1) NEUROPATHOLOGY UPDATE:

2) EQUITY IN GENOMICS:

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Tessa Jowell
BRAIN CANCER MISSION

Neuropath update: Need stakeholder meeting

- In order to be a Tessa Jowell Brain Cancer Centre of Excellence, Neuropath has to hit various metrics of Excellence: Turn Around Times, Research etc , Reapplication Feb 2024

- NBT: Neuropath hit s our targets for **Cancer treatment for brain tumour patients**.
- Initial first working diagnosis between 2-5 days
- Genetics: final integrated diagnosis within 14 days

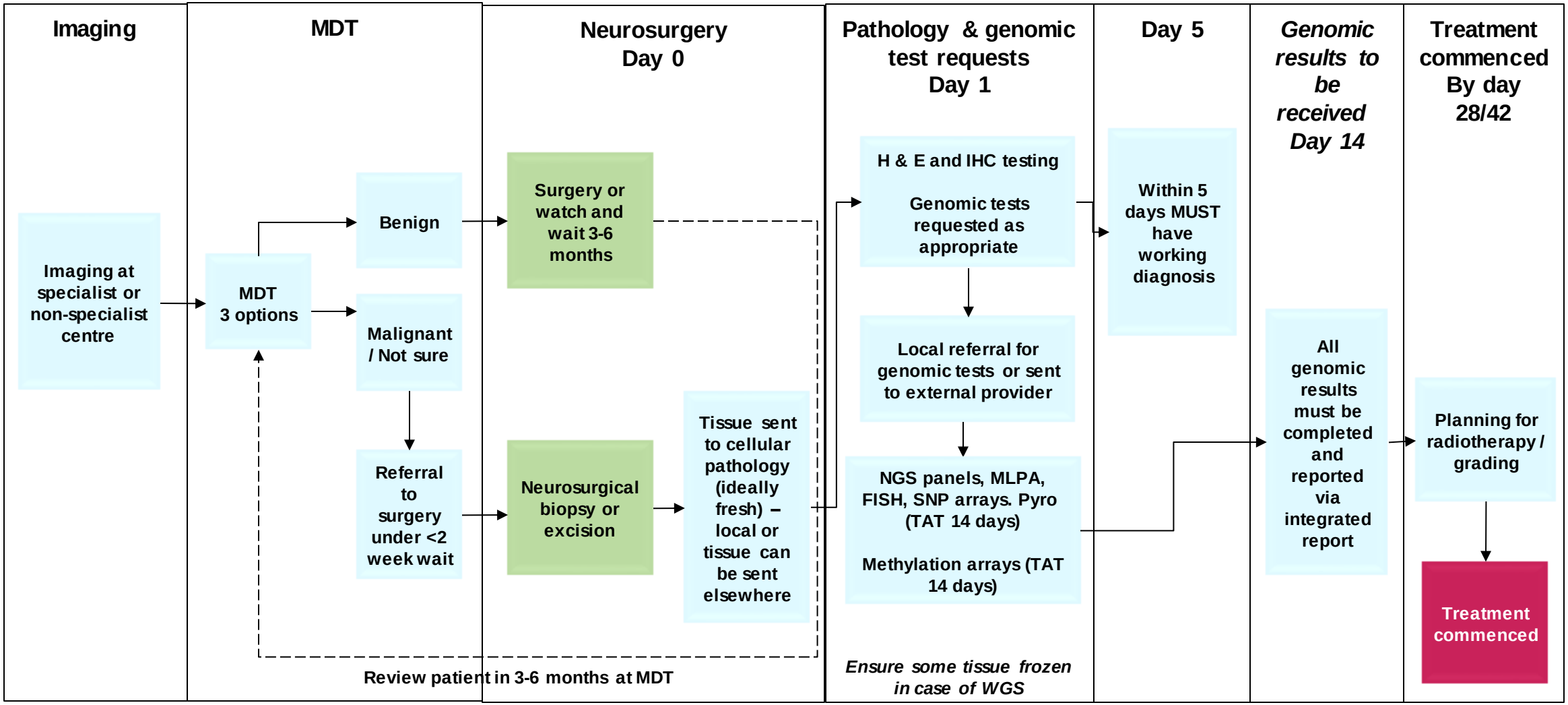
- In Neuropath we hit all (100%) our TATs in all our live patients
- Cell Path currently hit their 43% of the time, referred to NHS England

