RCPCH Genomic testing flow chart

Review Phenotype and Inheritance
Ensure complete and accurate phenotyping
Consider if familial/sporadic/incomplete penetrance

Consider differentials
Compile an *a priori* list of candidate disorders/genes

Select most appropriate testing option
Are key phenotypic features suggestive of a specific or broader range of disorders?

Is genetic testing required now?
Testing unlikely to change management
Prenatal/Environmental causes likely
➔ Consider testing in research setting

Specific Test Options

MLPA	e.g. SMA
Triplet repeat	e.g. Myotonic Dystrophy Fragile X syndrome
Methylation	e.g. Prader Willi syndrome Silver Russell syndrome
Karyotype	e.g. Chromosomal translocation

Mitochondrial WGS/rearrangements

Array

Copy number variants

Best for:
Cong.malformations, dysmorphism, developmental disorders

e.g. Developmental/ intellectual disability, autistic spectrum

NGS Panel (S)

10's to 100's genes

Best for:
Defined groups of disorders with some genetic heterogeneity

e.g. RASopathy panel in child with features of Noonan Syndrome

Trio WGS

1000's+ genes

Best for:
Non-specific phenotype or panel test negative

e.g. Multisystem involvement, delayed development, no recognisable syndrome

Rapid Trio WGS

1000's+ genes

Best for:
NICU/PICU setting
Where diagnosis likely to impact management

e.g. Infant multiple failed extubation, parents pregnant and elder child undiagnosed

Incidental/secondary findings
Unrelated to disorder being investigated
Feedback if clinically actionable and family have consented to receive

Check ACMG guidance

Variant interpretation:
Review ACMG guidelines and consider the following:

Reported frequency	Variant assessment	Family/Pt info.
Population Data	In silico Data	Segregation
Variant Databases	in cis/trans	De novo status
	Functional Data	Phenotypic fit

What is missed in NGS?
Somatic mosaicism
Deep intronic variants
GC rich domain
Structural aberrations
Homologous sequences

Multidisciplinary team meeting
Speciality consultant, clinical geneticist, clinical scientist
Review short list of variants - supporting evidence strength + phenotype concordance. Determine if further ix may aid interpretation (imaging, functional studies)

Decide on variant classification

Report directly
If clear diagnosis (Class 5)

No variant identified
Consider alternative test:
Add panels, WES/WGS
Sanger, array, karyotype
Deep sequencing NGS
Long-range PCR
MLPA, Triplet repeats

Nil/Class 1/2 variant
Negative/ Benign

Negative report
Consider additional testing/re-analysis

Class 3 variant
VUS

Research report
Family counselling
?functional studies
Reassess over time

Class 4/5 variant
Pathogenic

Diagnostic report
Family counselling
Surveillance/Mx implications