Genomic Answers FOR Children's Health ALLIANCE

Whole Genome Sequencing (WGS) – Current Workflows and Timelines

Prenatal Factors for Consideration

- Family history of suspected genetic condition without a definitive diagnosis.
- Recurrent miscarriages.
- Abnormal prenatal ultrasound indicating birth defects that may suggest a genetic syndrome.
- Prenatal genetic and/or genomic testing may have been performed.
    - While it is rare that WGS is performed prenatally, typical prenatal genetic testing includes carrier screening for autosomal recessive and x-linked disorders and non-invasive screening for trisomy.
- Pregnancy may be high risk for the fetus, e.g., polyhydramnios or fetal malformations.
- Consent and/or parental samples for WGS may be obtained in preparation for postnatal testing. Highly unlikely that prenatal WGS is performed on the fetus.

When and How WGS is Used

Rapid WGS in Neonatal and Pediatric Critical Care (NICU/PICU/CVICU or other high acuity pediatric unit)

1. Infant or child admitted to a high acuity inpatient unit (typically NICU, PICU, or CVICU).
    a. At this time, the majority of rapid WGS testing occurs among neonates in the NICU.
2. Identification of potential need and/or value of WGS for the patient by a neonatologist, genetics team, and/or pediatric subspecialist.
    a. *Estimated time:* immediately to weeks.
3. After review of patient's clinical presentation, the decision is made to initiate testing, either by the neonatologist, genetics team, or other pediatric subspecialist.

   a. The hospital may utilize telemedicine support to help make this decision, e.g., by engaging a genetic counselor subspecialist to review WGS with a consenting family member.
   b. *Estimated time:* immediately to weeks.
   c. *Potential complications:* many institutions have an internal review process before tests can be sent out due to the cost of the test. Processes vary by institution and may delay testing. Limited genetics resources may also cause delays in consults and/or test send-out.

4. Consent obtained—either in person, virtual, or over the phone—and order placed by ordering provider.
   a. *Potential complications:* any postpartum complications for the mother—in that case, consent will be obtained by a different family member.
   b. *Estimated time:* minutes to over an hour.
5. Sample(s) collected from baby and one or both biological parents depending on availability; in rare cases, a sample may be drawn from another 1st degree blood relative.
   a. This is usually blood but depending on the laboratory may also be a cheek swab, saliva, etc.
   b. Familial samples are useful for helping to classify variants as pathogenic or benign, and for inheritance and segregation testing.
   c. *Potential complications:* the health of the baby, the placing of IVs, and/or volume limitations for the blood draw; if the baby is from an outside hospital transfer; the availability of parents and/or relatives.
   d. *Estimated time:* hours to days.
6. Test requisition form generated by ordering provider to communicate phenotype and clinical information to the performing laboratory to inform analysis and interpretation.
   a. *Estimated time:* 30 minutes to 2 hours.
7. Samples shipped to laboratory, preferably with expedited shipping.
   a. *Potential complications:* Send-out shipment deadlines for each day; limited shipping availability during the weekend.
   b. *Estimated time:* 12-72 hours.
8. Samples received by testing lab, usually accessioned within several hours of receipt by the laboratory.
   a. This may take longer if received over the weekend or a holiday.

   b. All testing elements are needed to initiate testing, including all expected samples and clinical notes to aid genome interpretation. Delayed receipt of any of these may result in testing being held.

9. Testing performed and reported.
   a. Sequencing, analysis, and interpretation of the whole genome.
   b. Results returned to ordering medical team, either via phone, email, or through the EHR.
   c. *Estimated time:* 3-14 days.
10. Result reviewed by ordering team.
11. Disclosure of results to family, either in-person, virtually, or over phone; typically alongside a genetic counselor for post-test counseling.
12. Clinical action taken based on result—changes in management may include medication changes, dietary changes, decisions around surgical or other invasive procedures, earlier discharge planning, initiation of compassion care, additional follow-up with patient's family, etc.
    a. Follow-up testing and sample recollection if necessary.
13. Charges may be added to hospital inpatient claim and billed to payer.
    a. The vast majority of hospitals do not bill for rWGS due to low- to no-reimbursement for charges associated with inpatient WGS and the administrative burden of billing.

While the rWGS test has a turnaround time of 3-14 days for a final result, the process overall varies from case to case depending on patient identification, consulting with genetics, completing consents, obtaining samples, etc.

Other Inpatient (Hospital) Scenarios

While the workflow steps are identical, there are additional considerations when WGS is performed in other inpatient settings. Note that while rapid WGS is near-universally performed for WGS cases in the critical care setting, standard WGS may be performed outside of the critical care setting and is performed with longer turnaround times (test time ~ 30-60 days).

Hospital ward (non-critical illness)

- Few hospitalists suggest WGS and very few will consent patients.
- Much more reliant on clinical champion on-site or genetics team (if available).
- The clinical utility of rapid WGS in this setting is not as well as established as in the ICU, but may be considered for infants and children who are not critically ill

but for whom an underlying etiology of an extended hospital admission and/or multiple readmissions has not been determined.

Adult inpatients (typically cardiovascular or neurological ICU, or patients with medical declines for unknown reasons)

- Rare to consider WGS and difficult to obtain patient consent due to sedation or other external factors.
- Would need genetics team to consider WGS as a testing option if consulted.
- There is a growing evidence base that there is clinical utility for certain adults in the acute-care setting.

Outpatient Scenario

There are additional considerations when WGS is performed in the outpatient setting. WGS is nearly always performed with standard turnaround times in the outpatient setting as the patient is in stable medical condition.

- Patient evaluation and test ordering are performed in outpatient clinic by geneticist or other relevant medical provider.
- Test cost is billed to patient's insurance (Medicaid or commercial) rather than inpatient testing where the institution is billed.
- Prior authorization is universally required. This can take up to an additional 4-6 weeks or more beyond the lab time.
- Medical necessity and other criteria are set by the payor based on supportive literature and professional society position statements such as the American College of Genetics and Genomics (ACMG).

Since rapid WGS is generally not indicated, estimated lab timelines for outpatient WGS after insurance authorization are typically in the four-to-eight-week range.