- Merging/losing our staff to Cell Path having to absorb longer turnaround around times
- Paediatric Pathology- a specialised service similar to us, both consultants resigned

- Roughly speaking Longest wait for urgent report in Cell Path. in month = 42 days** and Longest wait for non-urgent report in month = 71 days***

- Need: Letters of support, and need support in Stakeholder meeting

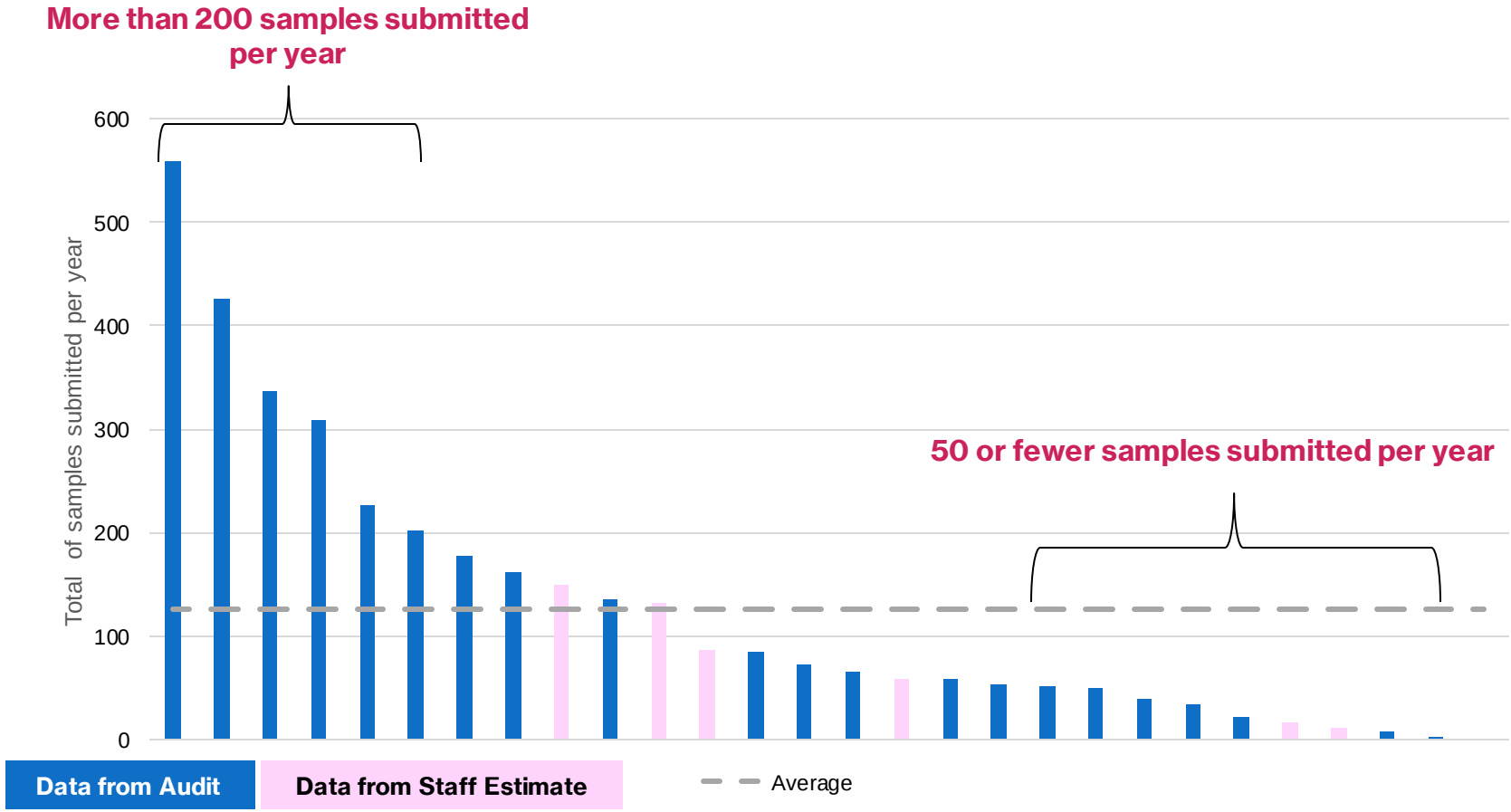
Overview of the diagnostic pathway



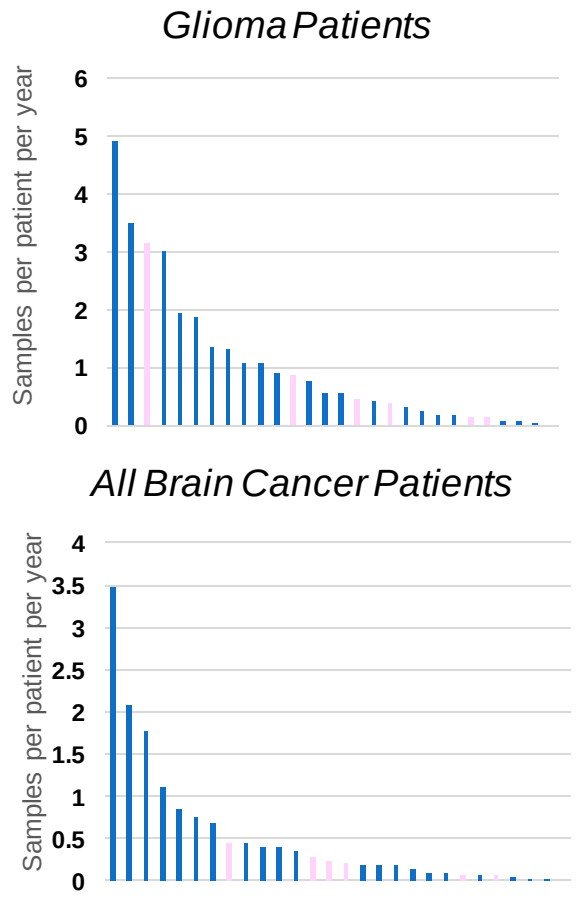
Lack of Equity in Genomics

Findings from the Tessa Jowell Brain Cancer Mission Centre of Excellence programme

Total samples submitted to Gene Panel / Sequencing, Methylation Array, Whole Genome and RNA Sequencing (samples per year)



