From Genomics England result to the clinical diagnostic report

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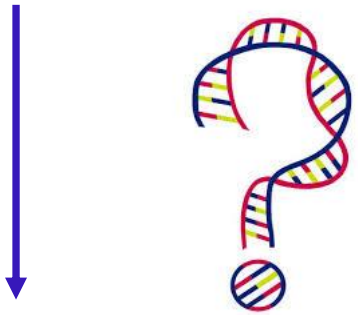
Genomics England result



Diagnostic report issued to patient's clinician

Validation of the bioinformatics pipeline

Genomics England result

Diagnostic report issued to patient's clinician

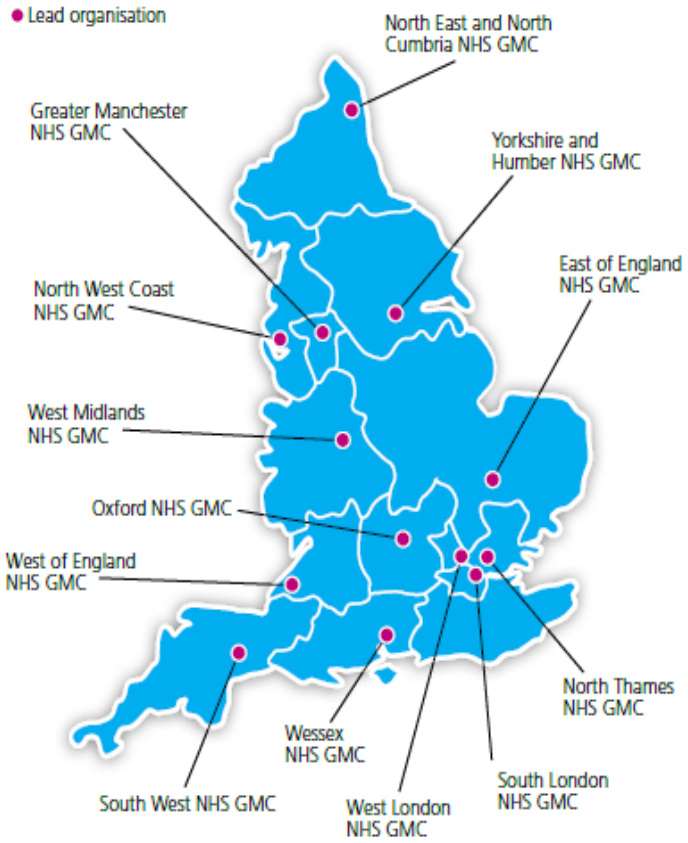
Validation of the bioinformatics pipeline

- What is the sensitivity (and specificity) of the 100,000 Genomes sequencing and analysis pipeline?

- What is the sensitivity for detecting different types of mutations? (SNVs, indels, CNVs, translocations/inversions, mobile elements, UPD and mosaicism)

- Does it detect previously identified variants? Compare with previous panel test results, exome data or aCGH.

