Whole-Genome Sequencing (WGS) in Patient Care

Scenario: A two-year-old male presents with developmental delay and physical characteristics (e.g., microcephaly, inverted nipples, up-slanting palpebral fissures) that do not conform to a known genetic syndrome. Due to a relatively unspecific phenotype, Whole Genome Sequencing (WGS) is performed.

STEP 1

Collect patient sample

WGS order received and sample is collected.

- Laboratory professional reviews patient history and discusses testing plan with ordering physician to confirm WGS is the best test for patient
- A blood or saliva sample is taken

STEP 2

Generate sequencing library from patient sample

8 hours
**HANDS-ON TIME

Technologist extracts the DNA from the sample, shears it into small pieces, and labels it, generating a sequencing library. (To focus sequencing efforts on genomic regions of interest, those regions are specifically enriched and only those regions added to the sequencer).

STEP 3

Perform sequencing

30-48 hours
**HANDS-ON TIME

Technologist loads sample on the sequencer, which determines the order of DNA bases across the entire genome (or across targeted regions if desired).

STEP 4

Perform initial analysis

2.25 hours
**HANDS-ON TIME

- Bioinformatician downloads sequencing data
- All potential alterations/mutations in the sample are identified
- Initial quality control performed

STEP 5

Verify Quality Control

.25 hour
**HANDS-ON TIME

Molecular professional confirms that each alteration/mutation is "real" and based on high-quality data.

STEP 6

Complete complex analysis

3.75 hours
**HANDS-ON TIME

Molecular professional narrows the list of alterations/mutations to those related to patient's symptoms. If needed, performs analyses to account for dominant and recessive alterations.

- Performs extensive research into primary literature; analyzes patient's medical record and history, and incorporates any previous diagnostic test results

STEP 7

Prepare report

1.25 hours
**HANDS-ON TIME

- Molecular professional prepares personalized report that explains the findings in the context of the patient's diagnosis/prognosis
- Suggests any follow-up testing or next steps

STEP 8

Present case to peers

.25 hour
**HANDS-ON TIME

Molecular professional may present case study to colleagues at Complex Case Conference/ Genome Board/etc. for further education and understanding of diagnostic process.

STEP 9

Communicate on ongoing basis

.25 hour
**HANDS-ON TIME

Molecular professional continues discussion with ordering physician to explain results in more detail, discuss treatment plan, and/or consider follow-up tests.

Comparison of PCR-based diagnostics vs Whole Genome Sequencing

	Targeted analysis via PCR*	Whole Genome Sequencing
TIME TO RESULT	2 days	4 days - 2 weeks, typically
# Individuals involved	2	5 -10
Professional hands-on time required	0.5 - 1 hour	10.5 hours
# of bases investigated for possible mutations	10 -100	Up to 3 billion bases x 30 (accounts for reading depth across genome)
Type of alterations detected	Single-nucleotide variants, small insertions or deletions	Single-nucleotide variants, insertions or deletions, rearrangements, gene copy number variations, fusions

*While PCR-based assays are a powerful tool for interrogating small, specific regions of the genome, WGS offers much broader coverage and the ability to screen the entire genome for disease-associated variants, including novel variants, gene and chromosomal rearrangements, and variants with combinatorial effects.

Molecular professionals are specialist physicians and doctoral scientists that develop, perform and/or interpret molecular tests. Average time estimate was gathered from the **AMP Professional Work Survey** for whole genome sequencing tests across all lab types. **Technician/Bioinformatician time is shown as hands-on time only; does not include time for incubation steps, data transfer, etc.

THE SURVEY READOUT CAN BE VIEWED AT: **www.amp.org/ProfessionalWorkReport**

AMP Association for Molecular Pathology

STEP 10

Outcome

After filtering and reviewing all possible disease-causing variants, a positive report with a diagnosis of a rare genetic disease is issued. A change of management specific to that disease's typical course of progression can be implemented without subjecting the patient to further invasive testing.