Samples submitted per patient per year



Please note: Centres not shown in the same order in left- and right-hand graphs; all graphs show centres listed from highest to lowest; "All brain cancer patients" includes glioma, meningioma, skull base and metastases; and presented results are a mixture of audit and estimated results.

Overview of the current test directory for gene panels

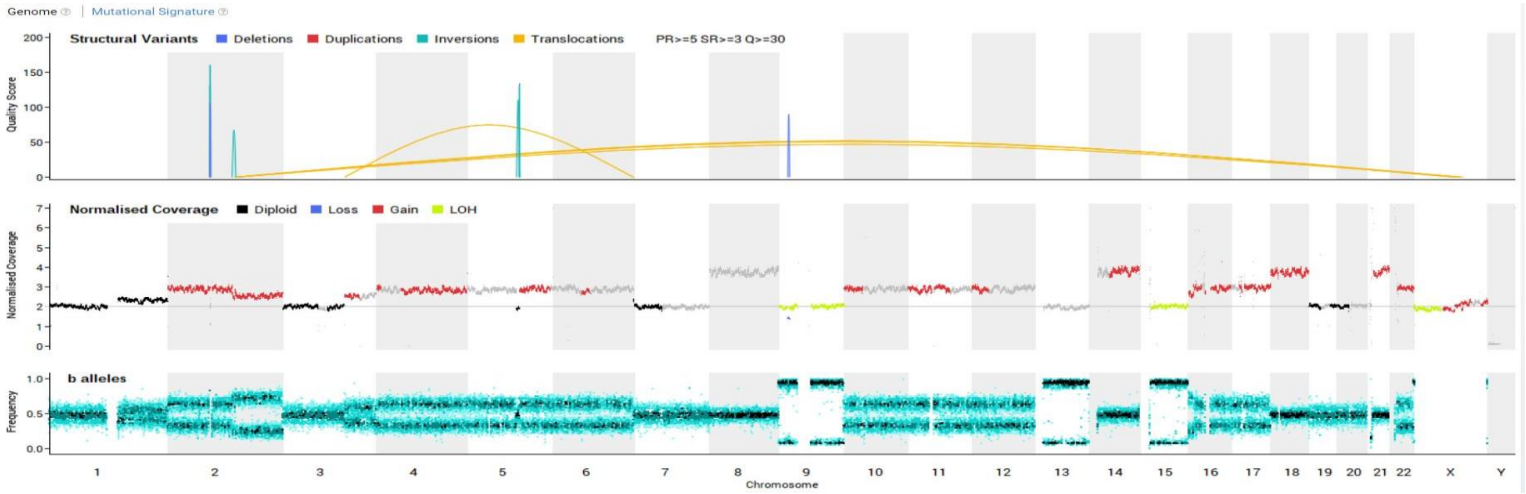
- Gene panels based on National Genomic Test Directory and local Neuropathologist input
- Streamlined TD from ~ 40 different gene panels to 11 relevant DNA panels and 2 relevant RNA fusion panels, with increased content relevant to WHO 2021