Validation: the size of the task

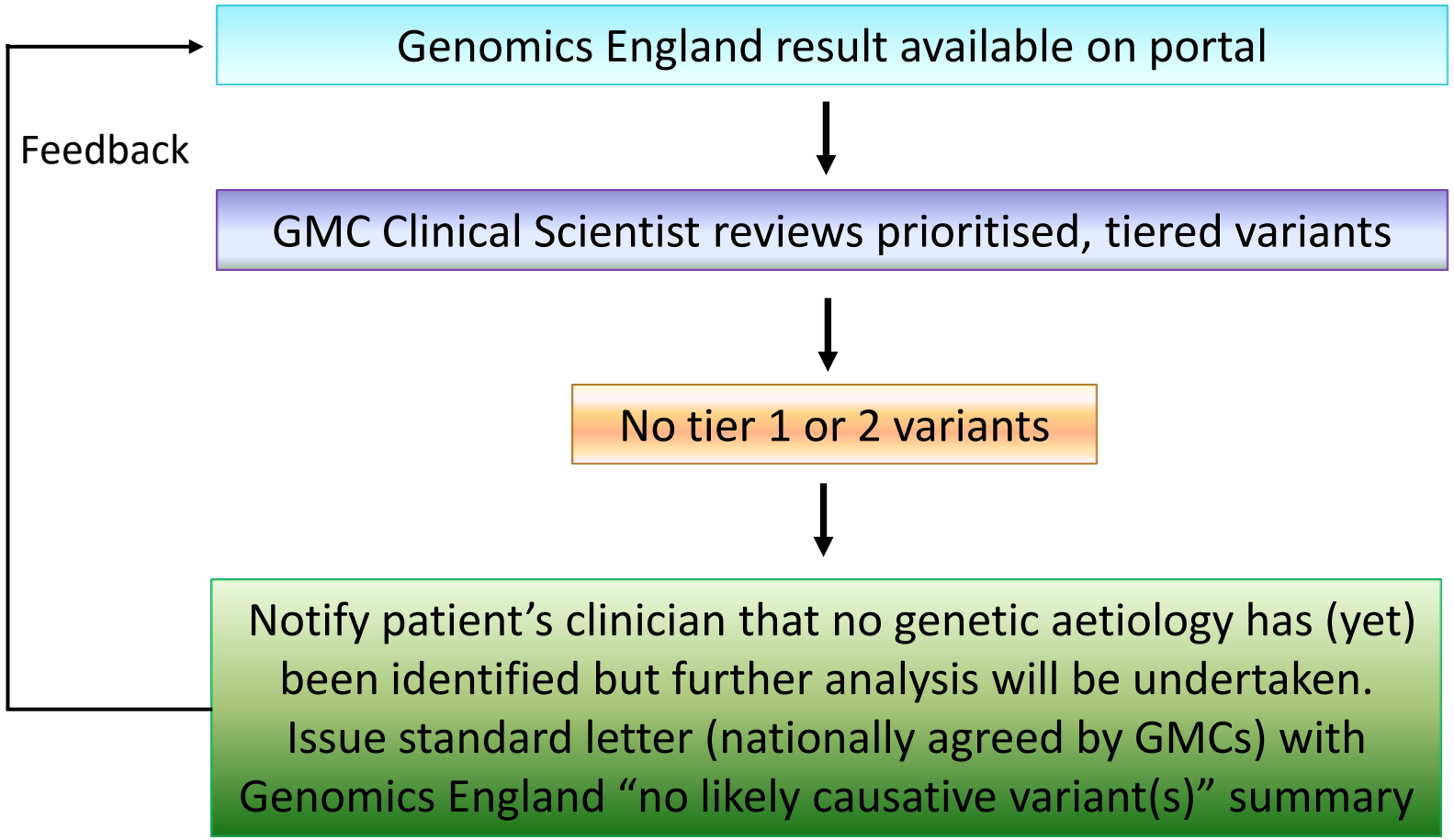


- Depends on your recruitment target!
- Additional findings <1% of participants
- Primary findings?

Validation of additional findings

- Report only definitely pathogenic mutations (class 5)
- Breast and colorectal cancer mutation list based on ENIGMA and InSiGHT databases
- Cystic fibrosis kit mutations and ethnic minority founder mutations
- MEN2/FMTC *RET* missense mutation list from clinical management guidelines
- MEN1, VHL and FH lists of missense, in-frame indels and non-AG/GT splicing mutations collated by UKGTN labs

Validation process overview



Validation process overview

Genomics England result available on portal

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GMC Clinical Scientist reviews prioritised, tiered variants

