healthcare provider to study staff about the disclosure session is critical to the fidelity of the trial
  - How disclosure was done
  - Who attended (which specific parents/caregivers)

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Genome Gateway

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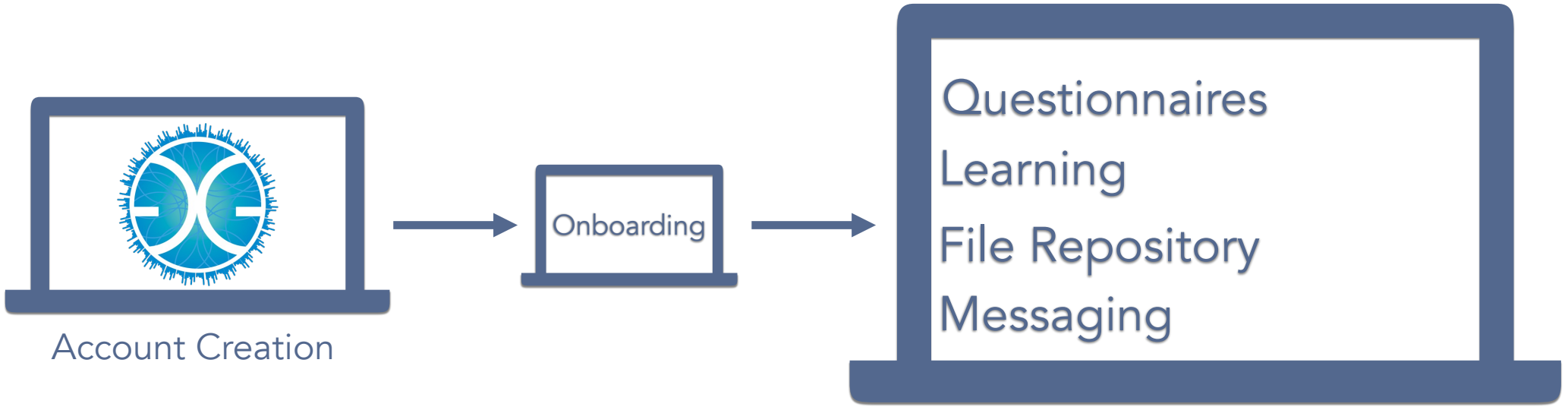

- A provider account has been created for you. This initiated an email to you with a link to finish the setup of your account.

- You will be asked some basic demographic questions and create a unique password for your Genome Gateway account

  (passwords must be at least 8 characters, contain upper and lower case letters, at least one number and one special character)

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- Once your account is set up, you will have access to the following
  - Participant information
  - Questionnaires you have been assigned
  - Learning articles written specifically for you
  - Files that have been shared with you
  - Anytime Messaging to SouthSeq study staff and genetic counselors

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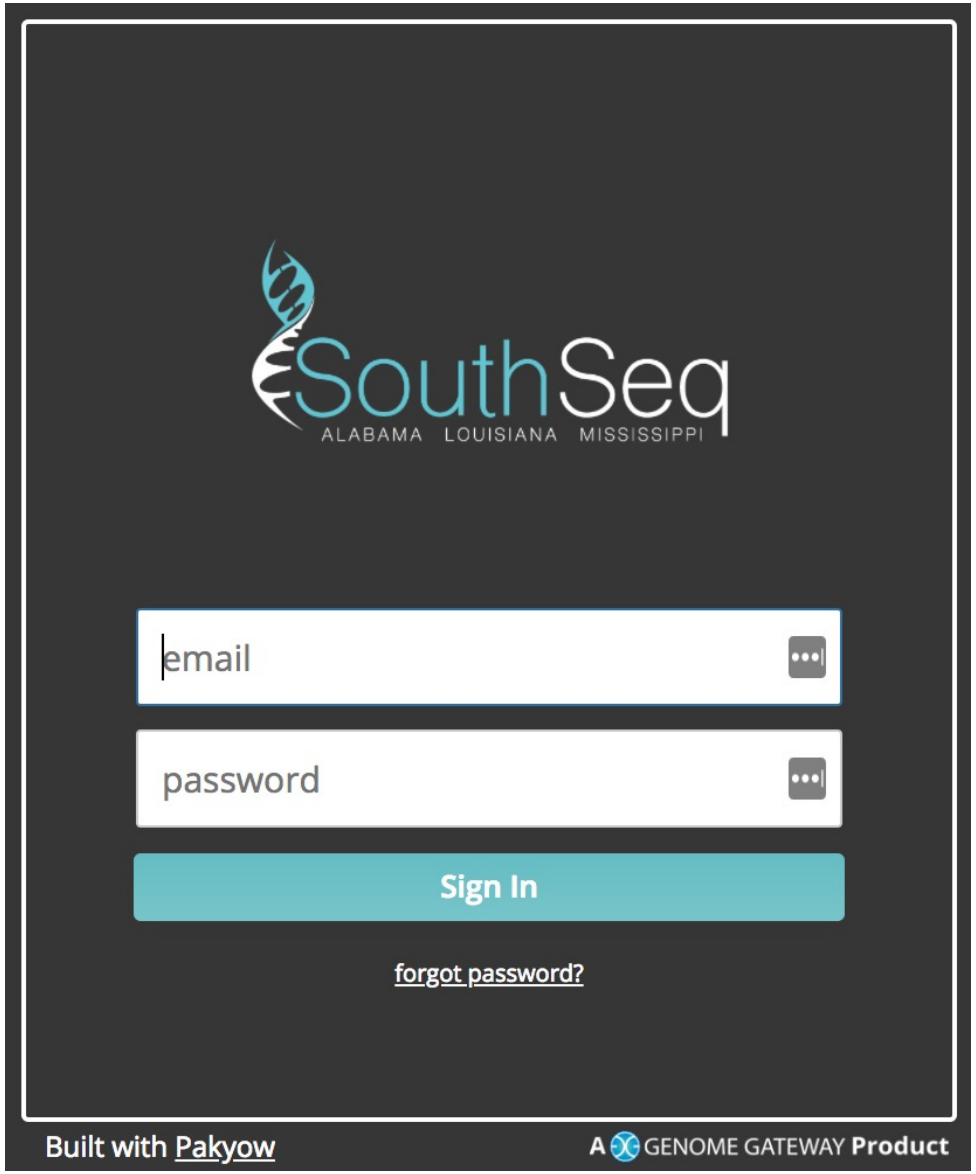
Log In

Bookmark this URL!

participants.southseq.org

- Once initial setup is completed, use your email address and the unique password for your Genome Gateway account



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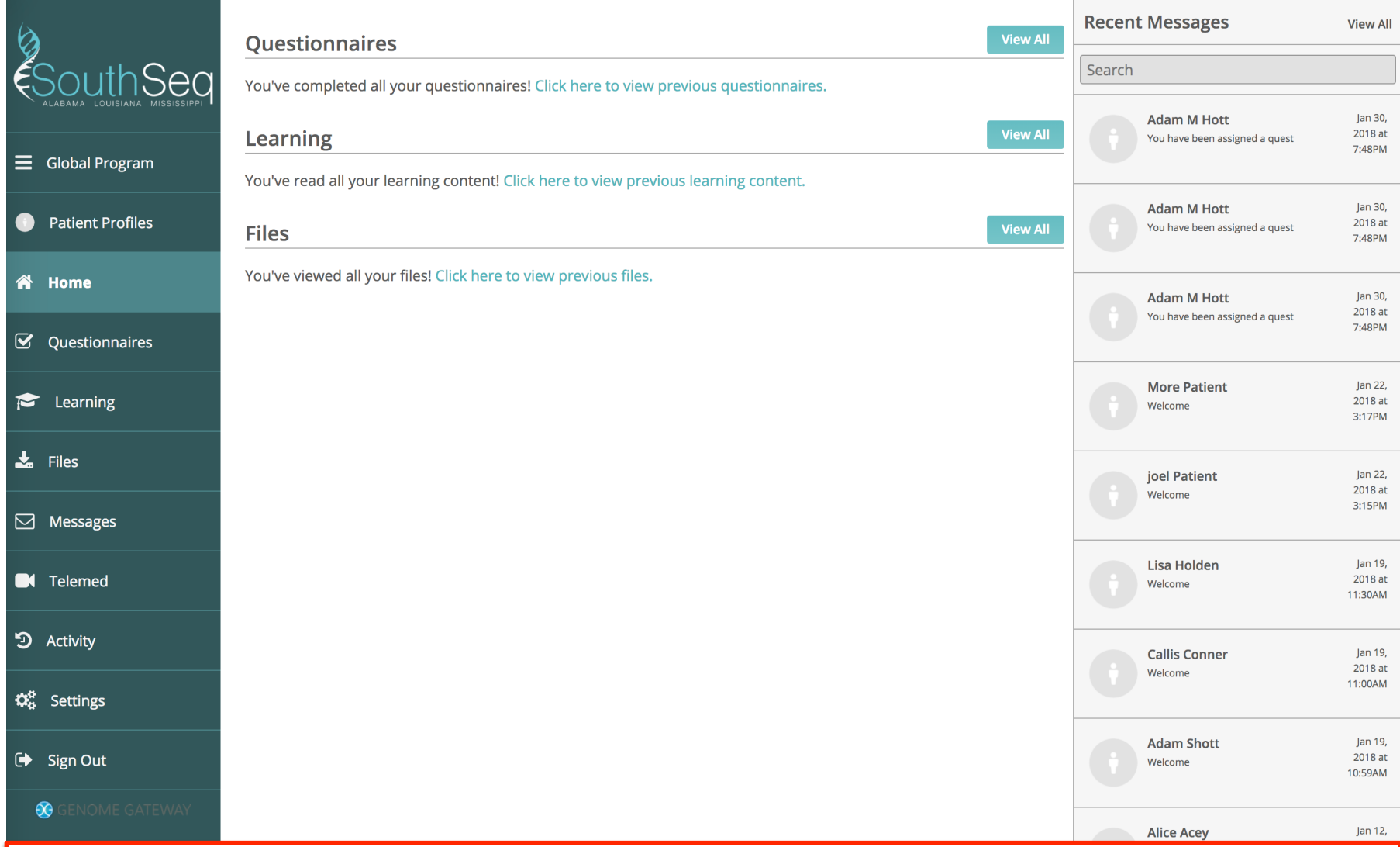
Navigating