Clinical Indication	Test Code	Test Directory Name
Adult Oligodendroglioma	M35.1 ☐	Adult Oligodendroglioma Gene Panel – small variants *(ATRX, BRAF, H3F3A, HIST1H3B, IDH1, IDH2, TERT promoter)*
Adult Astrocytoma	M21.1 ☐	Adult Astrocytoma Gene Panel – *small variants (ATRX, BRAF, CIC, H3F3A, HIST1H3B, IDH1, IDH2, MYB, NF1, NOTCH1, PDGFRA, PIK3CA, PTEN, SMARCA4, TP53, TERT promoter)*
Adult High Grade Glioma	M192.1 ☐	Adult High Grade Glioma Panel – small variants *(IDH1, IDH2, ATRX, BRAF, CDKN2B, CIC, FGFR1, FGFR2, FGFR3, H3F3A, H3F3B, H3F3C, HIST1H3B, HIST1H3C, HIST2H3C, HRAS, KRAS, NRAS, MDM2, MDM4, NF1, PDGFRA, PIK3CA, PTEN, RB1, SETD2, TERT promoter, TP53, VHL)*
Meningiomas	M33.3 ☐	Meningioma Gene Panel – small variants *(BAP1, KLF4, NF1, NF2, TERT, TRAF7)*
Embryonal Tumours	M194.1 ☐	Embryonal Tumours Gene Panel – small variants *(ALK, BCOR, CTNNB1, DICER1, EZH2, MYCN, NOTCH1, PIK3CA, PTCH1, PTEN, SMARCA4, SMARCB1, SMO, SUFU, TERT promoter, TP53, YAP1)*
Glioneuronal Tumours/LEATs	M32.1 ☐	Low Grade Glioma/Glioneuronal Gene Panel – small variants *(AKT1, AKT2, AKT3, BRAF, EGFR, H3F3A, HIST1H3B, FGFR1, FGFR2, FGFR3, IDH1, IDH2, NF1, NOTCH1, NOTCH2, NOTCH3, NOTCH4, NRAS, PDGFRA, PIK3CA, PTEN, RAF1, TERT promoter, TGFBR1, TGFBR2, TSC1, TSC2)*
Paediatric Diffuse Low Grade Glioma	M213.1 ☐	Paediatric Diffuse Low Grade Glioma Gene Panel – small variants *(ALK, ATRX, BRAF, CDKN2A, CTNNB1, FGFR1, FGFR2, FGFR3, FGFR4, HIST1H3B, H3F3A, H3F3B, H3F3C, KIT, MYB, NRAS, PDGFRA, PHOX2B, PIK3CA, RAF1, SMARCA4, SMARCB1, TP53)*
Paediatric Circumscribed Low Grade Glioma	M36.12 ☐	Pilocytic Astrocytoma Gene Panel – small variants *(BRAF, CDKN2A, FGFR1, FGFR2, FGFR3, NF1, RAF1)*
	M36.14 ☐	RNA fusion panel (*BRAF* fusions, *NTRK* fusions)
Paediatric High Grade Glioma	M184.1 ☐	Paediatric High Grade Glioma Gene Panel – small variants *(ATRX, BRAF, FGFR1, FGFR2, FGFR3, H3F3A, H3F3B, H3F3C, HIST1H3B, HIST1H3C, HIST2H3C, IDH1, IDH2, NF1, TP53, VHL)*
	M184.8 ☐	RNA fusion panel (*BRAF, NTRK, ALK, ROS, RET* fusions)
Paediatric Midline Diffuse Glioma	M183.1 ☐	Paediatric Midline Diffuse Glioma Gene Panel – small variants *(ACVR1, ATRX, BRAF, CDK4, CDK6, EGFR, FGFR1, H3F3A, HIST1H3C, HIST1H3B, PDGFRA, PIK3CA, PPM1D, PTEN, TP53, NF1, TERT promoter)*
Infantile Hemispheric Glioma	M184.8 ☐	RNA fusion panel (*BRAF, NTRK, ALK, ROS, RET* fusions)
Pineoblastoma	M37.1 ☐	Pineoblastoma Gene Panel – small variants *(DICER1, MYC)*