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No tier 1 or 2 variants

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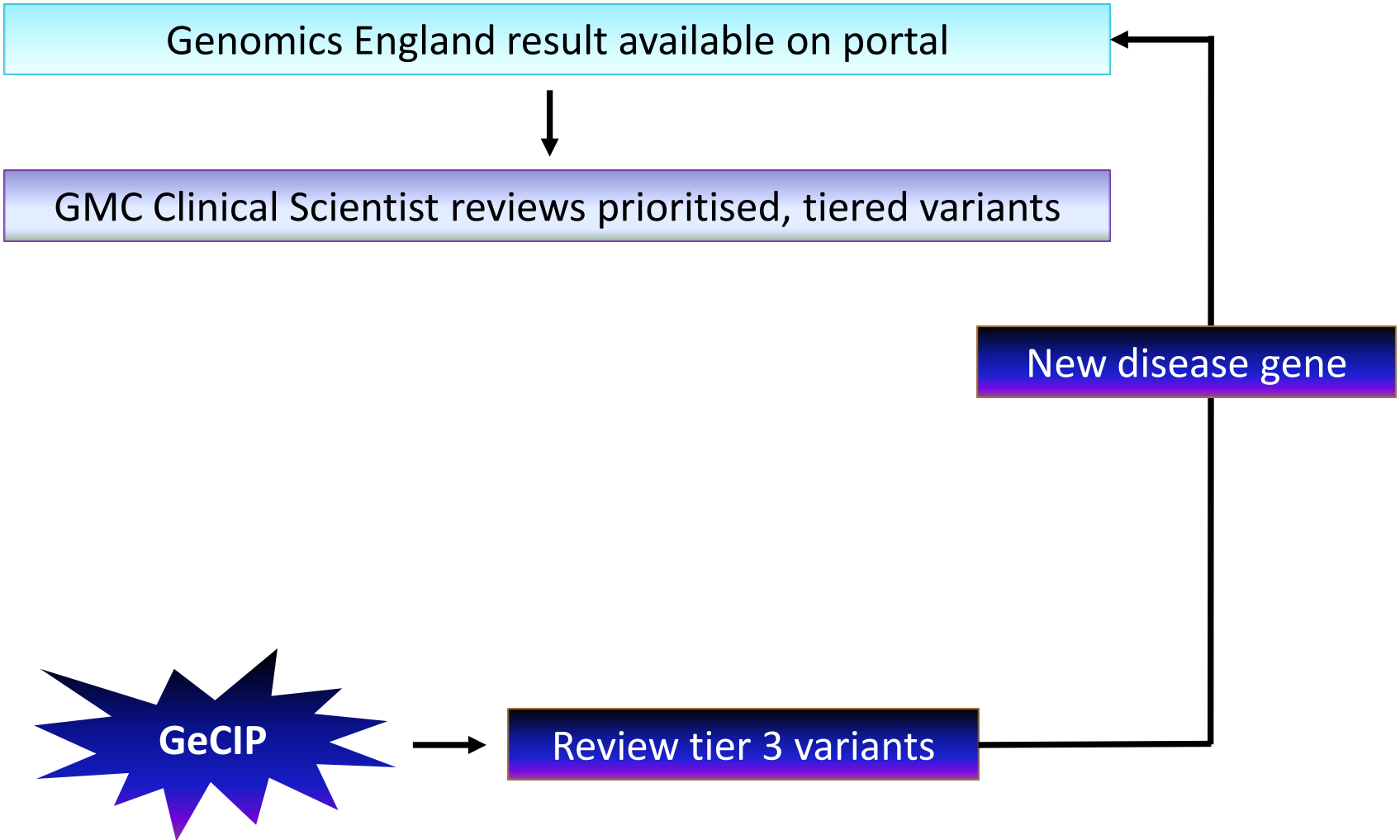