- Use the ‘Home’ page to navigate directly to the most relevant areas easily

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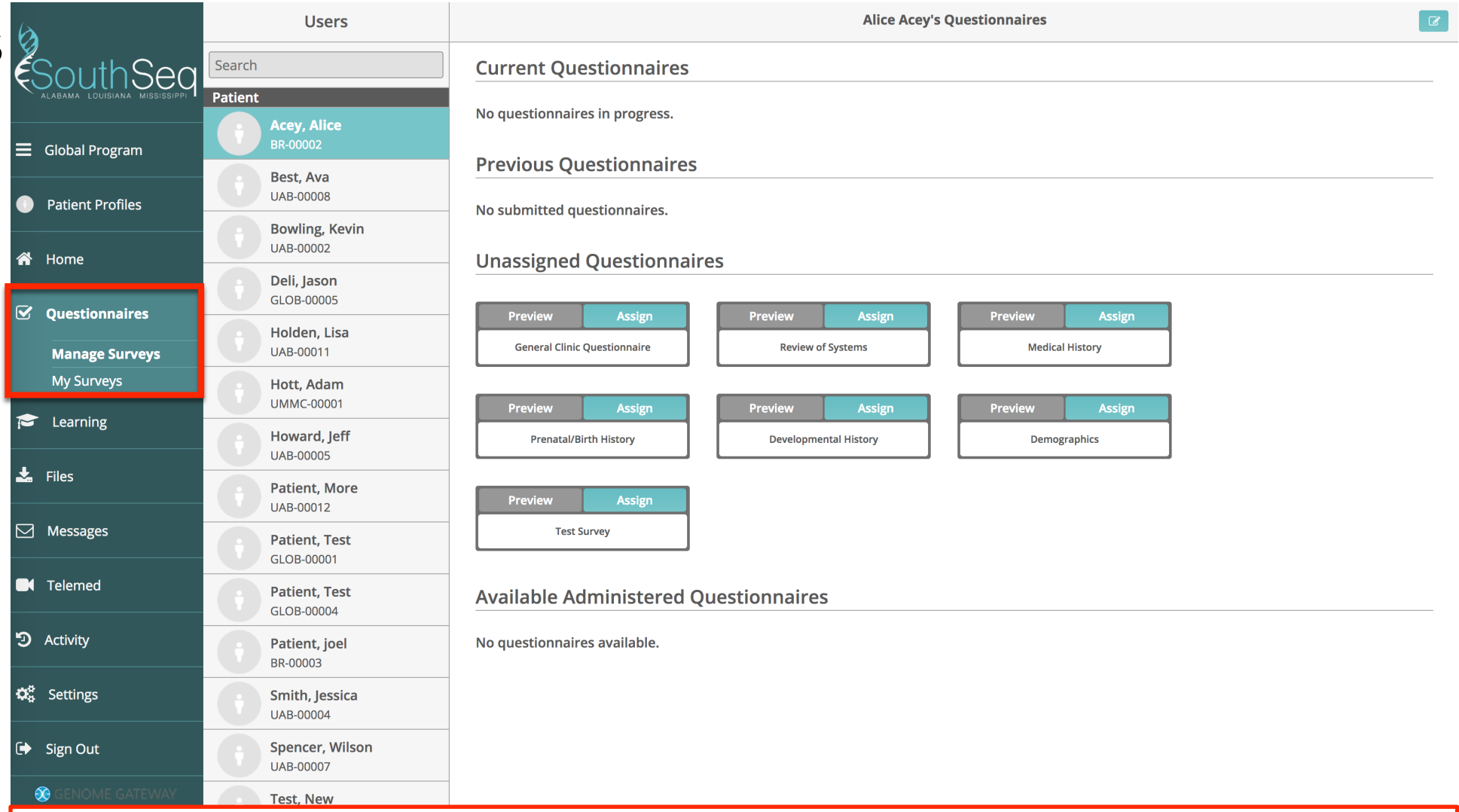
Questionnaires



- Navigate to ‘Questionnaires’ from the homepage

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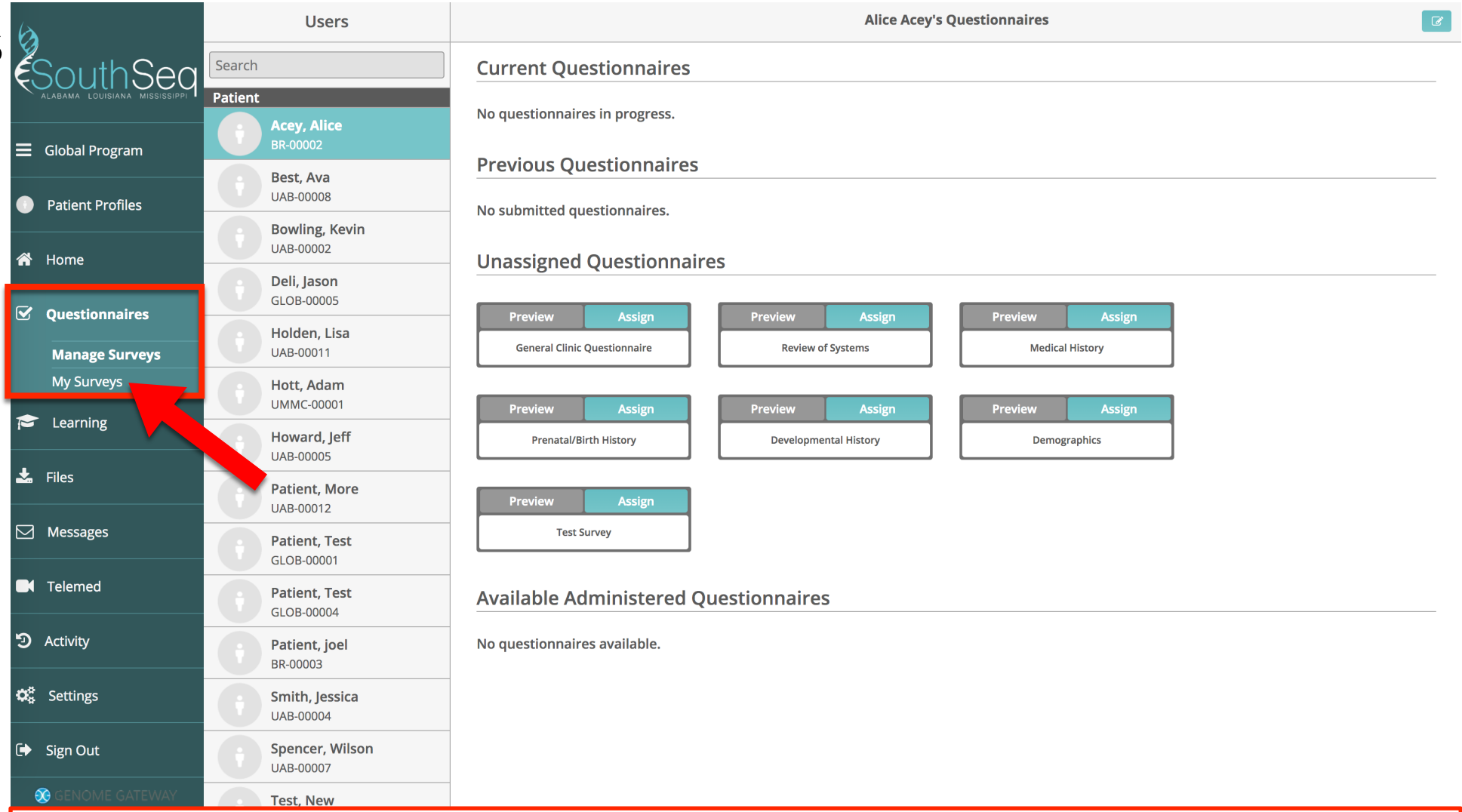
Questionnaires



- Complete the Questionnaires assigned to you by selecting ‘My Surveys’

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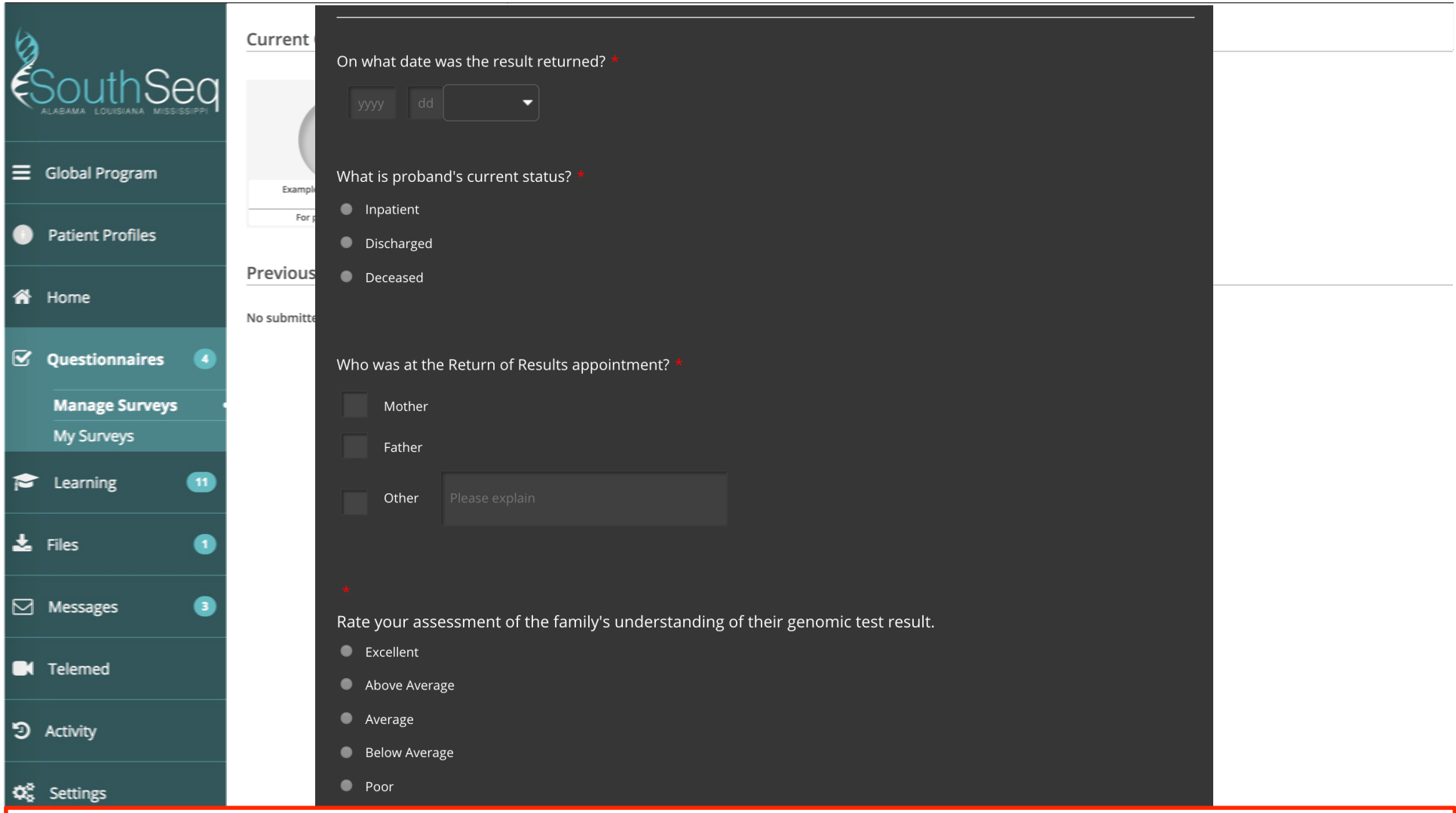
Questionnaires

