

Module 4: Practical aspects

The “Incidentalome”

- Unanticipated Pathogenic Variants: Variants that appear deleterious and might be of significance but were not what was originally being looked for.
- Chosen to be “actionable” - would improve the care of the patient
 - Example: Finding a hereditary cancer predisposition gene during the search for the cause of a neurodegenerative disease
- Are these Fortunate Discoveries or False Alarms?
- How much real good did you do uncovering these?
 - Actionability vs. Unnecessary anxiety & higher health care costs

Incidental findings during WGS

American College of Medical Genetics and Genomics recommendations (revised 2014)

- Unless the patient specifies otherwise, the laboratory must report any clearly pathogenic mutations in one of an initial set of 56 genes, regardless of the age of patient or the indication for which testing was originally ordered.

Where to get tested

- NIH Undiagnosed Disease Program (UDP)
- Rare Genomics Institute
- Academic medical center laboratories
- Many commercial options

Informed consent – proposed minimum elements to include

- Scope and Description – What is being tested
- Benefits
- Risks
- Testing is Voluntary
- Alternative test
- Confidentiality
- Future use
- Incidental findings

Informed consent for WGA – What must patients be told?

1. As with all medical care, the test is voluntary
2. What other testing options are available?
3. We may not find the cause of your condition
4. The study has limitations – we cannot find everything that may be significant to you
5. The study will uncover changes in your genes that we are not able to interpret today
6. If uninterpretable variants are later shown to be disease-causing, we cannot guarantee we can find you to give a revised report

Informed consent for WGA – What must patients be told (Part 2)?

7. The study may uncover changes in your genes that we think are of medical/clinical importance but are not the reason we sent the test – do you want them?
8. We may uncover variants that are of clinical significance not only to you but to other family members
9. Information will be saved and protected as with all other personal health information but it will be used for quality improvement and quality assurance purposes
10. There is a risk of unintended disclosure and, where applicable, impact on insurance or employment not currently protected under non-discrimination laws
11. There is a risk we may uncover variants that indicate family relationships are not what they are currently understood to be

The Bottom Line

- Whole Genome Analysis is complex at many levels including
 - Technology – limitations
 - Interpretation
 - Patient consent