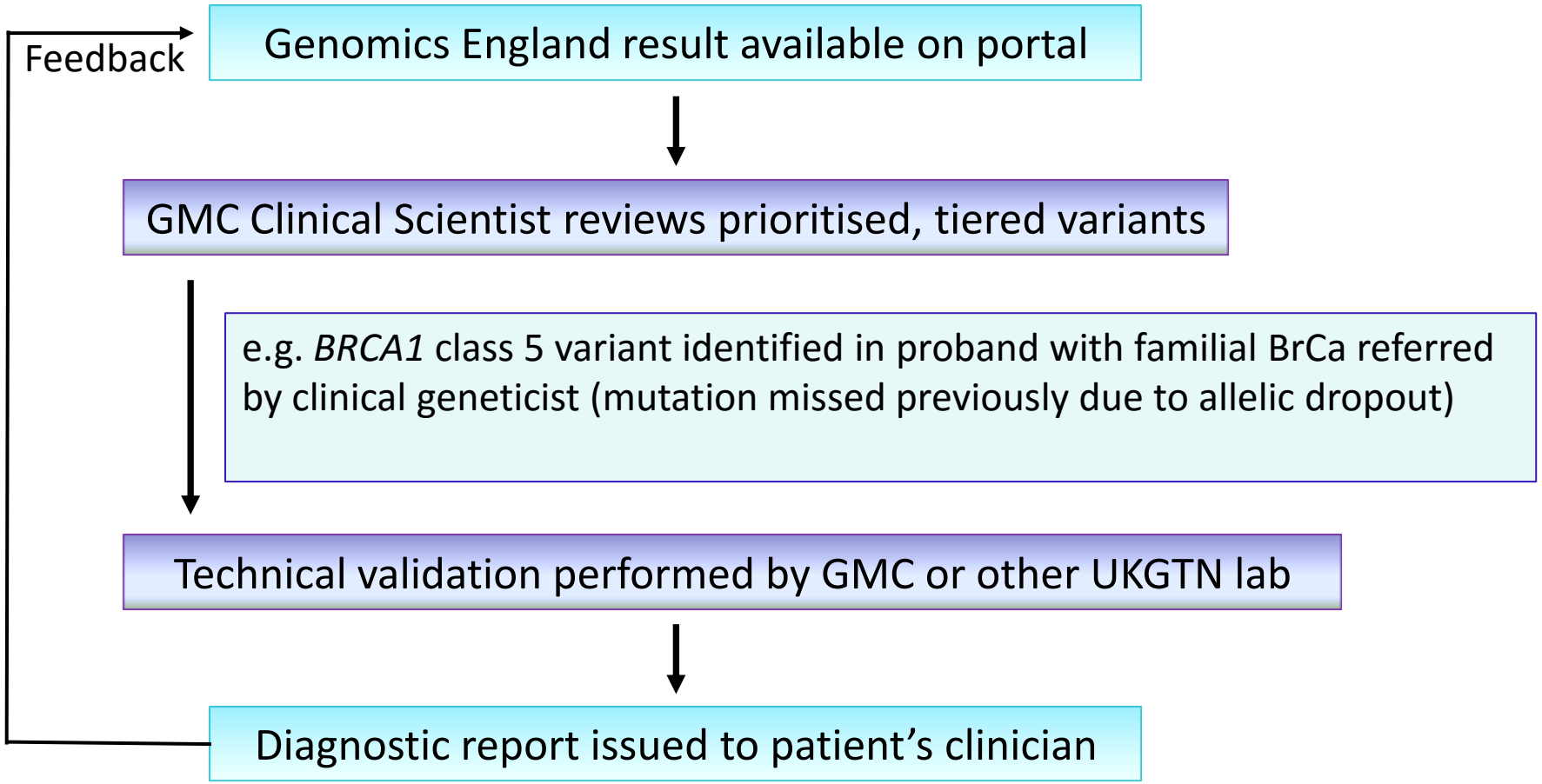
Notify patient's clinician that no genetic aetiology has (yet) been identified but further analysis will be undertaken