- Questions with a red Asterix are required
- Please click ‘Submit’ when finished



- Click on the Questionnaire for the appropriate patient to complete it. Note the patient ID is listed with each questionnaire

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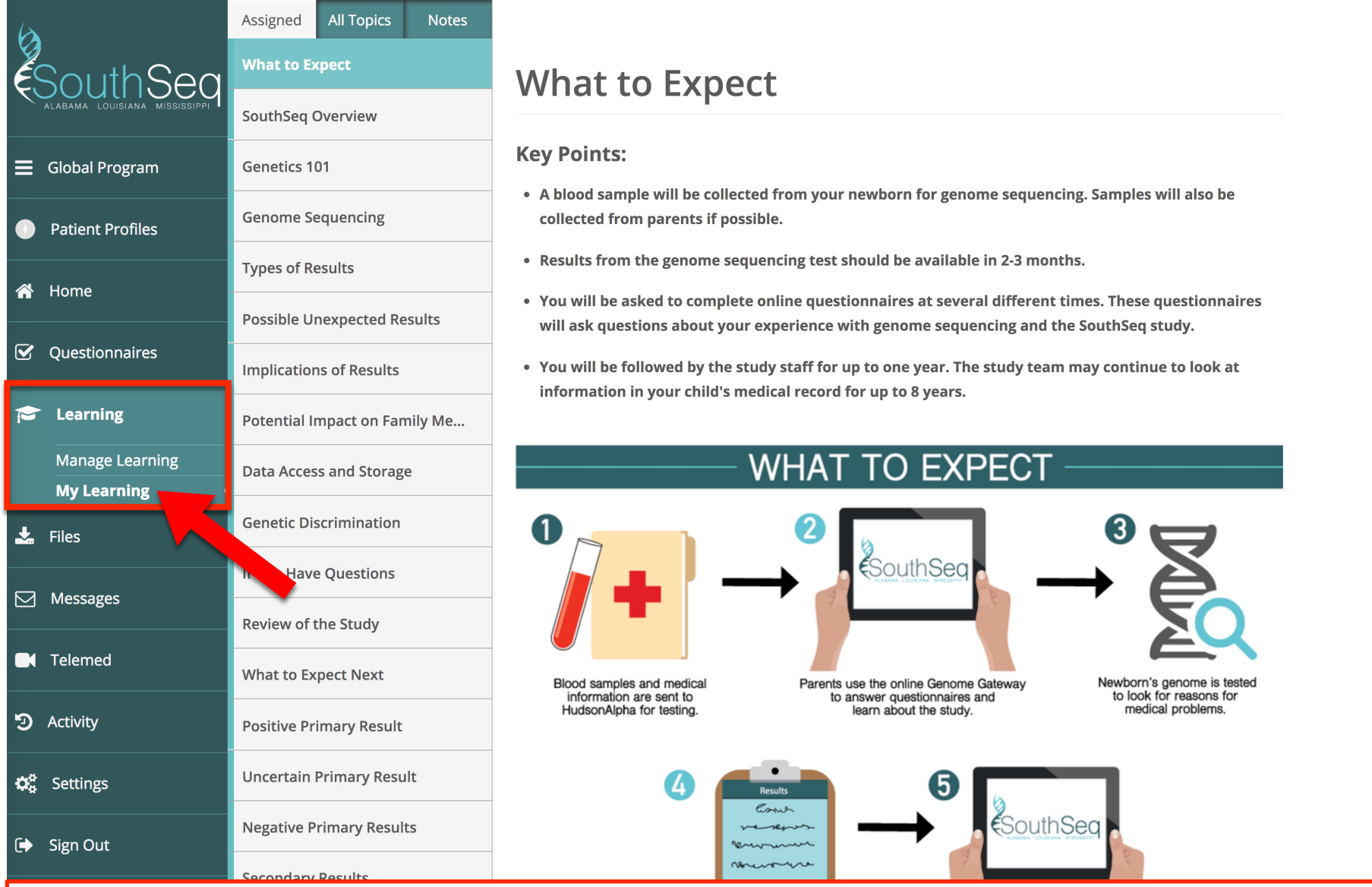
Learning

- A predetermined set of learning articles will be assigned to you
- You are able to see all learning topics (including participant topics) by clicking the “All Topics” tab at the top of the list.



- Navigate to ‘Learning’ from the homepage and select ‘My Learning’

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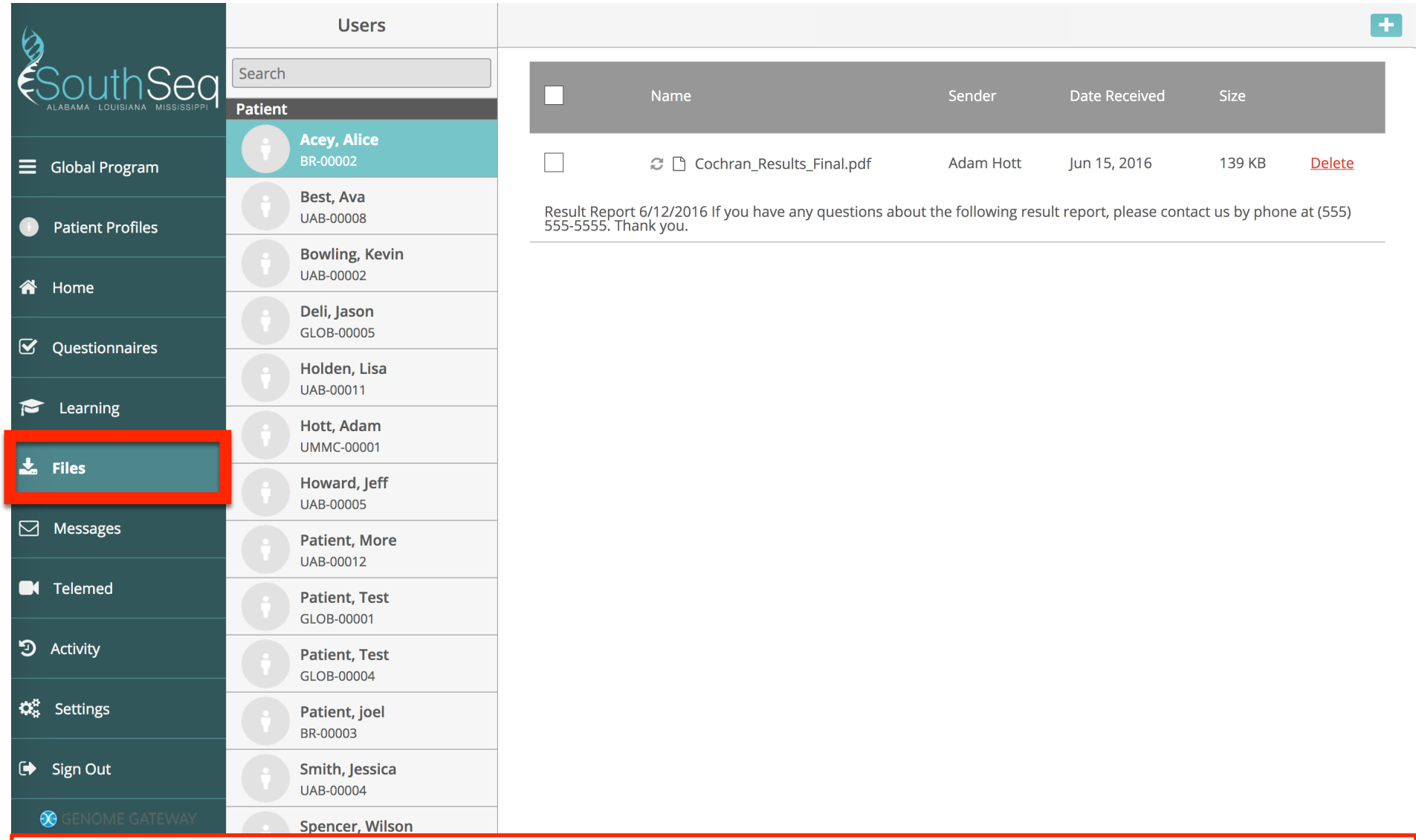
Files

- Files can be viewed in the internet browser or downloaded to your computer by clicking on the file name



- Navigate to ‘Files’ from the homepage and select the appropriate patient from the list of users

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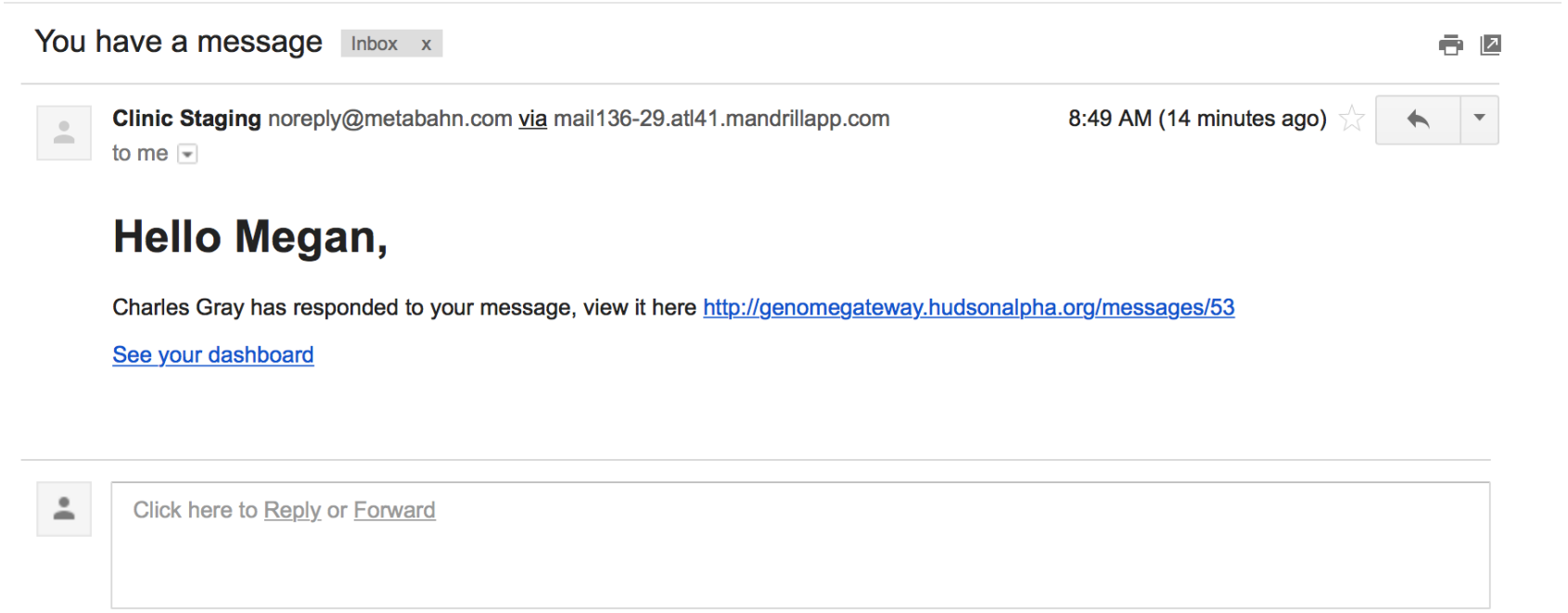
Messages


