St George's University Hospitals
NHS Foundation Trust

Dr Meriel McEntagart

Clinical interests

Dr McEntagart practices in general clinical genetics with a specialist interest in neurogenetics, particularly the genetics of neuromuscular disorders.

Professional profile

Dr McEntagart qualified in medicine in Ireland in 1991 (MBBS) and received her CCT in clinical genetics in the UK in 2004. As part of her academic training in genetics she undertook an MSc in clinical genetics at UCL in 1998 and completed her MD thesis in 2003.

She continues to maintain an interest in genetic research publishing work with national and international collaborators.

- Fellow: Royal College of Physicians (UK)
- Member: British Society for Human Genetics(BSHG)

Congenica

Outstanding care every time

St George's University of London

NHS
St George's University Hospitals
NHS Foundation Trust

Improving Rare Disease Diagnosis in The 100,000 Genomes Project (UK 100K)

EGM Korea

December 2021

Dr Meriel McEntagart

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Content

St George's University Hospitals NHS Foundation Trust

- Background
- UK 100K Workflow & Results
- St. George's University Hospitals Experience
- Case Studies from the UK 100K
- Summary

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Clinical and technical challenges for diagnosing Rare Disease

- **Diagnostic Odyssey**
- **Phenotype description**
  - ❖ Known phenotype- recognizable
  - ❖ Atypical presentation of a known phenotype
  - ❖ Specialty specific phenotype bias
  - ❖ Undescribed condition
- **Heterogeneity of molecular mechanisms**
  - ❖ SNV (truncating, missense), indel, CNV (gain, loss), SV (translocation, inversion), loss of function, gain of function, UPD (imprinting genes), mosaicism, STR, non-coding
- **Technology** (Targeted, panel, genome wide array, whole exome/genome)

Milestones of Human Genomics in UK

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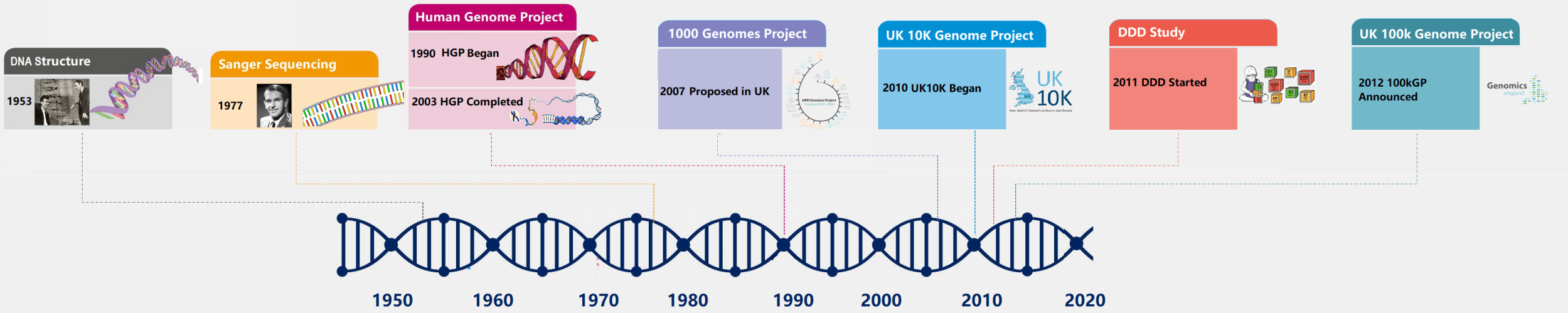

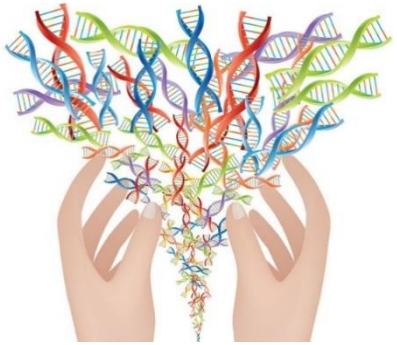

DDD Study: The Deciphering Developmental Disorders Study (Y2011-Y2021)

https://www.yourgenome.org/facts/timeline-history-of-genomics
https://www.genomicseducation.hee.nhs.uk/blog/70-years-of-genetics-and-genomics-in-healthcare/