→ Review tier 3 variants

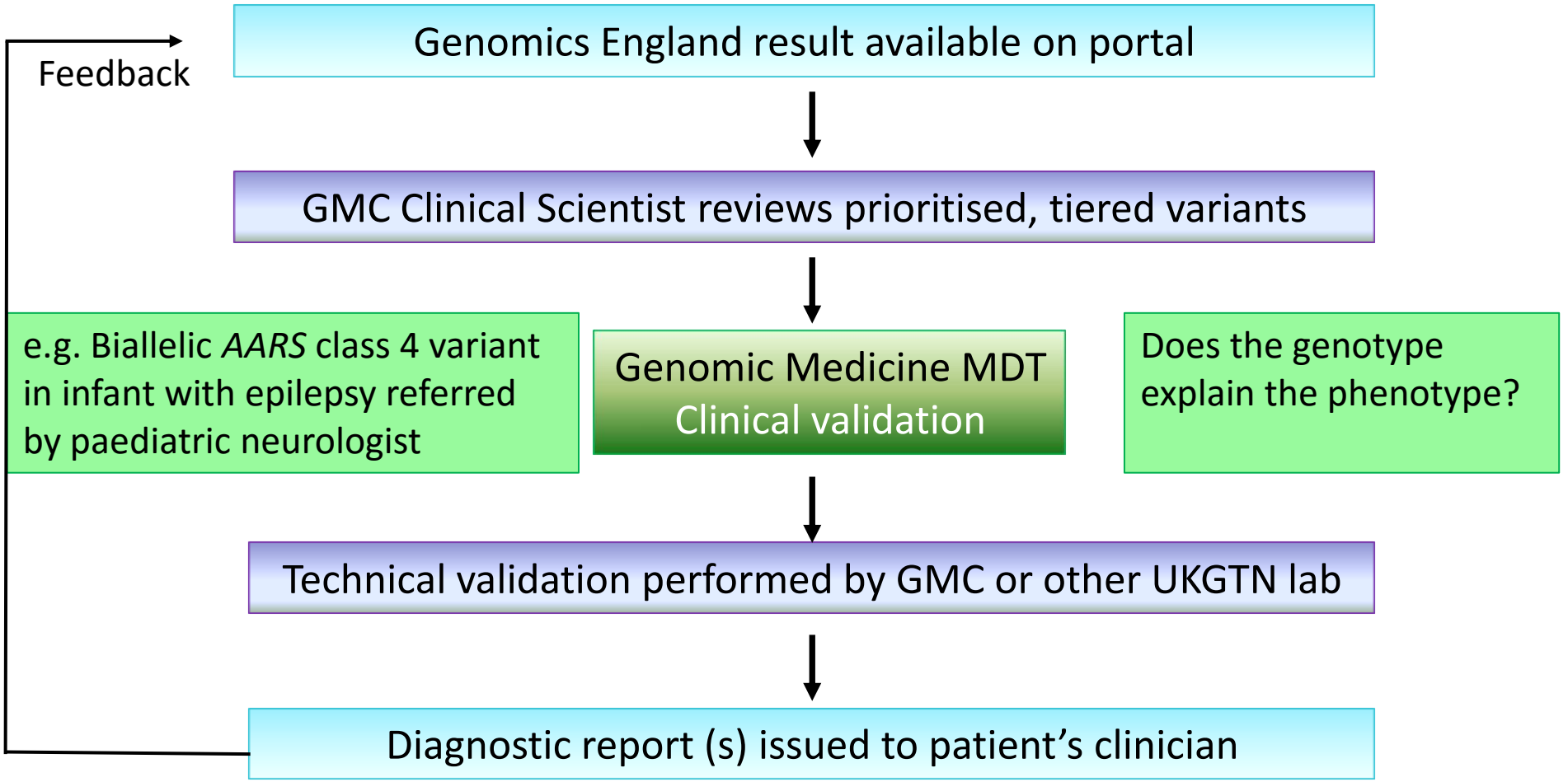
Validation process overview



Validation process overview



Validation process overview



Streamlining the validation process

- Refer to UKGTN provider laboratory for genes not tested in-house but already available in the NHS (utilise existing clinical expertise)
- Facilitate this by agreeing a standard price for Sanger sequencing tests?
- If gene is not listed on UKGTN directory, does the gene “fit” an existing panel? (Note – keep UKGTN panel gene lists up to date)