You have a message Inbox x

Clinic Staging noreply@metabahn.com via mail136-29.atl41.mandrillapp.com 8:49 AM (14 minutes ago)
to me

Hello Megan,

Charles Gray has responded to your message, view it here http://genomegateway.hudsonalpha.org/messages/53

See your dashboard

Click here to Reply or Forward

When you are sent a message in Genome Gateway, you will receive an email at your associated email account informing you that you have a new message and prompting you to log in to your account to read it

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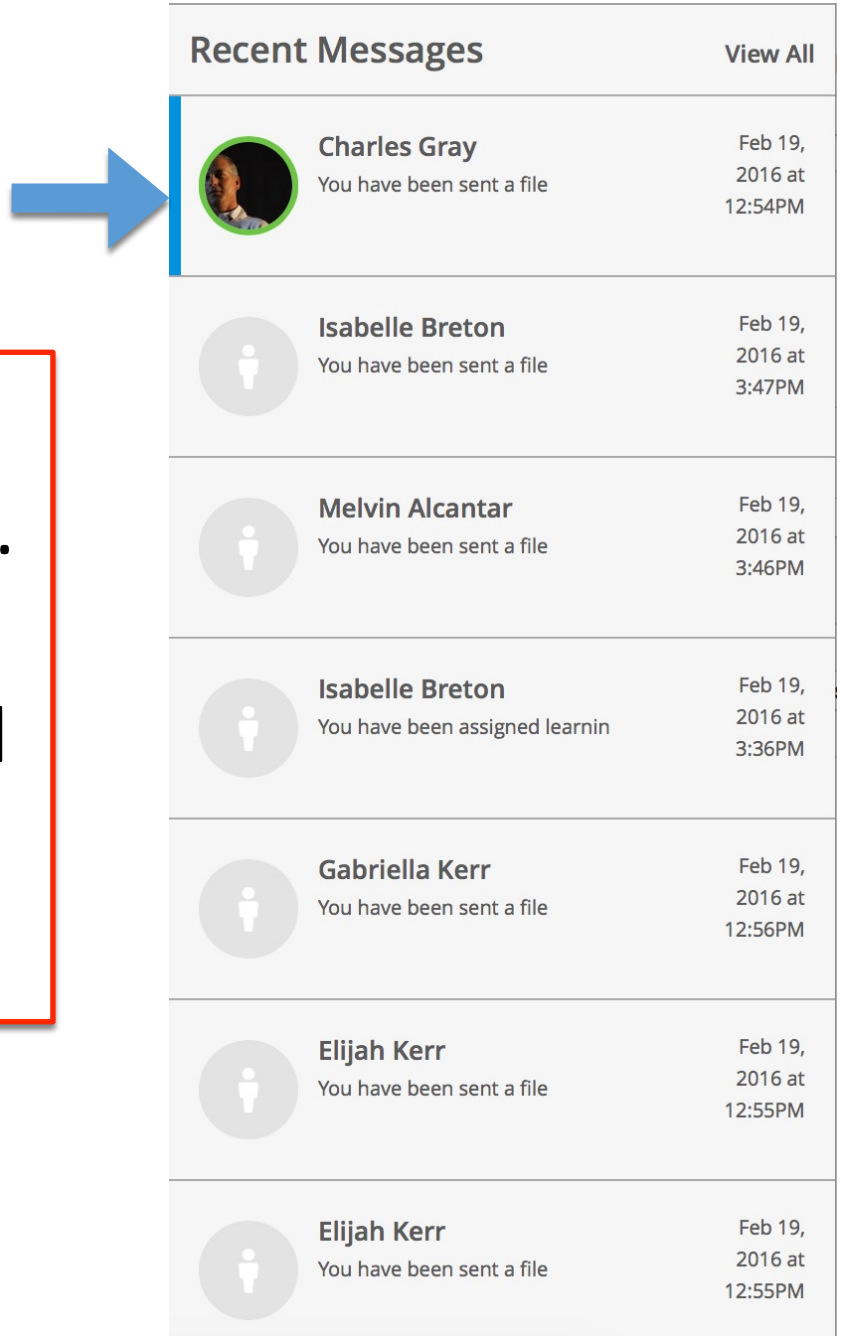
Messages

The most recent message threads are on the right side of the ‘Home’ screen. New messages will have a blue bar on the left side. Click on a message thread to open.



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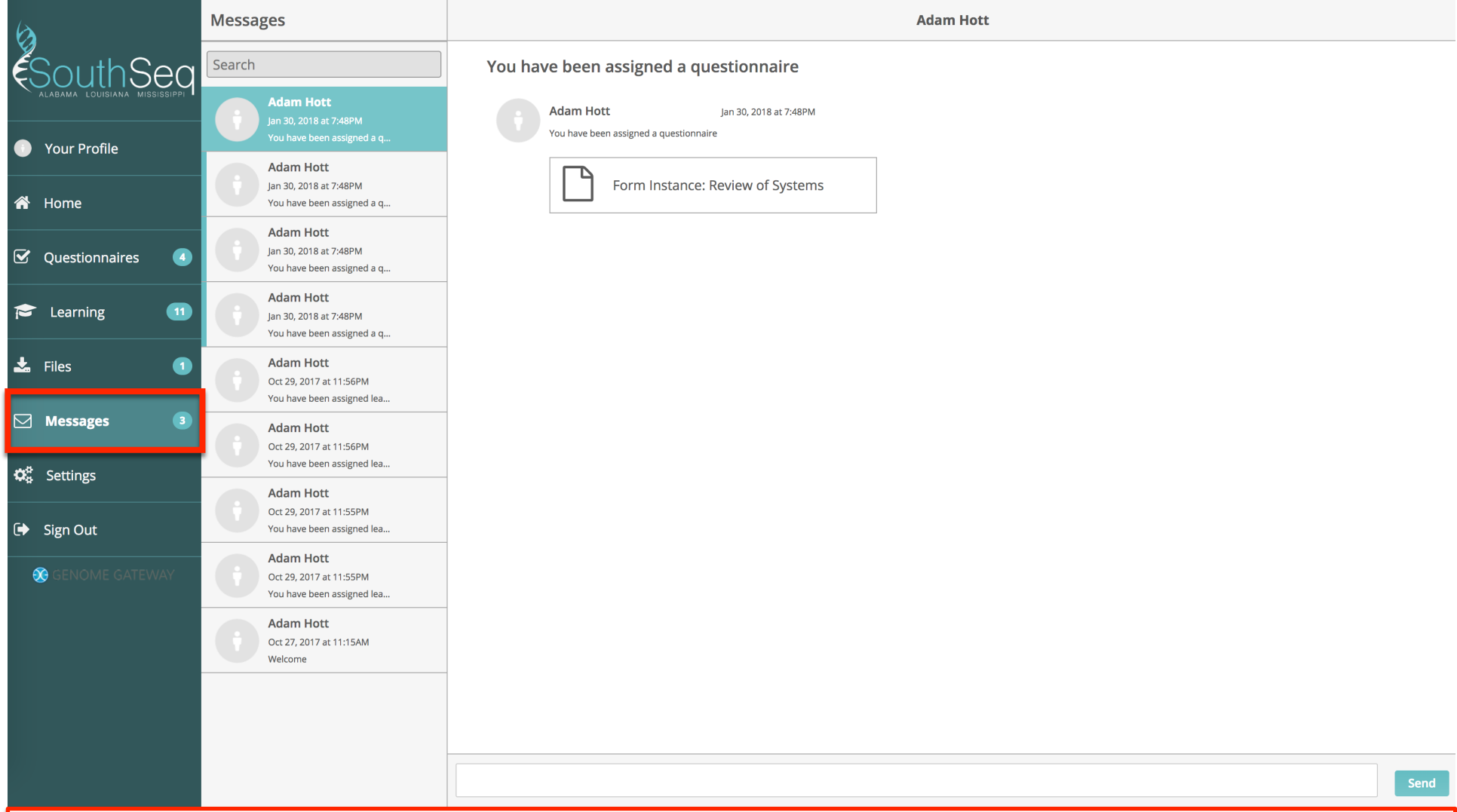
Messages