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UK 100K Genome Project

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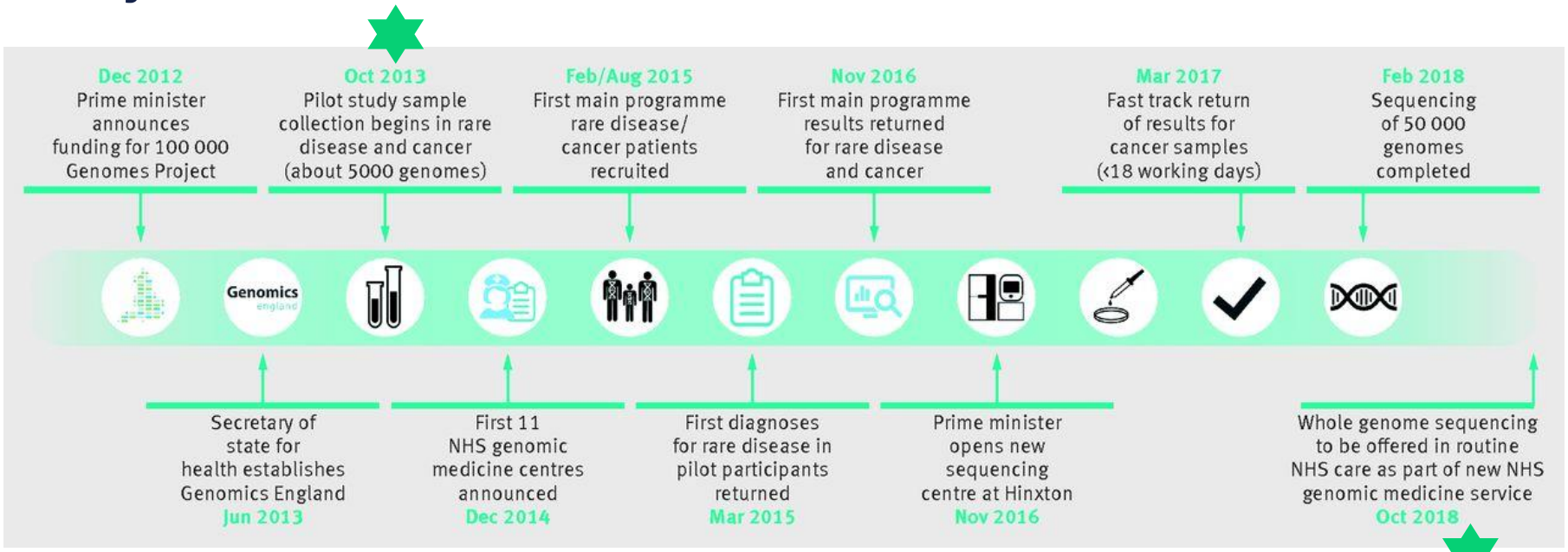

All clinical **WGS**(>30x)

Rare disease (proband/parent trios)-
Cancer (normal/tumour pairs)-

01 **Patient Benefit**
To bring benefit to NHS patients

02 **Ethical Programme**
To create an ethical and transparent programme based on consent

03 **Scientific Discovery**
To enable scientific discovery and medical insights

04 **UK Genomics**
To kick start the development of UK genomics industry

Turnbull C, Scott R H, Thomas E et al. The 100 000 Genomes Project: bringing whole genome sequencing to the NHS.BMJ 2018; 361:k1687

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The Interpretation Bottleneck

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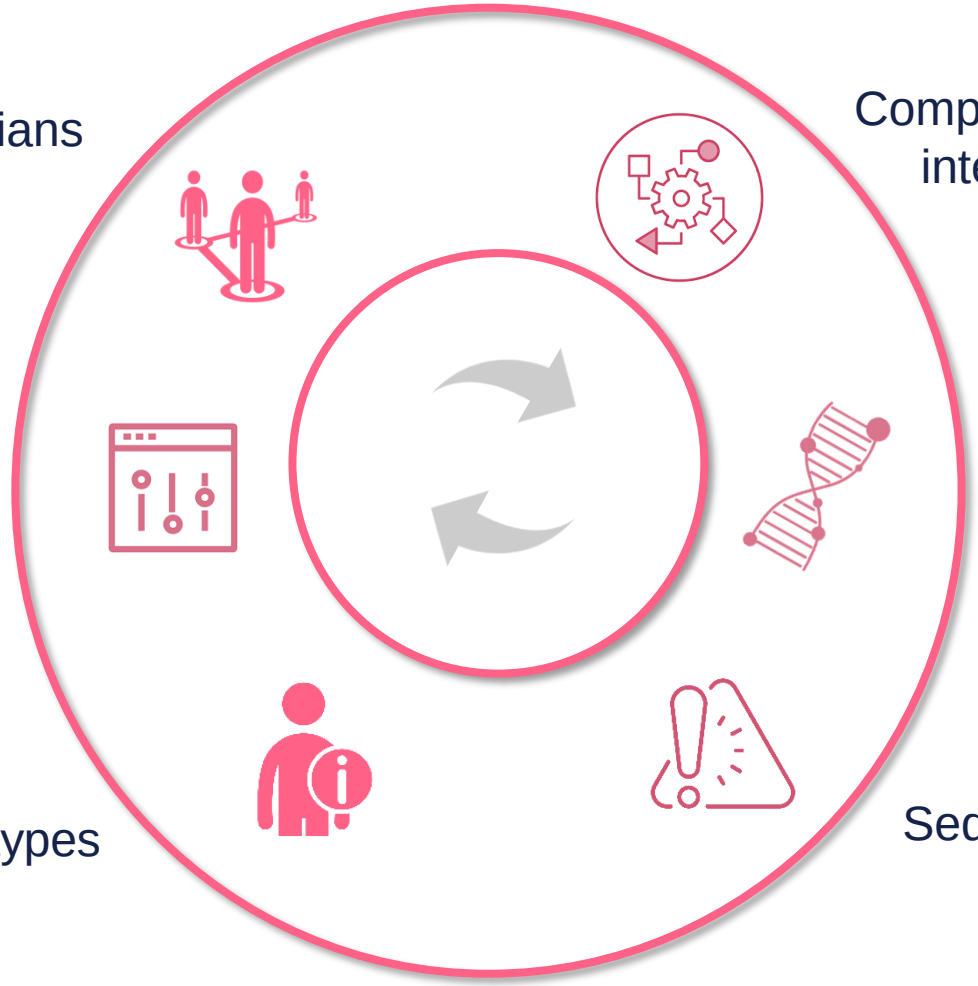
Lack of skilled clinicians