Streamlining the validation process

- If gene is not listed on UKGTN directory/doesn't fit an existing panel (an "orphan gene/disorder"), is testing for this gene/disorder already set up elsewhere? eg DDD confirmation or exome sequencing test confirmation

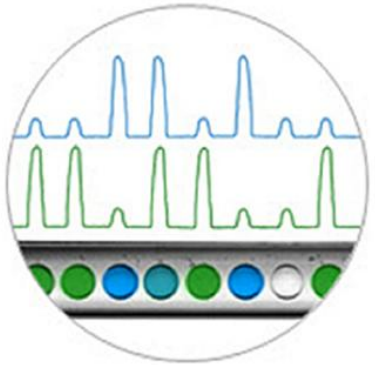
- Create a searchable central inventory of non-UKGTN tests listed by gene and hosted on the UKGTN website

A	B	C	D	E	F	G	H	I	J	K	L	M
Gene symbol (HGNC)	Laboratory	Laboratory contact email	Disorder	Phenotype OMIM	Transcript (LRG, RefSeq or Ensembl)	Exon	Variant (nucleotide description)	Variant (genomic description)	Forward primer sequence (5'-3')	Reverse primer sequence (5'-3')	Genomic location of forward primer	Genomic location of reverse pri
Essential	Essential	Essential	Optional	Optional	Optional	Optional	Optional	Optional	Optional	Optional	Optional	Optional
GNAO1	Exeter	rde-tr.molecular	Epileptic encephal	615473	NM_138736.2	6	c.607G>A	Chr16(GRCh37):g.56370	ccccatcctctgcctctcag	tcagagggctggcctatcc	Chr16(GRCh37):g.5637	Chr16(GRCh3

Streamlining the validation process

- Create an on-line NHS database of PCR amplicon primers for non-UKGTN tests (eg LabHelper: Bristol Genetics Laboratory – Marc Wadsley)

- Technique-based testing eg droplet digital PCR for CNVs where no MLPA kit is available/array CGH not appropriate