To access all messages, navigate to 'Messages' from the homepage

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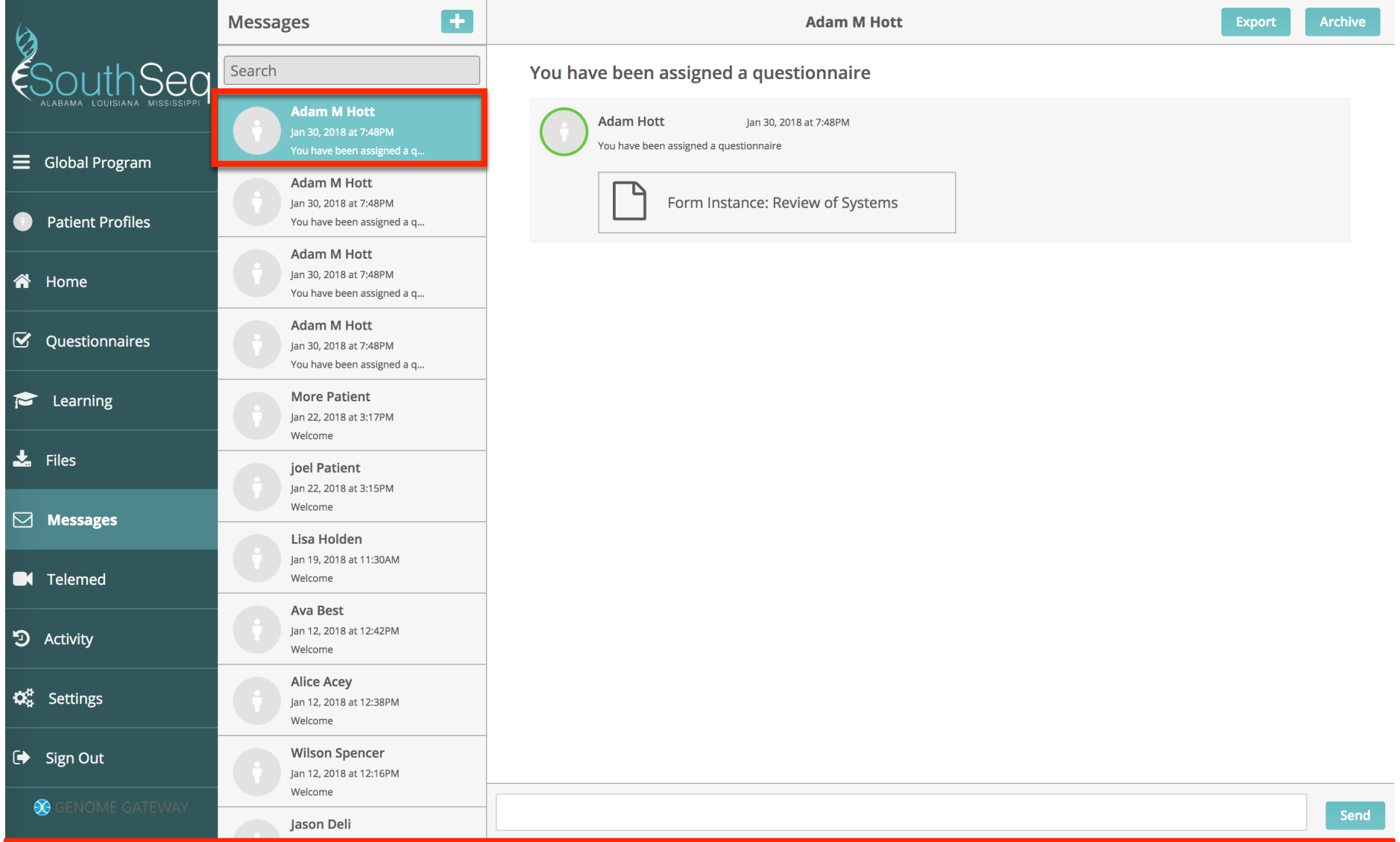
Messages



- Click on message to open the thread of messages

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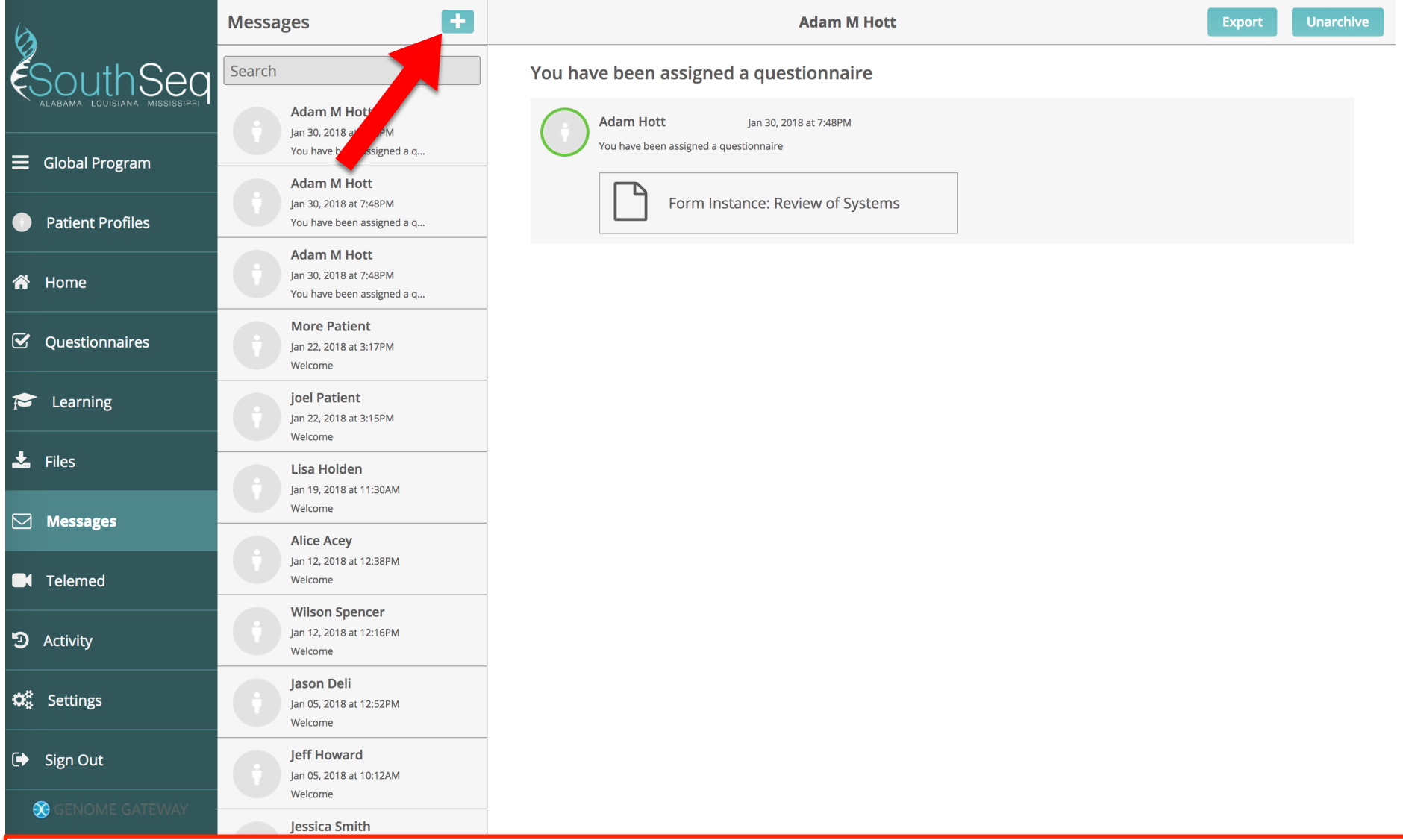
Messages



To start a new conversation with a SouthSeq user, click '+'

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Messages

Use drop-down menu to select recipient; you will be able to message SouthSeq study staff or patients.

Please do not message patients directly.

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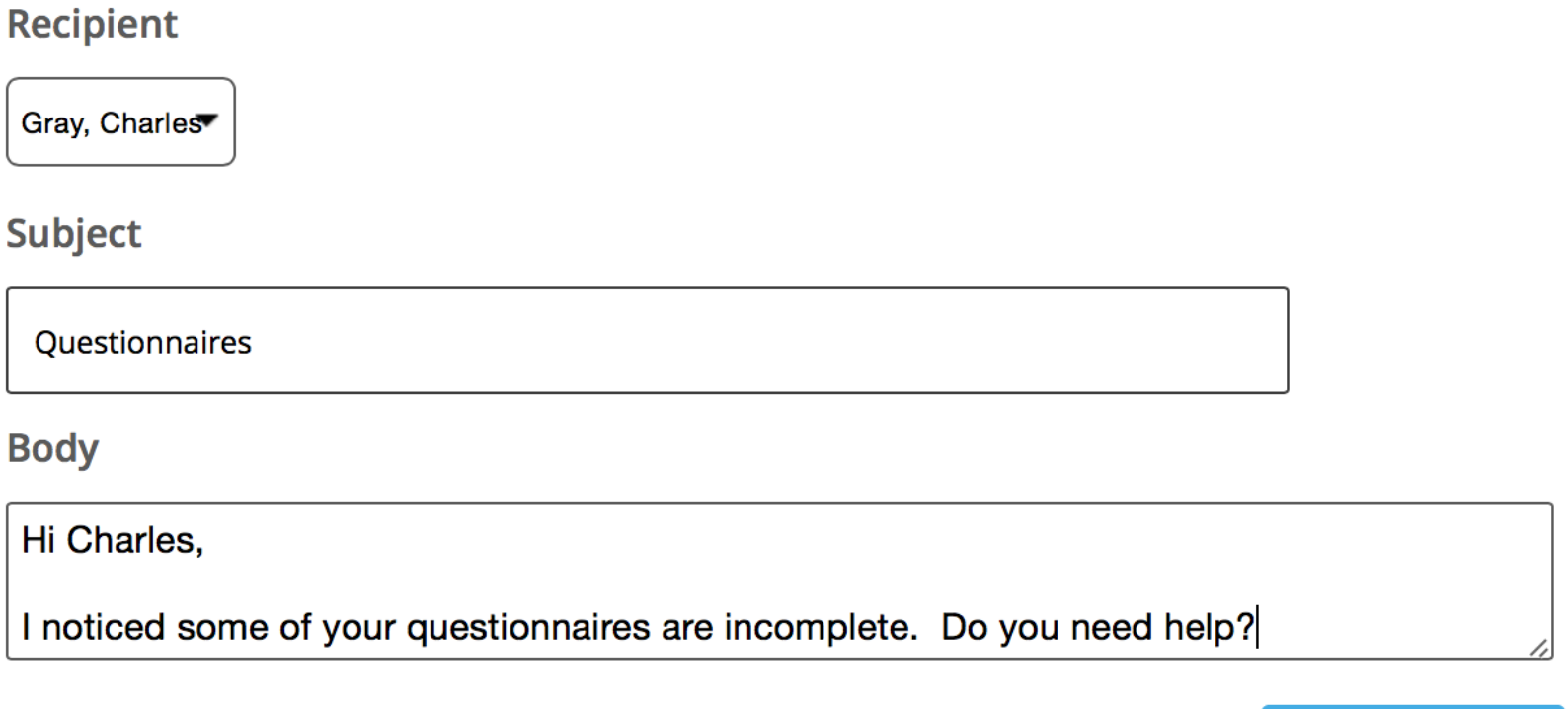
Messages



Add a subject for the message and text in the body, then click 'send message' to start a conversation

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Genome Gateway Technical Support

- Technical support can be obtained by contacting SouthSeq study staff
  - Susan Hiatt (shiatt@hudsonalpha.org)
  - Candice Finnila (cfinnila@hudsonalpha.org)
  - Adam Hott (ahott@hudsonalpha.org)

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Whole Genome Sequencing

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In this section we will:

- Review the technology and possible results of whole genome sequencing (WGS)
- Discuss how WGS differs from other available genetic tests
- Review limitations and important considerations to keep in mind when discussing WGS with patients