Complexity of the interpretation process



Gene panel selection

Millions of variants to analyse

Incomplete phenotypes

Sequencing artefacts

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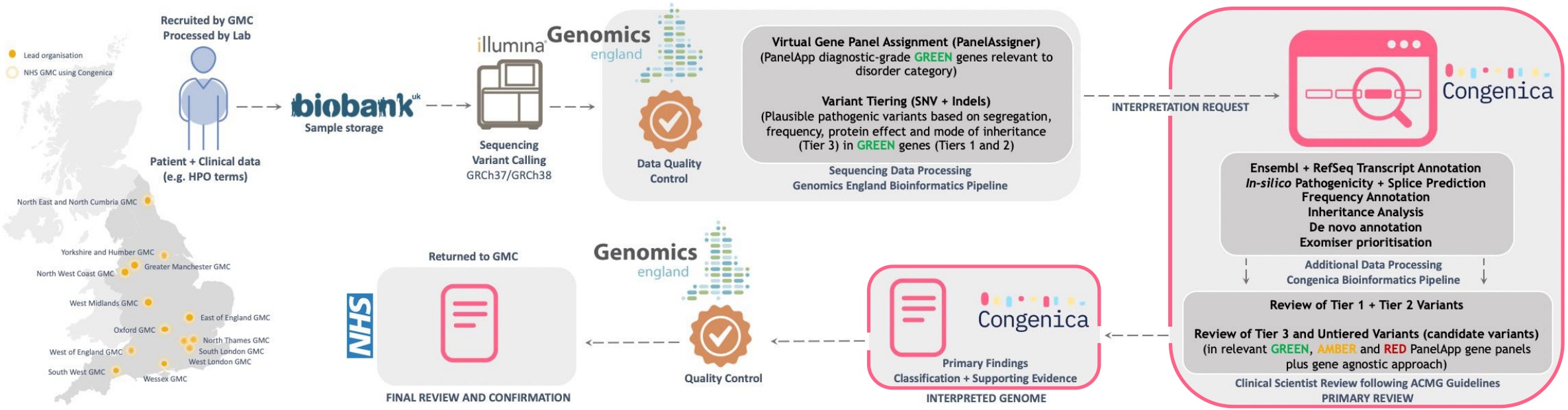
Genomics England UK100K

Rare Disease Pilot Workflow



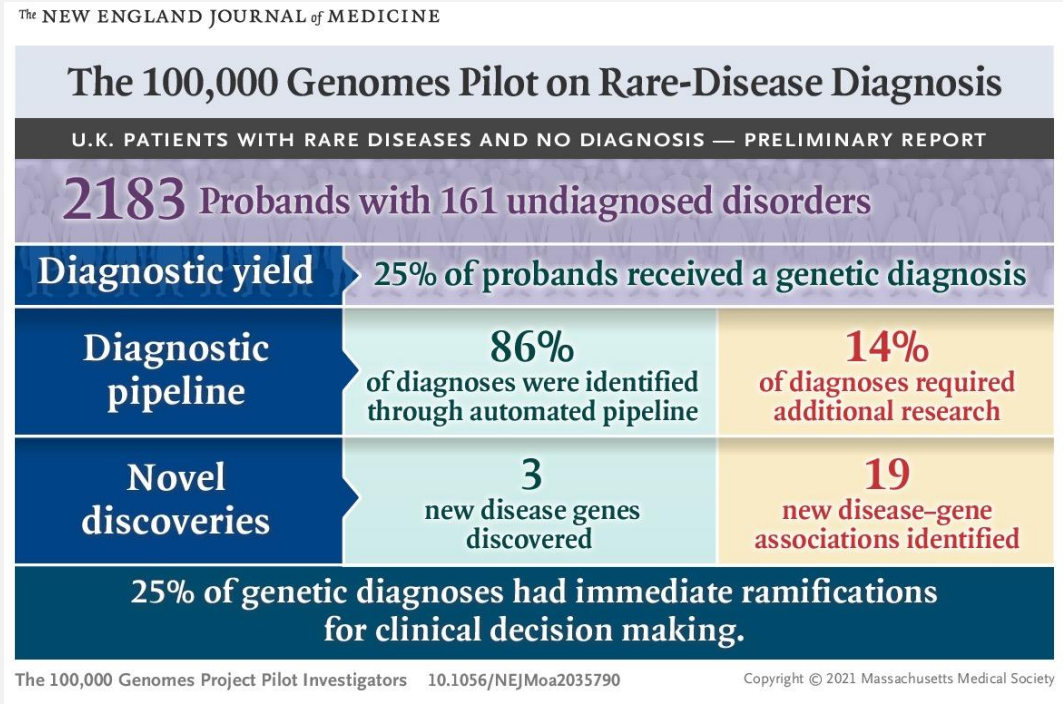
All participants had normal standard of care before entry to the 100K

