**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.

### Comparison of PCR-based diagnostics vs Whole Genome Sequencing

<table>
<thead>
<tr>
<th></th>
<th>PCR-based diagnostics</th>
<th>Whole Genome Sequencing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to Result</strong></td>
<td>2 days</td>
<td>4 days - 2 weeks, typically</td>
</tr>
<tr>
<td><strong># Individuals Involved</strong></td>
<td>2</td>
<td>5 - 10</td>
</tr>
<tr>
<td><strong>Professional hands-on time required</strong></td>
<td>0.5 - 1 hour</td>
<td>10.5 hours</td>
</tr>
<tr>
<td><strong># of bases investigated for possible mutations</strong></td>
<td>10 - 100</td>
<td>Up to 3 billion bases x 30 (accounts for reading depth across genome)</td>
</tr>
<tr>
<td><strong>Type of alterations detected</strong></td>
<td>Single-nucleotide variants, small insertions or deletions</td>
<td>Single-nucleotide variants, insertions or deletions, rearrangements, gene copy number variations, fusions</td>
</tr>
</tbody>
</table>

Whole Genome Sequencing tests across all lab types. **Comparison:** PCR-based assays were possible tools for interrogating small segments of the genome, such as single nucleotide variants, and are sensitive to small insertions or deletions. **Whole genome sequencing** provides more comprehensive genetic insights, enabling a more comprehensive understanding of the patient’s genetic landscape.

**ASSOCIATION FOR MOLECULAR PATHOLOGY**

**AMP Professional Work Survey**

**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.

---

**Whole Genome Sequencing (WGS) in Patient Care**

**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 tool for patient.
- A blood or saliva sample is taken.

**STEP 2:** Generate sequencing library from patient sample
- Technologist extracts the DNA from the sample, shears it into small pieces, and labels it, generating a sequencing library.

**STEP 3:** Perform sequencing
- 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
- Bioinformatics downloads sequencing data.
- All potential alterations/mutations in the sample are identified.
- Initial quality control performed.

**STEP 5:** Verify Quality Control
- Molecular professionals ensure that each alteration/mutation is “real” and based on high-quality data.

**STEP 6:** Complete complex analysis
- 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
- 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
- Molecular professional may present case study to colleagues at Complex Case Conference/Gene Board/etc. for further education and understanding of diagnostic process.

**STEP 9:** Communicate on ongoing basis
- Molecular professional continues discussion with ordering physician to explain results in more detail, discuss treatment plan, and/or consider follow-up tests.

**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.