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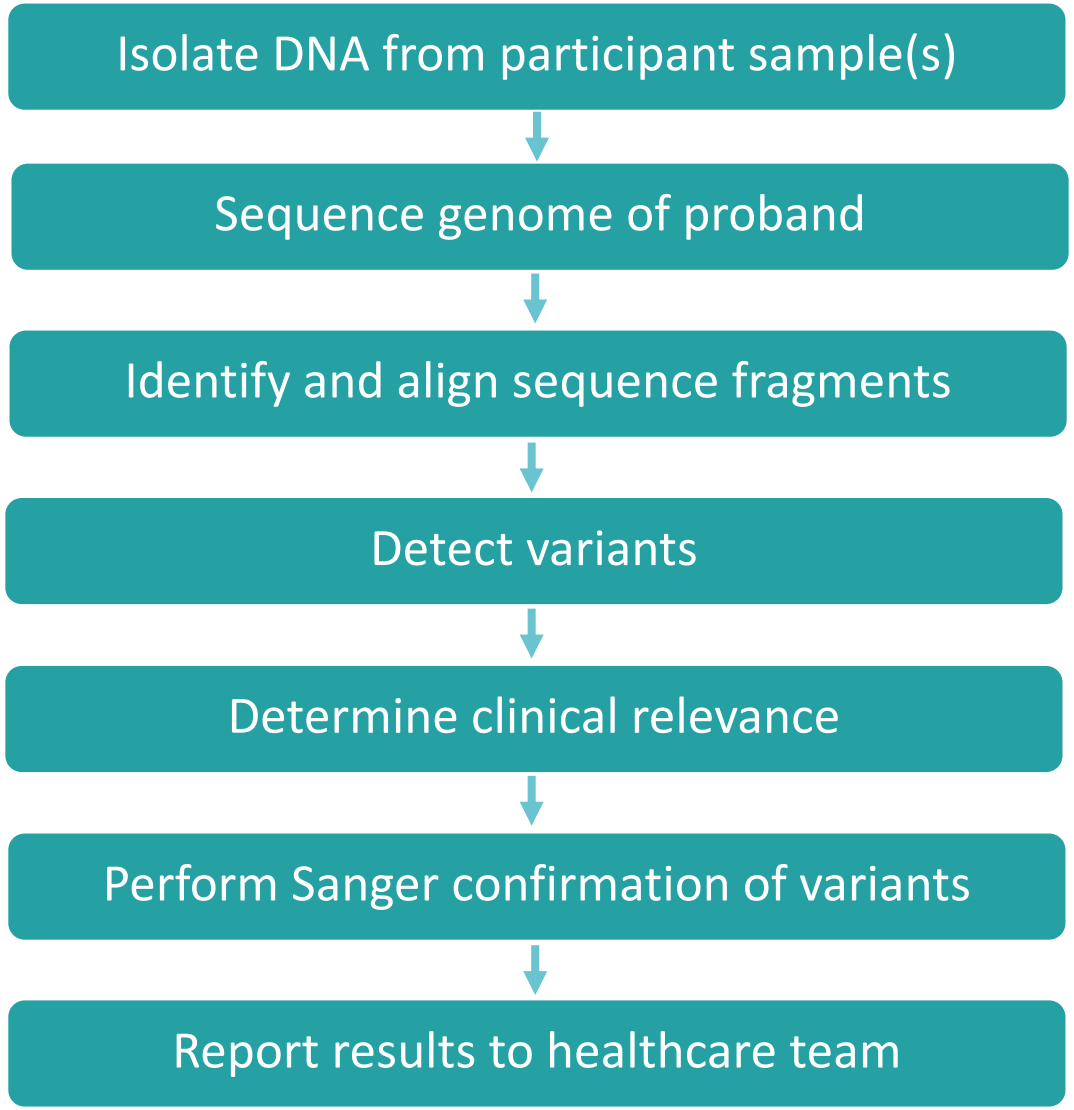
WGS sequencing pipeline



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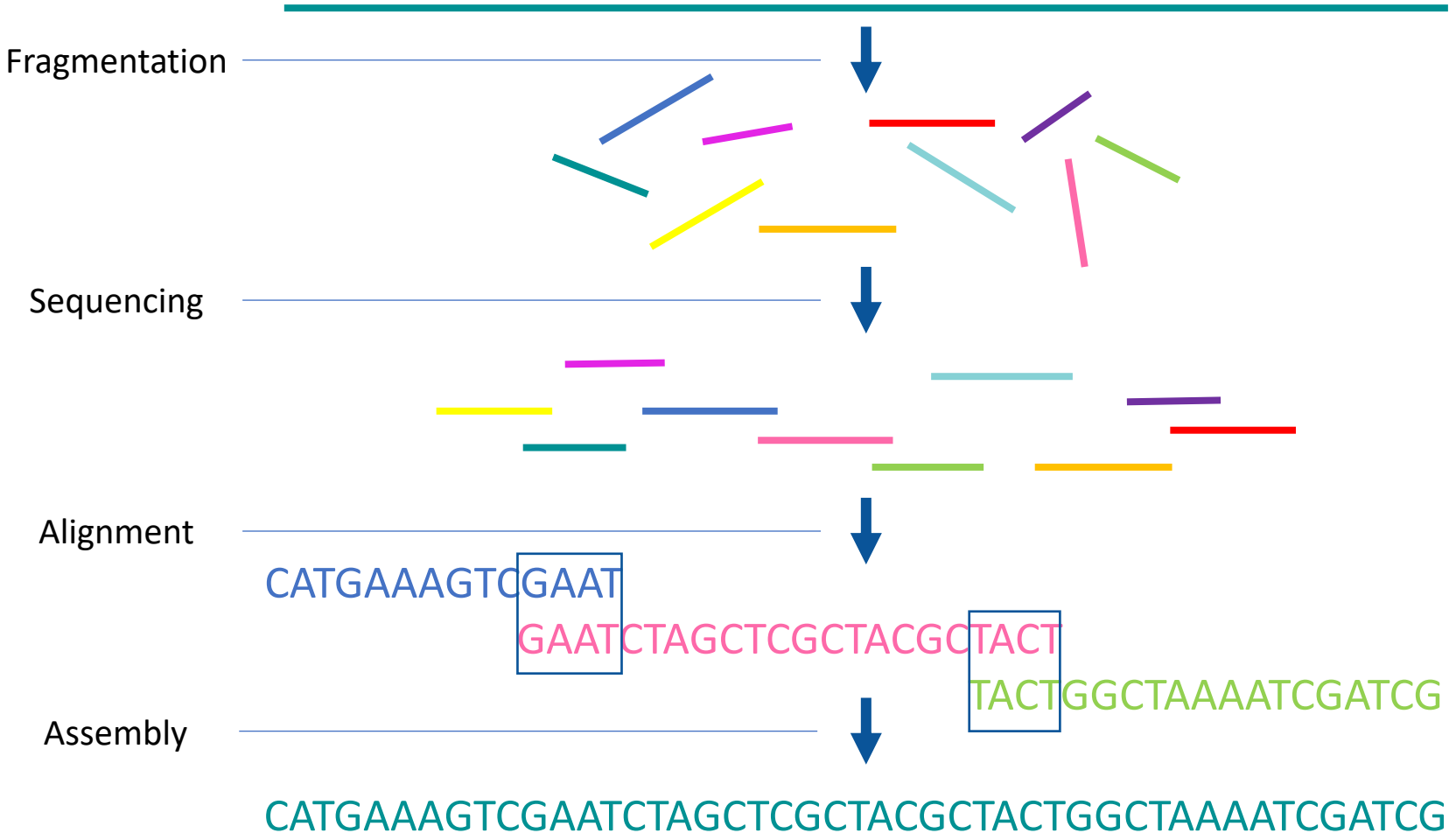
WGS…inside the box



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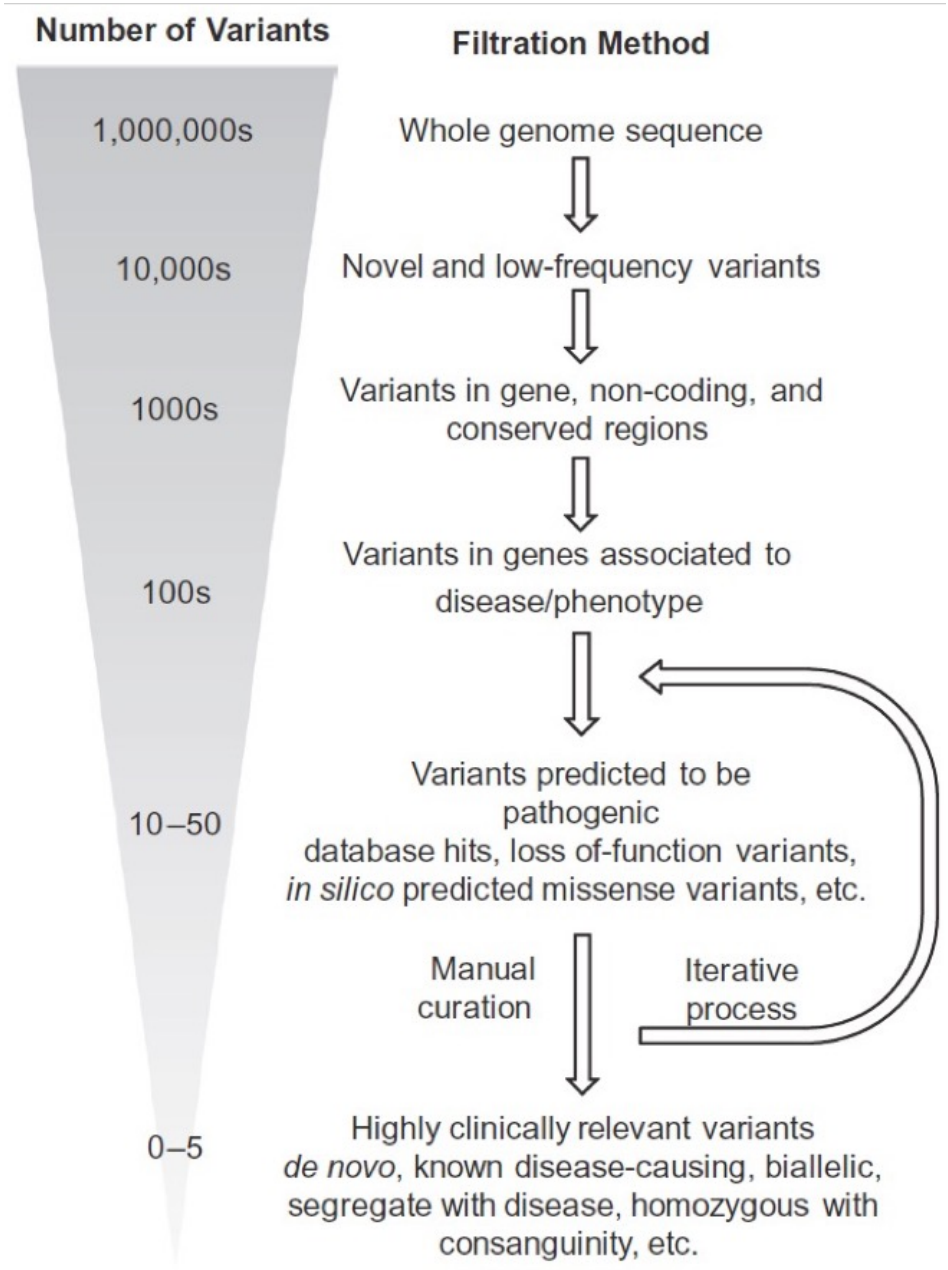
Variant filtration

computer programs

people



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Classifying variants

- make up vast majority of variation found
- typically don't even get reported

- conflicting or absent evidence about disease association
- treat as innocent until proven guilty

