

Talking to Parents about the Utility, Benefits and Limitations of Exome Sequencing and Genome Sequencing

Obtaining Informed Consent

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December 9, 2024 @ 12:30 pm

Learning Objectives

1. Discuss the benefits, limitations and utility of ES/GS in a family-appropriate manner
2. Describe the ACMG recommendations for obtaining informed consent
3. Identify resources for obtaining informed consent

Why is it important for clinicians to talk to parents about WGS / WES?

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SYSTEMATIC REVIEW

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Mainstreaming genetics and genomics: a systematic review of the barriers and facilitators for nurses and physicians in secondary and tertiary care

Stephanie White, M. Gen Couns, BN¹, Chris Jacobs, PhD, MSc² and Jane Phillips, PhD, PGDipHlthProm¹

Results:

- **These authors reviewed over 7000 articles and concluded that there is a knowledge-practice gap. Building the capacity of NON-genetics providers to integrate genetics and genomics into clinical care is essential in order for patients' to access genetic information that is vital for their medical care.**
- **Barriers** were limited genetics knowledge and skill, low confidence initiating genetics discussions, lack of resources and guidelines, and concerns about discrimination and psychological harm.
- **Facilitators** were positive attitudes toward genetics, willingness to participate in discussions upon patient initiation, and intention to engage in genetics education

Scenario

- Parents are with their 4-day old infant who was born with multiple birth defects (prenatally identified) and who developed seizures on day 2. The neonatologist recommends a genetic test to determine “whether the baby has a genetic abnormalities.” Blood can be drawn that day. When parents are asked whether they want the test, they murmur “Okay.”
- Is this informed consent?

My goals when providing informed consent

- I want the family to understand the testing in a way that is meaningful to them.
- I want the family to understand that it is their **choice** to pursue this testing. Careful consideration is important because this testing could give us important medical information for their child that could influence treatment.
- This testing can also give us information about their child's long term prognosis. Sometimes the testing gives us information about other relatives.
- If I did a good job, the family should be able to tell me in their own words:
 - What type of testing will be completed?
 - What are the possible results?
 - What will be the next steps?

Why obtain informed consent?

- Many unique issues arise when information is revealed through genomic testing
 - Information related to child's presenting symptoms
 - May provide an explanation for child's clinical manifestations – possibly ending a diagnostic odyssey
 - May be results the parents are not expecting about child's long-term prognosis
 - May also result in a direct or indirect diagnosis for another family member – another child also has the same recessive condition
 - Secondary findings that may be related to adult-onset genetic conditions – stay opted into these?
 - Non-health related information – important to know in advance how the lab will handle these results
 - Non paternity
 - Consanguinity
- Promotes collaborative decision-making, assess understanding and manage expectations
 - This testing is an option
 - Okay for families to say yes, no, or maybe later to the testing
 - Teach-back
 - The goal of teach-back is to ensure that you have explained medical information clearly so that patients and their families understand. Engage families to facilitate active participation in decision-making.
 - The results of this testing can have a lasting impact
 - The words you use will become part of that family story

Obtaining Informed Consent: ACMG Policy Statement (not inclusive or exclusive)

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ACMG POLICY STATEMENT

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Points to consider for informed consent for genome/exome sequencing

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It is important to facilitate decision-making and prepare patients for testing by discussing the potential clinical and emotional implications of results. Considering their feeling about results is an important part of the process.

ES and GS – Facilitating decision-making for possible emotional implications of results

- Consent for clinical genome sequencing: considerations from the Clinical Sequencing Exploratory Research Consortium *Per Med.* 2019 Jul 17;16(4):325–333
- It is important to facilitate decision-making and prepare patients for testing by discussing the potential clinical and **emotional** implications of results. Considering their feeling about results is an important part of the process.

Table 2. . Sample questions to aid elicitation of medical and personal context.

1. What has been your experience with genetic testing?
2. What would the benefits of this genetic test (genome sequencing) be for you?
3. What questions do you have about this genetic test?
4. What are your concerns about this genetic test?
5. Have you already made a decision about having the test? How can I help you to decide? What additional information would help you make a decision?
6. How might you react to different kinds of results, for example, if you got a result indicating that the cause of your child's condition wasn't identified?

Informed consent for ES / GS - when, what, why

- **When?**

- Obtain consent **before** collecting samples
- Testing is an option – any alternatives to this testing?

- **Why** is test being done?

- **What** is this testing?