UK 100K Result - Pilot Study

Congenica are Co-authors

St George's University Hospitals NHS Foundation Trust

Genomics england



The 100,000 Genomes Project Pilot Investigators. Impact of the 100,000 Genomes Pilot on Rare Disease Diagnosis in Health Care – Preliminary Report. N Engl J Med 2021;385:1868-80.

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UK 100K Results

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- WGS for **13,037** participants
- **4 novel non-coding** variants that cause disease through the disruption of transcription of ***ARPC1B, GATA1, LRBA,MPL***
- Study demonstrates a synergy by using **WGS** for diagnosis and aetiological discovery **in routine healthcare**
- The exploration of **regulatory variation** is a promising focus for future research and clinical intervention

Turro, E., Astle, W.J., Megy, K. et al. Whole-genome sequencing of patients with rare diseases in a national health system. Nature 583, 96–102 (2020).

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UK100K Pilot Publication: Health Outcomes and New Discoveries

Healthcare benefits of genome sequencing

Of the genetic diagnoses made, **25%** had immediate impact on clinical decision making for the patients or their relatives and only 0.2% were described as having no benefit

13 cases
allowing eligibility for clinical trial

4 cases
where a diagnosis led to a suggested change in medication

26 cases
where the diagnosis impacted suggesting additional surveillance for the proband or relatives

59 cases
where diagnosis informed future reproductive choices

32 cases
with other benefits

New Discoveries

Cohort-wide burden testing across 57,000 genomes has to date enabled the discovery of

- **3** new disease genes which were independently confirmed ***UBAP1, FOXJ1*** and ***SORD***
- **22** candidate genes have been identified which likely represent new mendelian disease genes.

https://www.genomicsengland.co.uk/about-genomics-england/participant-stories/

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At the end of the recruitment phase

Improving Health Outcomes

To date:

- Actionable findings have been found for 1 in 4/1 in 5 rare disease patients
- Analysis and reanalysis continues in research mode

Credit: Sample numbers from Professor Sue Hill (CSO NHS England) slide deck

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Improve Diagnostic Yield

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- UK 100K analysis in NHS is focused on tier 1/2 and Exomiser ranked variants
- Remaining rare variants sit in tier 3 or are untiered

Is it possible to improve?

Additional diagnosis in tier 3 or untiered variants?