- strong evidence about disease association
- should alter medical management based on result if indicated

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WGS vs other genetic tests

Karyotype and Microarray

Helpful in detecting large-scale chromosomal changes and gains/losses of genetic information

Best as a first-line test or when a specific diagnosis is highly likely (ex: Trisomy 21)

Low resolution – a normal result does not rule out much

Single-Gene and Panel Testing

Uses Sanger or NextGen sequencing to thoroughly interrogate a list of genes of interest for single nucleotide variation

Best when the gene list is small and the diagnostic suspicion is high

Limited possibility for reanalysis

Whole Genome Sequencing

Massively parallel sequencing allows investigation of a person's entire** genetic code with "future-proof" data output

Best when the phenotype is nonspecific or the gene list is large

Higher likelihood of VUS/GUS and secondary findings

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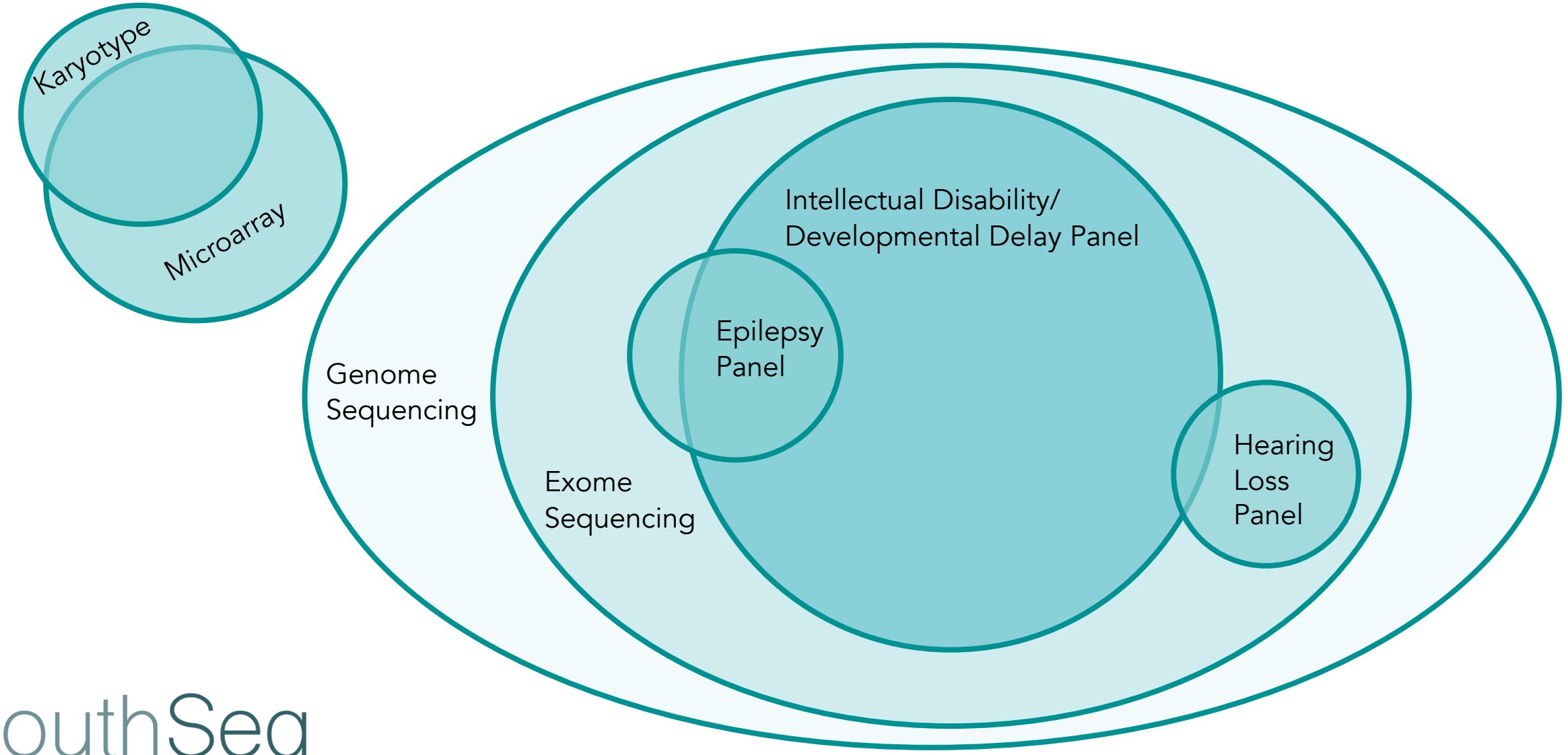
**in actuality there are some limitations in coverage

WGS vs other genetic tests



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Limitations of WGS

Technical limitations:

- Lower depth of coverage overall
- Does not reliably detect certain kinds of genetic changes (CNVs, repeats, pseudogenes)

Analytical limitations:

- High likelihood of variants of uncertain significance
- Many genes not currently associated with a specific disease or phenotype

Logistical limitations:

- Labor-intensive → results in higher costs and longer turnaround times
- Massive amounts of data

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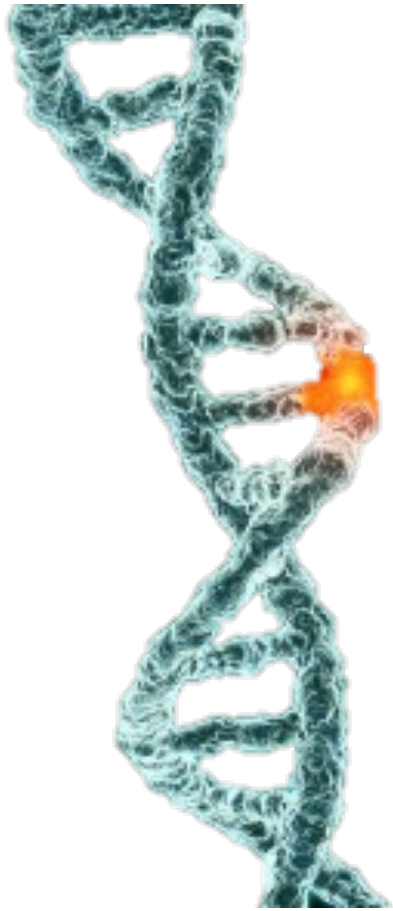
Words of caution



- Not all variants are harmful
- Disease-causing variants are not blinking lights
- Increased detection = increased uncertainty
- A negative result does NOT mean “not genetic”

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Questions?

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Returning Genome Sequencing Results

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In this section we will:

- Review the format and contents of SouthSeq result reports
- Discuss how to use result reports to prepare for the result disclosure conversation
- Practice preparation for result disclosure using a series of example case reports

→ *through individual hands-on work time and small group discussion*

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Contents and structure of SouthSeq result reports

All SouthSeq participants will receive a letter from HudsonAlpha summarizing their results.

If a genetic variant is being returned, a technical "Sanger" lab report will accompany the letter.

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Participant Name:
Participant ID#:
Participant DOB:
Report Date:

This letter describes genetic test results from the SouthSeq research study (research protocol No. 300000328).

Your child was enrolled because he or she was in the neonatal intensive care unit (NICU) and had symptoms that may be due to a genetic problem.

Reason for testing: Based on information provided to the research lab, the child has a history of ***[symptoms]***.

PRIMARY RESULTS

Results related to the reason for testing (also called primary results):

Genetic change found (also called a positive result)

- **The whole genome sequencing test found a change in the *SATB2* gene that is likely the reason for most or all of your child's symptoms.**
- Changes in this gene have been seen in people with glass syndrome.
- People with glass syndrome typically have difficulty learning, speech delay, and certain physical differences.
- This genetic change is new in your child and not found in the blood of either parent. The chance that these two parents have another child together with the same gene change is less than 1%.
- For your child, the chance of having a child with the same *SATB2* change is 50%.
- Your child's doctors and nurses may decide to change the way they care for your child based on this result.
- Other genetic tests may be needed for your child based on ***[his/her]*** personal and family medical histories.
- Please continue follow-up with your child's healthcare providers to learn about new information, testing options, or research studies.
- Please see the attached lab report for more specific information about this genetic change.

SECONDARY RESULTS

Results NOT related to the reason for testing (also called secondary results):

No other genetic changes found (also called a negative result). Keep in mind:

- The whole genome sequencing test did not find any specific genetic changes associated with risk of developing a disease in the future.
- **This does not mean your child will not develop a genetic disease in the future.**
- This test looked at 59 genes associated with the risk of this disease. There are many genetic changes that cannot yet be found or understood by the lab.

Participant Name:
Participant ID#:
Participant DOB:
Report Date:

RESOURCES

For More Information:

- About *[insert gene/condition]*:
  - [Insert Source]: [insert link]
- For support related to *[insert gene/condition]*: [insert link]

If you have questions, please contact your child's healthcare team at the NICU where **[he/she]** was enrolled.

You may also contact a study genetic counselor at the information below.

Kelly East, MS, CGC
Certified Genetic Counselor
HudsonAlpha Institute for Biotechnology
256-327-0461

Information about the test
Keep this information for future use

Whole genome sequencing was done on a research basis at the HudsonAlpha Institute for Biotechnology (not in a CAP/CLIA environment). Sequencing was done on an Illumina HiSeq X sequencer at an approximate depth of 30X. Variant pathogenicity was determined using ACMG criteria.

Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. Genet Med. 2017.

In addition to the affected child, laboratory reports may be available for parent samples. The last digit of the "ID2" section of the laboratory report header indicates whether a report is for the child/proband (P), mom (M), or dad (D).

Sanger Confirmation and Interpretation of Variants

CLIENT
Client Name: Molly Schroeder
Hospital/Institution: HudsonAlpha Institute for Biotechnology
Mailing Address: 601 Genome Way NW, Huntsville, AL 35806
Phone Number: 256-327-9670

SPECIMEN
Specimen Type: DNA
Collection Date: Not provided
Receive Date: 04/19/2018
Report Date: 05/14/2018

PATIENT
Patient's PKI ID: 27860
Accession Number:DS180735
ID1: C1095-GC-0016
ID2: BR-12345-P
Gender: female

Test Performed: Sanger confirmation and interpretation of variants

TEST RESULT SUMMARY

Sample Name	Gene	Chr	Genomic Coordinate	DNA Change	Variant	Zygosity	Classification
C1095-GC-0016	*GLB1 (NM_000404)*	3	33099713	G>A	c.601C>T (p.R201C)	Heterozygous	Pathogenic
C1095-GC-0016	*GLB1 (NM_000404)*	3	33055549	T>C	c.1733A>G (p.K578R)	Heterozygous	Pathogenic

METHODS AND LIMITATIONS

GLB1 c.601C>T (p.R201C) - Pathogenic. This c.601C>T (p.R201C) variant results in the substitution of an arginine with a cysteine at amino acid position 201. This variant has been previously reported in individuals with disease. This variant has been observed in the general population in a heterozygous state.[1] MutationTaster, PolyPhen2 and SIFT imply a potentially deleterious effect.