https://www.england.nhs.uk/publication/national-genomic-test-directories/

WGS provides an integrated analysis for all types of variants:

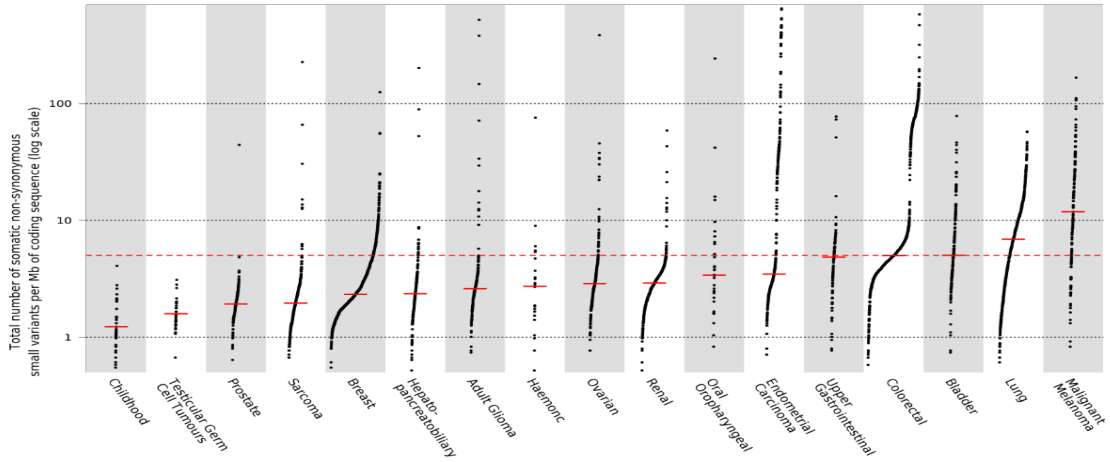
- SNVs/Indels
- Copy Number
- Loss of heterozygosity
- Structural e.g. *PDGFR, NTRK*
- Germline (pertinent)
- Pharmacogenomics (Currently only *DPYD,* but potentially *TPMT, NUDT15 etc.*)
- **Cannot detect epigenetic or methylation changes currently-** awaiting Oxford Nanopore Technology



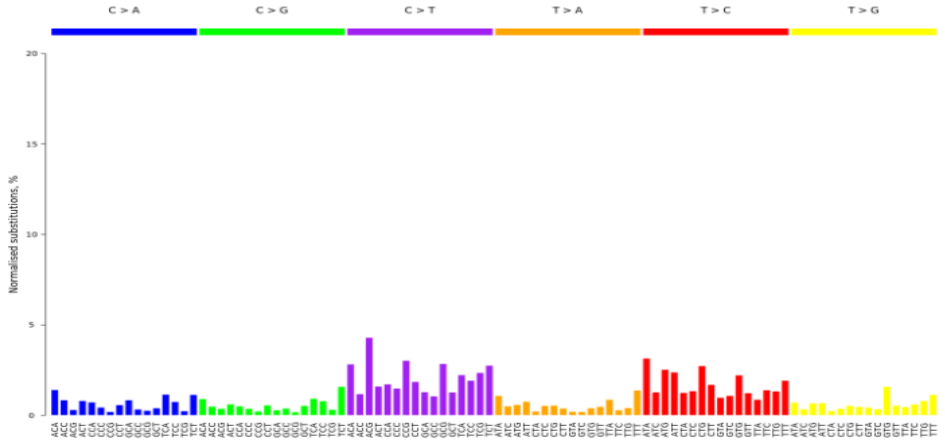
WGS provides analysis methods not currently embedded in clinical practice but may have future clinical utility