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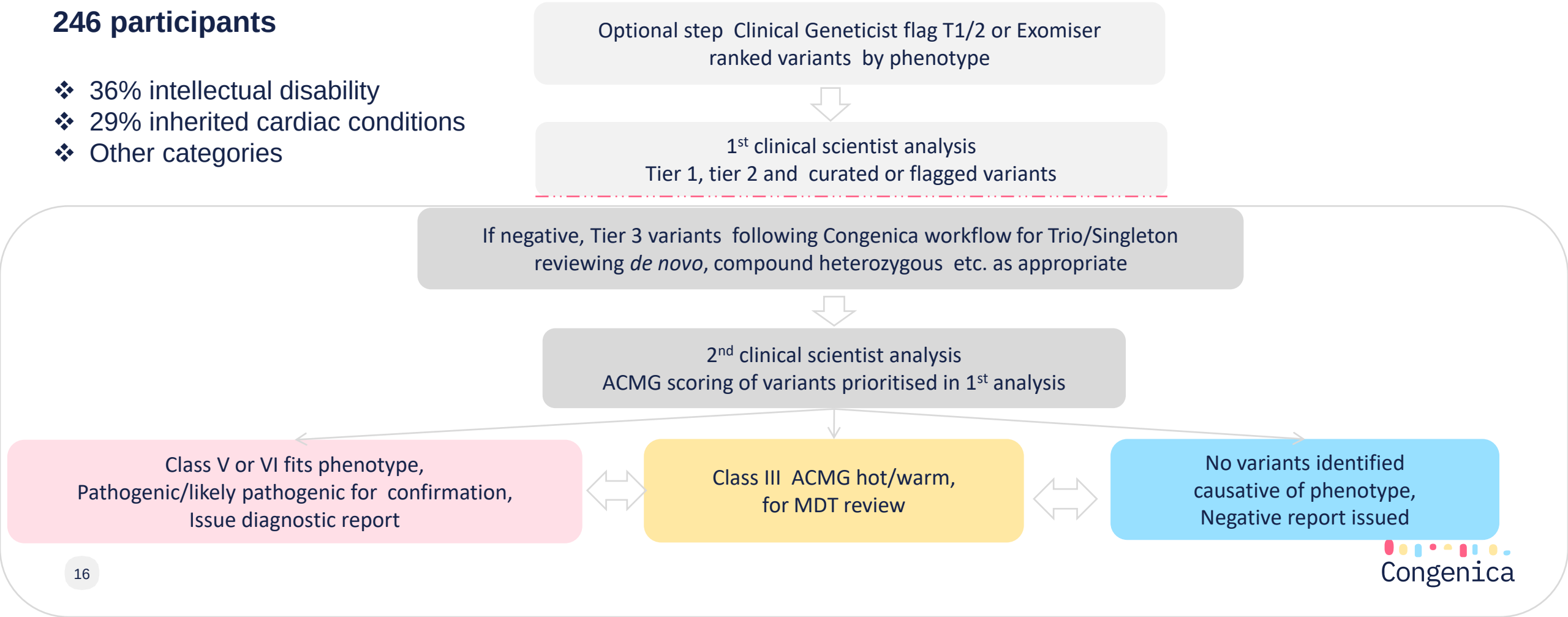
An approach to 100,000 genomes project tier 3 and untiered SNV analysis: An NHS diagnostic lab preliminary

246 participants

- 36% intellectual disability
- 29% inherited cardiac conditions
- Other categories



Tier 3 & Untiered SNVs Analysis Audit

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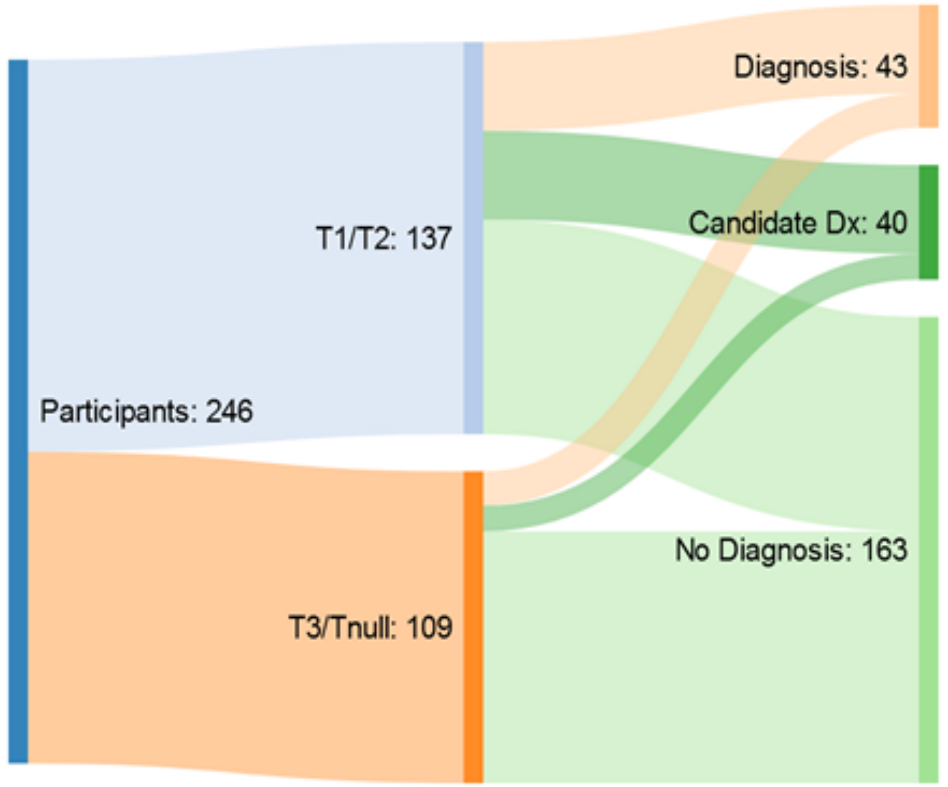
Results

- **33.7%** [(43+40)/246] cases definite or candidate* diagnosis
  - **17.4%**(43/246) definite
  - **16.2%**(40/246) candidate diagnosis
- **8.5%** (21/246) findings outside Tier 1 and Tier 2
- **Exomiser** ranking showed **>80%** correlation with definite and candidate diagnosis irrespective of Tier