GLB1 c.1733A>G (p.K578R) - Pathogenic. This c.1733A>G (p.K578R) variant results in the substitution of an lysine with a arginine at amino acid position 578. This variant has been previously reported in individuals with disease. This variant has been observed in the general population in a heterozygous state.[1] MutationTaster, PolyPhen2 and SIFT imply a potentially deleterious effect.

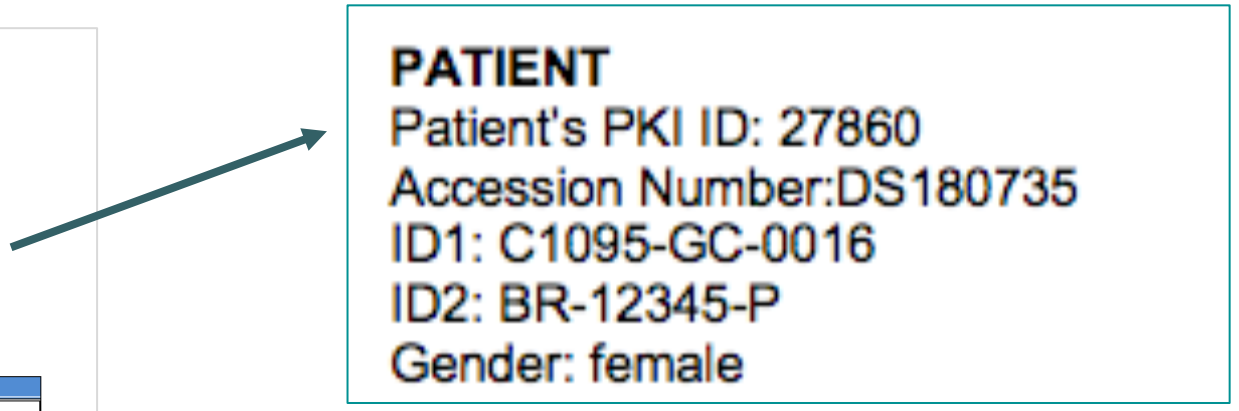
DNA was amplified using region specific PCR primers followed by bidirectional Sanger sequence analysis.[2] Possible diagnostic errors include sample mix-ups, genetic variants that interfere with analysis, and other sources.

References:

1. genome Aggregation Database (gnomAD): gnomad.broadinstitute.org/
2. Tsai, M.F, et al. Nucleic Acids Res. 35 (Web Server issue):W63-65

Possible sources of testing error include rare genetic variants that interfere with analysis, sample misidentification, and other sources. Pursuant to the requirements of CLIA '88, this test was developed and its performance validated by PerkinElmer Health Sciences. It has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes.

This document is for training purposes only and does not represent an actual patient's clinical report.



Technical "Sanger" Report about any gene changes found

ID2 = SouthSeq Participant ID

First two letters indicate site (BR = Baton Rouge)
Followed by unique set of numbers

Final letter indicates which individual in the family the report pertains to

- P = proband (affected baby)
- M = mom
- D = dad
- S = sibling (not usually applicable)

What you will not find in the result report

- Confirmation of paternity or non-paternity
  not reported by the study

- Consanguinity (parental relatedness)
  not reported by the study

- Secondary findings
  would automatically put the case in the control arm (for return by GC)

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The result report/letter is your guide

Key talking points and take home messages

Resources to share with participant/family

Written in patient-friendly language

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If you have questions…

Your HudsonAlpha GC:

[Birmingham: Meagan Cochran; Jackson: Whitley Kelley; Baton Rouge: Veronica Greve]

Genome Gateway messaging best and most secure communication method (can discuss PHI/clinical details).

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Let's Practice…

- 6 example result reports, cover a wide range of possible results and implications
- Read result report as if you are preparing to disclose it to a family
  - Think about key messages, likely questions, if there is other information you want or need to gather prior to patient interaction
  - Highlight words/topics you want clarification on
  - Fill out chart
- Next will break up into small groups for in-depth discussion about the results with a genetic counselor

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Psychosocial considerations in the context of genetics

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Veach, P., LeRoy, B., & Callanan, N. (2018). *Facilitating the Genetic Counseling Process Practice-Based Skills* (2nd ed. 2018.. ed.). Cham: Springer International Publishing : Imprint: Springer.

Delivering Genomic Results

- Are genomic result disclosures different from other patient interactions? How?

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Kaphingst, K. A., Ivanovich, J., Elrick, A., Dresser, R., Matsen, C., & Goodman, M. S. (2016). How, who, and when: preferences for delivery of genome sequencing results among women diagnosed with breast cancer at a young age. *Molecular genetics & genomic medicine*, *4*(6), 684-695.

Delivering Genomic Results

- Understanding the familial context of the result makes information more meaningful
- Counseling the family, not the result

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Delivering Genomic Results

- Avoid information overload
  - Proceed slowly and divide up information

- Try to use terminology participants understand

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Delivering Genomic Results

- What if participants don’t want to hear part or all of results?
  - Inheritance
  - Recurrence risks
  - Prognosis
  - Medical management recommendations

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Assessing Patient Understanding - Questions

- Questions are helpful to clarify patient meaning and check your assumptions
- Avoid over-questioning and interrogating patients
- Open-ended questions are helpful for assessment
- Try to avoid close ended questions

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Assessing Patient Understanding - Information

- Start from relevant basics
- After concepts, pause to assess
  - “What’s your understanding of what we’ve just discussed?”
- Look for nonverbal cues
- Emotional reactions may impede information understanding

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Assessing Patient Understanding – Emotional Reaction

- Anger
- Grief
- Guilt
- Shame
- Relief

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Krabbenborg, L., Vissers, L. E. L. M., Schieving, J., Kleefstra, T., Kamsteeg, E. J., Veltman, J. A., ... & Van der Burg, S. (2016). Understanding the psychosocial effects of WES test results on parents of children with rare diseases. *Journal of genetic counseling*, *25*(6), 1207-1214.

Assessing Patient Understanding - Emotional Reaction

- Positive coping strategies:
  - Seek social support
  - Plan
  - Positive reappraisal
- Negative coping strategies:
  - Confrontative
  - Distancing
  - Self-controlling
  - Self-denigrating
  - Escape-avoidance

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Assessing Patient Understanding - Misconceptions

- Participants may have underlying misconceptions about genetics and disease
- Numerical risk information may be difficult for participants to understand
- Consider whether you are challenging a family's misconception or cultural perspective

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Let’s Practice

- Case assignment

- Review the case and list on your result return sheet:
  - Three key points you want to convey to the participants
  - Three key points you think participants want to know

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Simulation

- 15 minutes for case simulations
- Deliver these results as if the genetic counselor is an actual participant
- Feel free to use the resources and information identified in the previous activities

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Role-play Wrap-up

Did you feel adequately prepared?

What happened that was expected? Unexpected?

What opportunities were missed?

What additional information or resources would you have liked to have had?

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Case F

Singleton with UNC13A *VUS (no associated syndrome)*

Connecting with other families

"Do you know other people that have this?"

Utility

"Why did you give me this result if there is no way to help him? I don't care ***why*** *it happened."*

Overinterpretation

"If a mutation was found, it must be bad."

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Case B

Mother-proband duo with likely pathogenic HDAC8 *variant (Cornelia de Lange syndrome)*

Assumption of inheritance

"If it didn't come from me, it came from her dad, and he's fine, so my child will be fine too."

Blame

"This must be her dad's fault."

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Case B

Mother-proband duo with likely pathogenic HDAC8 *variant (Cornelia de Lange syndrome)*

Misunderstanding of natural history of condition

"I know this came from her dad's side because his mother has heart problems."

Discussion of intellectual disability during neonatal period

"Will my child be able to live independently as an adult?"

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Case C

Trio, proband with GLB1 *compound heterozygous variants inherited from parents (GM1 gangliosidosis)*

Misunderstanding of inheritance

"No one in our family has anything like this. The test must be wrong."

Seeking solutions

"Is there anyone who can help her? We will try anything."

Religious/cultural beliefs + potential denial

"God will heal my baby."

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Case E

Trio, proband with NF1 *likely pathogenic variant inherited from mother (neurofibromatosis type 1)*

Guilt

“This is my fault.”

“Why are his symptoms so much worse than mine? Did I do something to make them worse?”

Misunderstanding of variable expressivity

“You’re saying I have this too, but I’m not sick. The test must be wrong.”

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Case D

Trio, proband with de novo *likely pathogenic* CDKN1C *variant (Beckwith-Wiedemann syndrome)*

Misunderstanding of natural history and purpose of surveillance guidelines

"Will doing the tests you're talking about cure her?"

Misunderstanding of inheritance

"Does this mean he is not/I am not the father?"

Guilt/blame, misunderstanding of de novo *variants*

"This is because of the chemicals on the farm I grew up on."

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Case A

Negative result

Misunderstanding of limitations

“So this isn’t genetic?”

“Now I can tell my sister this isn’t something her kids can get.”

Guilt, personal narrative

“I knew nothing was going to come back, because I drank a glass of wine when I was 10 weeks pregnant and that’s what caused this.”

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Example of Complex Result

Child born with multiple congenital anomalies and hearing loss

Result: maternally inherited pathogenic PALB2 *variant*

PALB2*: tumor suppressor; homozygous or compound heterozygous variation causes Fanconi anemia*

Heterozygous variation causes increased breast and pancreatic cancer risk

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Example of Complex Result

Primary result with secondary implications

Unable to identify "second hit" in PALB2
Uncertain diagnostic result

Discussing increased adulthood cancer risk for an infant

Disclosing increased risk of cancer to a parent for whom this should have immediate medical management implications

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Resource-finding

Take 2-3 minutes to Google your case's result (including Google images)

What do you find?

What, if anything, would be helpful for families?

What, if anything, would you rather families NOT see immediately after receiving their result?

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Resource-finding

GeneReviews, Genetics Home Reference

Unique

Simons VIP Connect

Facebook groups

Parent blogs

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Recap of your role: for each result you disclose

1. Review letter/report, prepare
2. Return the results to the family
3. Complete survey in Genome Gateway
3. Transition result knowledge to clinical team

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Wrap Up
Questions?
Next Steps

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