Currently less than 10% actionable mutations

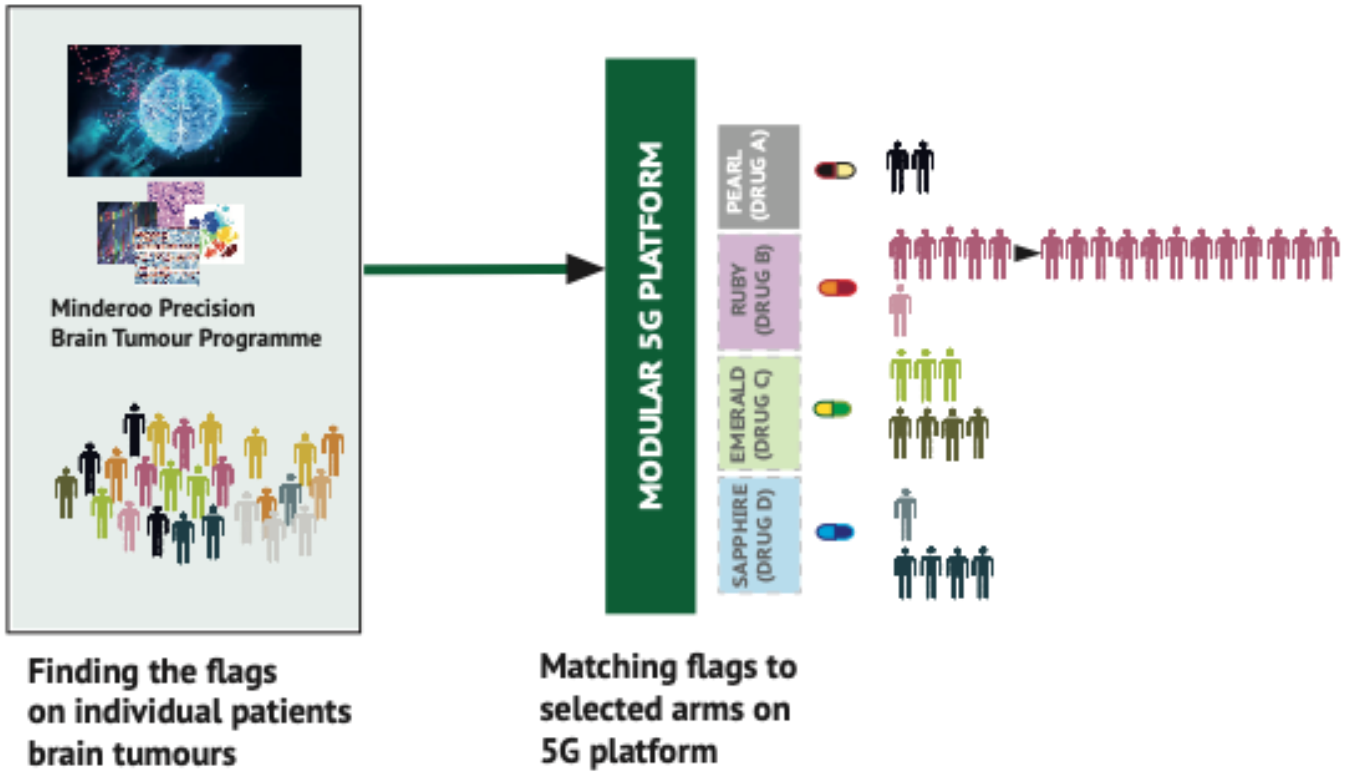
Tumour Mutational Burden (TMB)



Mutational Signatures



in partnership with



- 5G-PEARL : targeting PI3K pathway
- PI3K pathogenic mutation (30%)
- PTEN loss (55%)

5G-RUBY : targeting MAPK

- BRAF mutations/fusion (<5%)
- NF1 loss (20%)

5G-EMERALD : targeting EGFR

- EGFR amplification (40%)

New flags and new arms will be added as we learn more about what drives brain tumours

2024 – first 3 subprotocols

How do new techniques translate to clinical care?

Routine: Timely for Diagnosis, Prognosis, Prediction

WGS (Oxford Nanopore Technology): **Education, research,** trials, drugs

Professor Kathreena Kurian
– **Prof** of Neuropathology, University of Bristol, UK

No conflcts of Interests:
Employment, Grants, Honoraria, Stocks, Partner, Other

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