Sankeymatic audit results flow diagram

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Analyze and report faster than ever

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Standard workflow

22 hours to complete tertiary analysis & reporting

Average times from 400 whole genome and whole exome samples in Oxford University Hospital [1]

Congenica

30 minutes from data to report

Average times with Congenica from 2,000 whole genome and whole exome samples

20X faster analysis

95% reduction in manual effort

Congenica Express

5 minutes from data to report

Average times with Congenica from 4,000 whole genome and whole exome samples

Fully automated from sequencer to report

1. Schwarze, K. et al,. 2020. Genet Med 22, 85–94

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UK 100K Case Studies: Proving pathogenicity

Further Investigation of 8 patients with VUS variants

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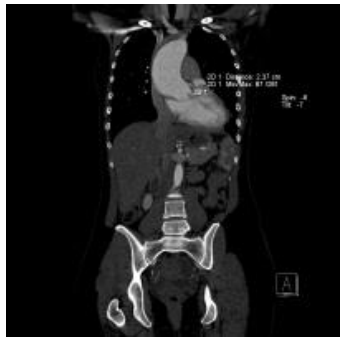
1. Familial thoracic aortopathy

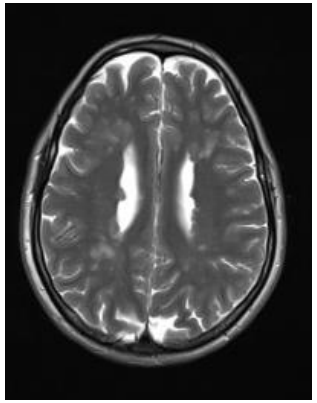


- 19y female
- Ascending aorta replacement
- Joint hypermobility
- No seizures
- Prominent leg veins
- Negative NGS panel

Results

- *FLNA* c.7157-1G>A *de novo*
- Several X-linked disorders
- XLD Periventricular nodular heterotopia associated with arterial aneurysms
- MDT recommendation

- Brain imaging

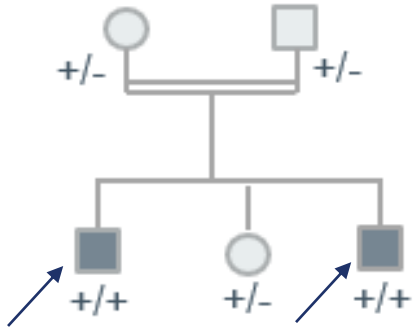


- PVNH confirmed

Outcome Diagnosis:

- ❖ Reproductive options
- ❖ Screening arterial tree

2. Intellectual disability



- 2 affected male sibs
- Global delay , microcephaly
- Hypothyroidism
- Hyperinsulinism
- Neutropenia
- Sensorineural hearing loss
- Ataxia
- Demyelinating neuropathy

Results

- *DNAJC3* c.1367_1370delAGAA; p.(Lys456SerfsTer85) homozygous both brothers
- Ataxia, combined cerebellar and peripheral, with hearing loss and diabetes mellitus
- *DNAJC3*, Arg194Ter single family
- MDT recommendation good phenotype fit

- Segregations studies

- Unaffected sister not homozygous

Outcome Diagnosis:

- ❖ Reproductive options
- ❖ Additional phenotypic features- insulin dysregulation
- ❖ *Published Ocansey S, et al Clin Dysmorphol 2021 PMID:34654017*

Note: all variants were class III (hot/warm) or above

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Proving pathogenicity

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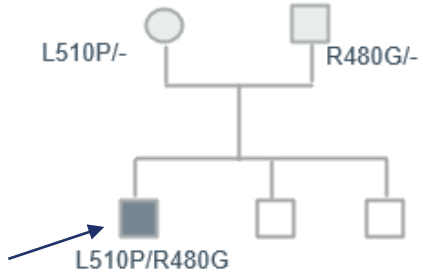
3. Hereditary spastic paraplegia



- Proband 17y onset
- Abnormal gait
- Back pain
- Review 20y
- Hyperflexia
- Ankle clonus
- Negative NGS HSP panel

Results

- *DDHD1* c.1529T>C; p.(Leu510Pro) and c.1438A>G; p.(Arg480Gly) compound het
- SPG 28, autosomal recessive, onset 6-15y
- MDT recommendation good phenotype fit

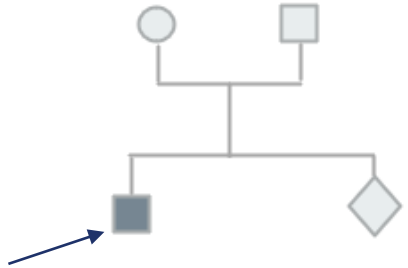
- Segregations studies

- Asymptomatic brothers examined
- One brother hyper-reflexia and sustained ankle clonus

