Lessons learned about whole genome sequencing from Northern Ireland's participation in the 100,000 Genomes Project

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Main body (250/250 words)**:**

Until recently, clinical molecular diagnostics within the National Health Service for rare and inherited diseases, have utilised targeted gene panels or exome sequencing approaches. These approaches do not necessarily yield a diagnosis for all genetic conditions. Whole Genome Sequencing (WGS) shows potential to increase diagnostic yield and, if integrated into care pathways, could potentially decrease the diagnostic odyssey timeline.

Northern Ireland (NI) recruited 448 rare disease probands to the *100,000 Genomes Project* (100KGP, https://www.genomicsengland.co.uk/about-genomics-england/the-100000-genomes-project/) and to date 1 in 4/1 in 5 participants have received a diagnosis. As part of the *100KGP* in NI, we also carried out a translational research workstream. This was a collaborative approach including healthcare professionals, researchers and patients. Outputs will be used to inform how WGS may be integrated into NI healthcare. Areas under consideration included:

(1) Comparison of NI diagnostic yield to the wider United Kingdom (UK)
(2) How we can improve diagnostic yield
(3) Clinical utility of WGS
(4) Cost-effectiveness of WGS
(5) How we can better integrate WGS into multi-disciplinary healthcare

Key findings included that diagnostic yields and operational process challenges were comparable between NI and the wider UK, yet significant developments are required for WGS implementation (*e.g.* information technology infrastructure). There is considerable scope to extend research collaborations given adequate resources. Additional investigation of variants of unknown significance, improved phenotyping depth, and extended multiomics may improve diagnostic yield. WGS holds significant promise for the future of NI healthcare although discussions surrounding clinical utility and cost-effectiveness of WGS are ongoing.