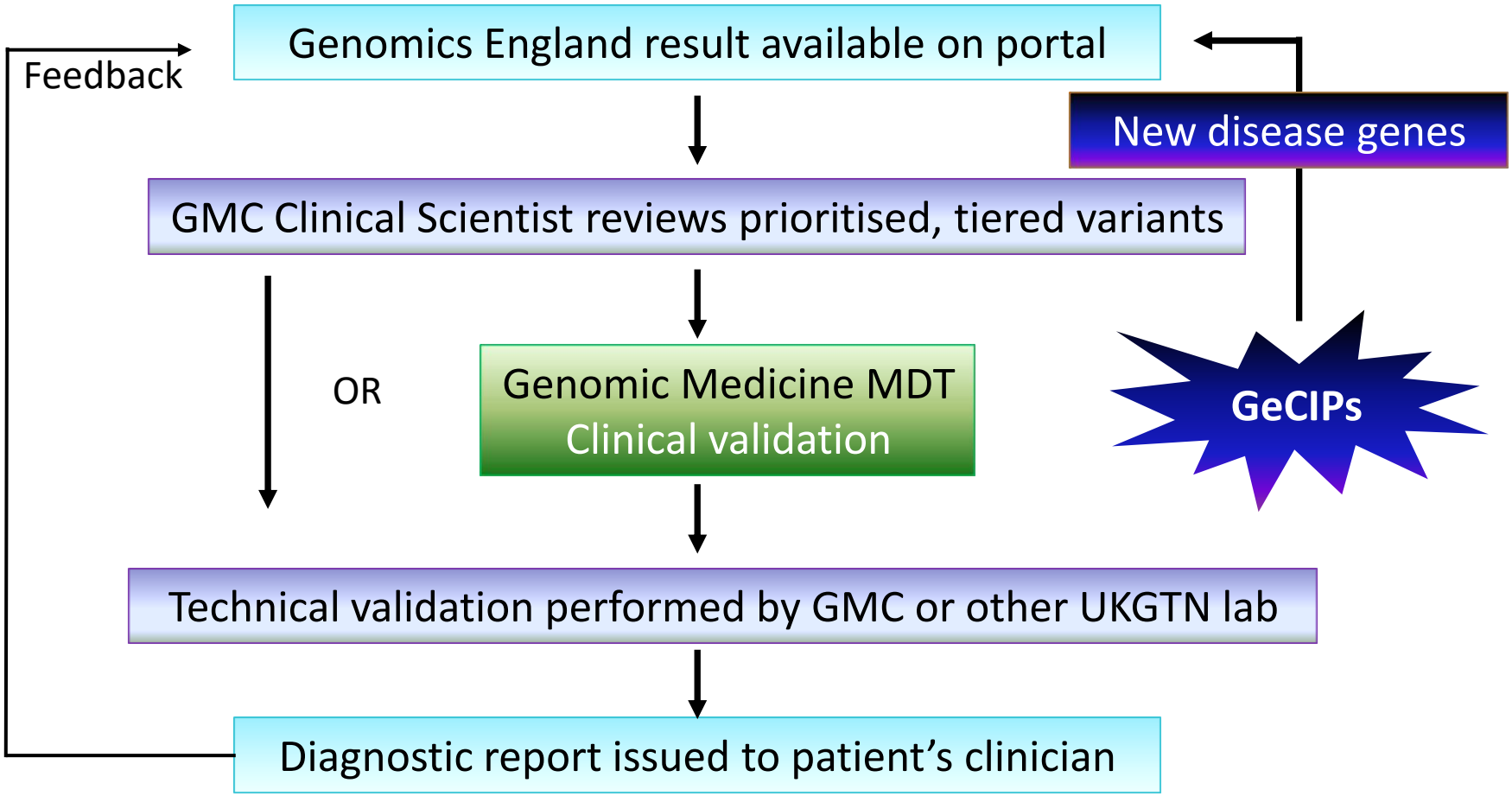
Future requirement for the validation process

- For how long will there be a need for technical validation?
- False positive rate for NGS tests in NHS labs is very low/family member WGS can provide variant and sample identity confirmation
- ISO15189 accreditation of Illumina pipeline from extracted DNA to annotated variants
- Clinical validation via MDT required and issue of a clinical diagnostic report from an accredited provider that includes clinical interpretation of the genomic results

Improving the quality of NHS genomic medicine laboratory services

- Increased repertoire of tests for rare diseases (UKGTN gene dossier-approved tests, panels and very rare “orphan gene” disorders)
- Central, secure NHS database of genomic variants to inform clinical interpretation
- Standardisation of report format with an emphasis on providing clinical interpretation of genomic results in a way that is more easily understood by non-specialists and patients

Validation process overview



Turnaround time for validation

- Suggested 4 week turnaround
- Validation of WGS results includes three stages: GMC review of the Genomics England results, the MDT assessment (which may require additional tests/clinical assessment) and the technical validation/issue of the diagnostic report.
- 4 weeks from MDT decision to issue of diagnostic report?

Summary

- GMC is responsible for reviewing tiered & candidate variants, undertaking clinical evaluation via an MDT process and issuing a clinical diagnostic report after technical validation

- Feedback results from validation testing to Genomics England portal to ascertain specificity of variant calling, build database of clinical diagnostic results and patient/family outcomes

- We need a validation process that meets the requirements for the 100,000 Genomes Project AND enhances current/future NHS genomic testing provision