Outcome Diagnosis:

- ❖ Proband and sub-clinically affected brother both cpd het
- ❖ Diagnosis for individual who considered himself to be unaffected

4. Intellectual disability



- First child
- Global delay
- Short stature
- Autistic spectrum
- Mother pregnant
- WES no diagnosis

Results

- *ANKRD17 c.4403T>G; p.(Leu1468Ter) de novo*
- No associated condition
- DDD research track- two *de novo* SNV similar phenotype
- Contacted DDD clinicians- research cohort similar phenotype associated with *de novo* mutation (34 individuals PTV and missense)
- New condition **(skin biopsy research studies)**

Outcome Diagnosis:

- ❖ Likely diagnosis
- ❖ Low recurrence risk
- ❖ *Published Chopra M et al Am J Hum Genet. 2021 Jun 3;108(6):1138-1150*

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Proving pathogenicity

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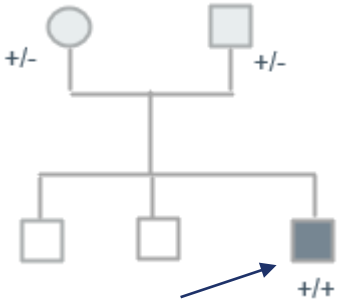
5. Congenital muscular dystrophy



- Third child
- Parents unrelated/ same African ethnic group
- Hypotonia
- Mildly delayed motor milestones
- Creatine kinase - elevated
- Muscle biopsy- dystrophic features

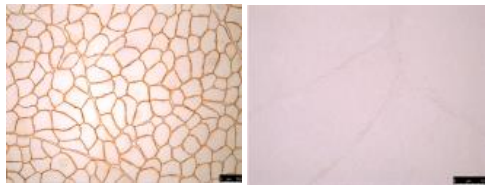
Results

- *CAV3 c.10_17del; p.(Glu4Hisfs*17) homozygous*
- Control 1/4352 African heterozygote
- AD muscle and cardiac phenotypes- rare recessive reports
- MDT recommendation

- CAV3 IHC muscle biopsy

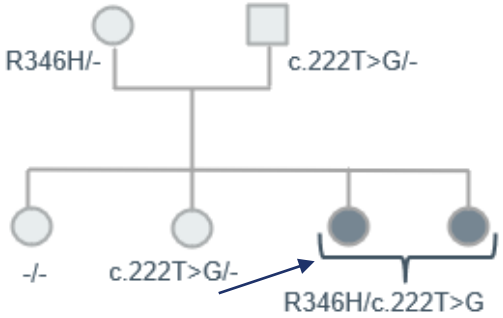
Outcome Diagnosis:

- ❖ Genetic findings -targeted IHC
- ❖ CAV3 absent- diagnosis confirmed



Left: CAV3 IHC positive control above
Right: Patient absence of CAV3 expression

6. Epileptic encephalopathy



- Proband 4m sudden squint
- Global delay
- Seizure disorder
- Non-ambulant
- Younger sib 4 m sudden squint
- Severe seizure disorder

Results

- *ALG11* c.[222G>T];[1037G>A] p.[(Ala74=)];[(Arg346His)]
- Congenital disorder of glycosylation, type Ip
- MDT good phenotype fit BUT
  - Normal transferrin pattern
  - significance synonymous variant (PM2)
  - ?exonic splice enhancer (PP3)

• MDT recommendations

- segregation studies (segregated with disease)

- skin biopsies for fibroblasts – LLO analysis HPLC truncated sugar structure (Man3-Man4-GlcNAc2-PP-Dol),RT-PCR did not resolve role synonymous variant ? Tissue specific ?LD with unidentified variant

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Proving pathogenicity

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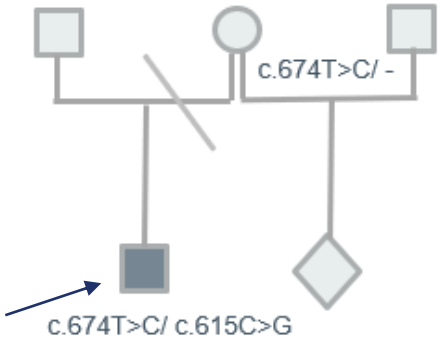
7. Congenital muscular dystrophy



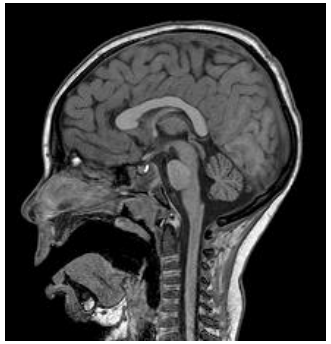
- 3y3m male
- Delayed walking/frequent falls
- Language delay ?dysarthria
- Creatine kinase 1000 I/U per L
- Muscle biopsy dystrophic but non diagnostic
- Duo WGS 100k