- Building knowledge so that you understand this testing well enough to explain it
 - Difference between ES and GS
 - This testing cannot find all genetic conditions even if present
- With most labs currently, for ES or GS – the FULL test is only run on the patient (IF something relevant found, then parents samples analyzed for that specific variant)
- Diagnostic yield for finding a relevant result is higher with trios than singleton – parental samples are important for comparison

Results of ES / GS

Types of results

- **Positive** – (wide range for diagnostic yield, in general about 35%) – a result that
 - The testing found a variant (classified as either pathogenic or likely pathogenic) which is thought to be relevant or related to the medical information provided to the lab
 - Before sharing results - KNOW about the condition, read, research, call a genetics friend
 - Cognitive and emotional stressors may limit understanding and memory. **Shock of the diagnosis can create both a need for information and an obstacle to absorbing information (Stromsvik et al 2022).**
 - Clinicians need to repeat information over time. Provision of ongoing and CONSISTENT information among team members is necessary
 - Some level of prognostic uncertainty in most medical diagnoses, not unique to genetics

Our Job is that Whole Gray Zone in Between There": Investigating Genetic Counselors' Strategies for Managing and Communicating Uncertainty

- Health Commun. 2020 Nov;35(13):1583-1592. [Lingi Zhong¹](#), [Jihun Woo²](#), [Mary A Steinhardt²](#), [Anita L Vangelisti](#)

MANAGEMENT OF UNCERTAINTY IS LARGELY INFLUENCED BY HEALTHCARE PROVIDERS

For helping families cope with uncertainty and re-painting or imagining their child's future, authors suggest three main strategies to manage uncertainty:

- Engaging in open and honest communication
- Adapting to patients' needs
- **Focusing on known information**
 - Example – what will my child with condition X be like?

Results of ES / GS – when results identify a rare condition

- **If there is scientific uncertainty**

- When there is scientific uncertainty, this is NOT helpful to families:
 - We just don't know
 - We don't have any data
 - We have never seen this before
 - No available research
- Try a different approach:
 - While there are more questions regarding this, what we DO know is _____ scientists are curious about whether that means _____ or _____ and we are still learning.
 - In the meantime, what we know is _____.
 - We will take the best care of (name) and will stay on top of any medical issues that arise.
 - (Name) is in good hands, our PLAN is _____.

- **If there is provider uncertainty**

- Is the uncertainty present because the clinician does not know enough about the condition and prognosis *but this information exists and the provider is uninformed?*
 - You are likely here because you want to learn more about genetic complexity, **well done**
 - A deeper understanding of genetics concepts is important when relaying complicated genetics information
 - Keep reaching out when you need more information – recognize when you don't know enough – utilize resources and your genetics friends

Results of ES / GS

- **Negative**

- This testing did not give us an explanation – this does not rule out a genetic explanation
- Remember: not all genetic variants are reported – the lab will report results that fit the information they received about the patient on the test requisition
 - **The clinical history you give the lab matters a lot – it's a phenotype driven test**
 - Important to inform the lab later if new clinical history arises
- Future reanalysis offered by most labs, often reasonable to complete in ~ 2 years
- Consider referral for medical genetics evaluation when warranted

- **Variant of uncertain significance (VUS)** – clinical significance is UNKNOWN

- Be careful NOT to give it too much significance

- **Secondary findings** – option to receive positive results in any of 73 medically actionable conditions as recommended by ACMG – you can opt out

- **Unexpected findings** – there is possibility of unexpected findings about paternity or family relationships – know in advance how your lab handles such findings

Results of ES / GS

- Potential benefits and risks
 - Benefits: Find a diagnosis, inform medical decision making, identify recurrence risk for this in the family
 - Risks: Social, emotional, legal implications to proband and family
- Limitations of testing
 - This testing has limitations, it cannot tell us about many types of genetic conditions (imprinting disorders, repeat expansion disorders, etc.)
- Potential implications for family members
- Legal protection against genetic discrimination (GINA)
- Expected turn around time (TAT) and plan for delivering results
 - Know if your lab will provide preliminary results and how will these results be delivered to your team, how will your team handle these results? The final results may be different than the preliminary results.
 - Many labs will not send any written information about the preliminary results

ES and GS education and informed consent

- Why don't we always give patients the chance for proper informed consent?
 - Communicating the breadth and scope takes time, assumptions, and understaffing
 - The knowledge-practice gap can impede proper informed consent
- Great news – research team below show that participation in the live training intervention led to an increased level of confidence in critical skills needed for real-world implementation of genome sequencing. Providers reported a significant increase in confidence level in their ability to review, understand, and use genome sequencing result reports to guide patient care.

▶ [J Pers Med. 2022 Mar 5;12\(3\):405. doi: 10.3390/jpm12030405](#) 

Education and Training of Non-Genetics Providers on the Return of Genome Sequencing Results in a NICU Setting

Questions, comments, discussion?

Resources

- ACMG Policy Statement: Points to consider for informed consent for genome/exome sequencing, ACMG Board of Directors, Genetics in medicine | Volume 15 | Number 9 | September 2013
- Guide to Interpreting Genomic Reports: A Genomics Toolkit A guide to genomic test results for non-genetics providers
<http://www.ashg.org/education/csertoolkit/index.html>
- Coming mid 2025: BBN developed parent brochures, FAQs and video