Results

- *MSTO1 c.615C>G p.(Phe217Leu) c.674T>C, p.(Leu225Ser)*
- Myopathy, mitochondrial, and ataxia (cerebellar hypoplasia)
- MDT recommendations
  - **MRI brain scan** (cerebellar hypoplasia present)

Outcome Diagnosis:

- ❖ Confirmed diagnosis
- ❖ Low risk to current pregnancy



T1W saggital MRI brain showing mild widening of the cerebellar folia

8. Proteinuric renal disease

- 53y female
- Progressive renal impairment
- Proteinuria and haematuria
- Focal segmental glomerular sclerosis (FSGS)
- Requiring transplant (brother, husband, children work up living donor in progress)
- Maternal hx hematuria in 30s; renal impairment 60s

Results

- *COL4A4 c.1820C>T p.(Ala607Val)*
- Alport syndrome type 2- recessive
  - Benign haematuria dominant
  - New association increased risk FSGS
- **MDT recommendations**
  - **Segregation studies**
  - **Urinalysis and renal profile relatives**

Adult children 29 and 27

Outcome Diagnosis:

- ❖ One child also affected so not suitable for donor selection and referred for renal surveillance

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Perform NGS analysis at scale

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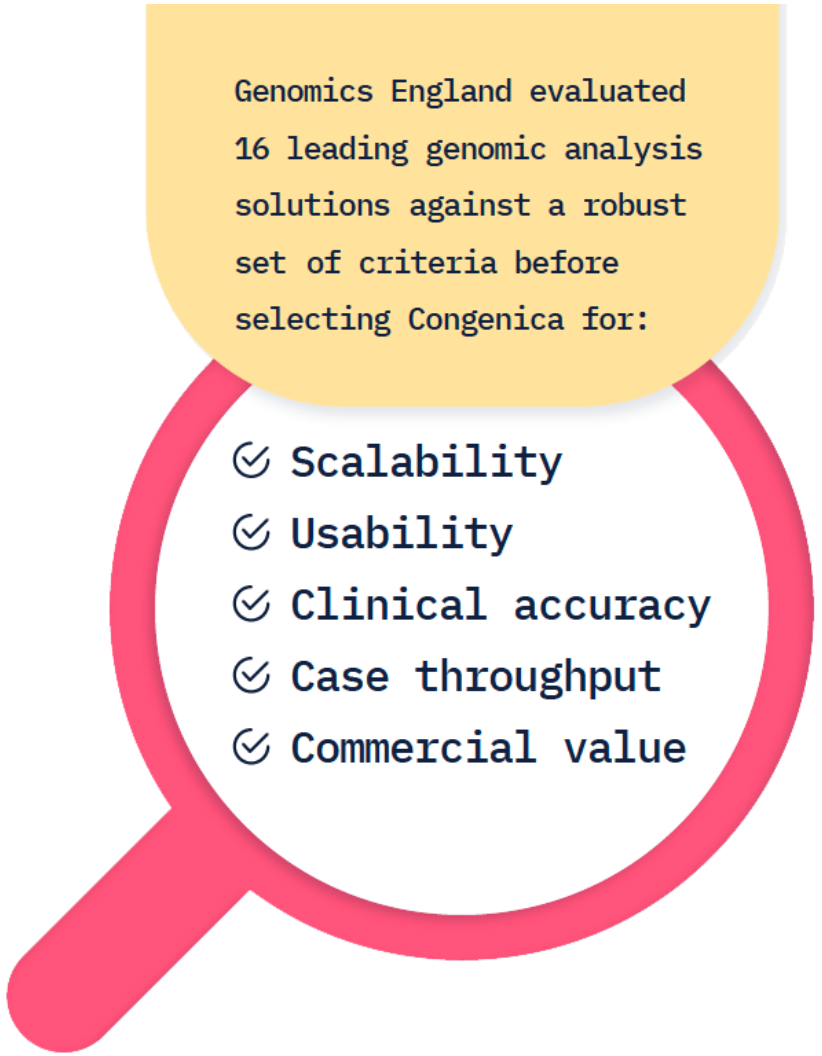
Genomics england

NHS

Genomic analysis for UK National Health Service

Congenica has enabled NHS & Genomics England to achieve:

- 50% increase in diagnostic yield
- 95% reduction in manual data processing
- Scale of >2,500 whole genomes processed per week



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Summary

St George's University Hospitals NHS Foundation Trust

- UK 100K is the first example of WGS integrated into a healthcare system
- WGS improves diagnostic yield, includes non-coding variants
- Further investigation and re-analysis can lead to additional diagnoses
- Access to powerful interpretation platform plays a critical role
- Congenica platform with Exomiser, Congenica Express, Auto-ACMG, and Congenica AI helps scale genome projects

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Enabling genomic medicine

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