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Genomic Medicine Service

NORTH THAMES GENOMICS SHOWCASE

19 MARCH 2025

Welcome to our event!

**For those attending on Zoom,
please submit questions via the Q&A Box**

9:30 - Welcome

9:45 – The journey of a genetic sample: Request to result

Follow the genomic testing pathway for prostate cancer patients all the way from early conversations with families to the support they receive along the way.

11:00 – Coffee break

11:30 – ‘What I want my healthcare professionals to know about genomics’

Join us for a roundtable discussion with patients, families and carers about how we as healthcare professionals can support them through a genetic testing journey.

13:00 – Lunch and networking

14:00 – Equity: Meeting real world needs

Hear from the North Thames Genomic Medicine Service team about how we are centring equity in all that we do, from targeted projects, creating an equitable workforce and our organisational strategy.

15:30 – Coffee break

16:00 – Highly specialised testing: Now and the future

This session will focus on how highly specialised laboratories in the North Thames region are improving patient lives.

16:45 – Closing remarks

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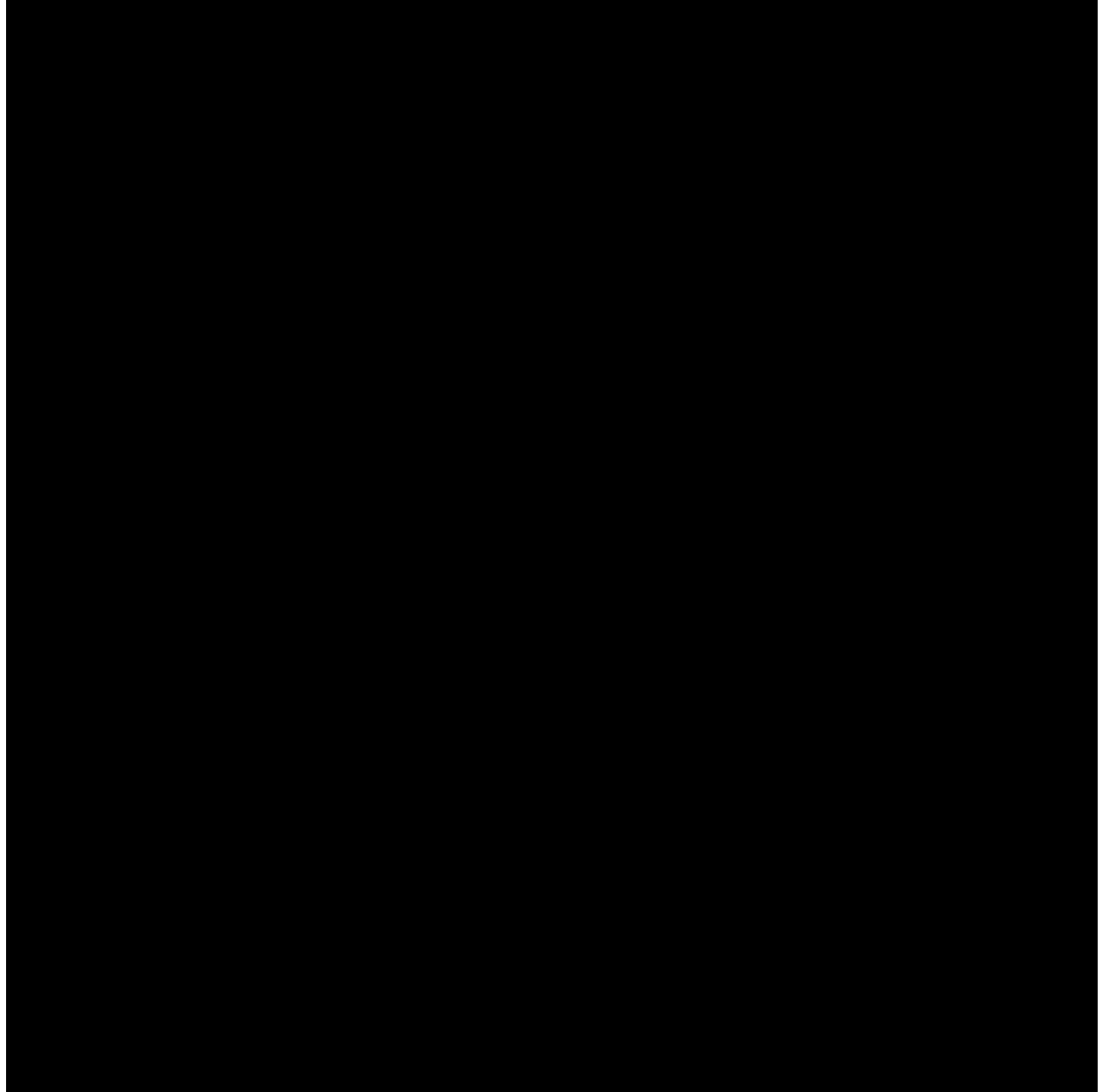
A year in the North Thames Genomic Medicine Service

Anthony Sullivan – North Thames GLH COO



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An expert in liquid biopsy delivery

Lung cancer ctDNA pilot

- Phase 1: GMSAs partnered with commercial provider to deliver testing across 40 trusts
- Phase 2: Technology transferred to Royal Marsden NHS lab to deliver testing across 80 trusts
- Phase 3: NT and NW GLH's commissioned to deliver 10,000 tests to patients across England
- Phase 4: To be commissioned test on the test directory starting from the 1st April 2025!

An expert in liquid biopsy delivery

Lung cancer ctDNA pilot - outcomes

- Liquid biopsy tests results returned *2 weeks faster* than tissue biopsy
  - ➢Translates to faster access to targeted treatment

- Laboratory: Successful transfer of commercial test to NHS lab setting

- Economic savings: estimated to save the NHS £11 million / year (net)

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An expert in liquid biopsy delivery

Liquid Biopsy network of excellence

- Network was stood up in 2024 to provide an evidence-driven framework to expedite the evaluation and introduction of ctDNA and other liquid biopsy tests into clinical diagnostic service in England

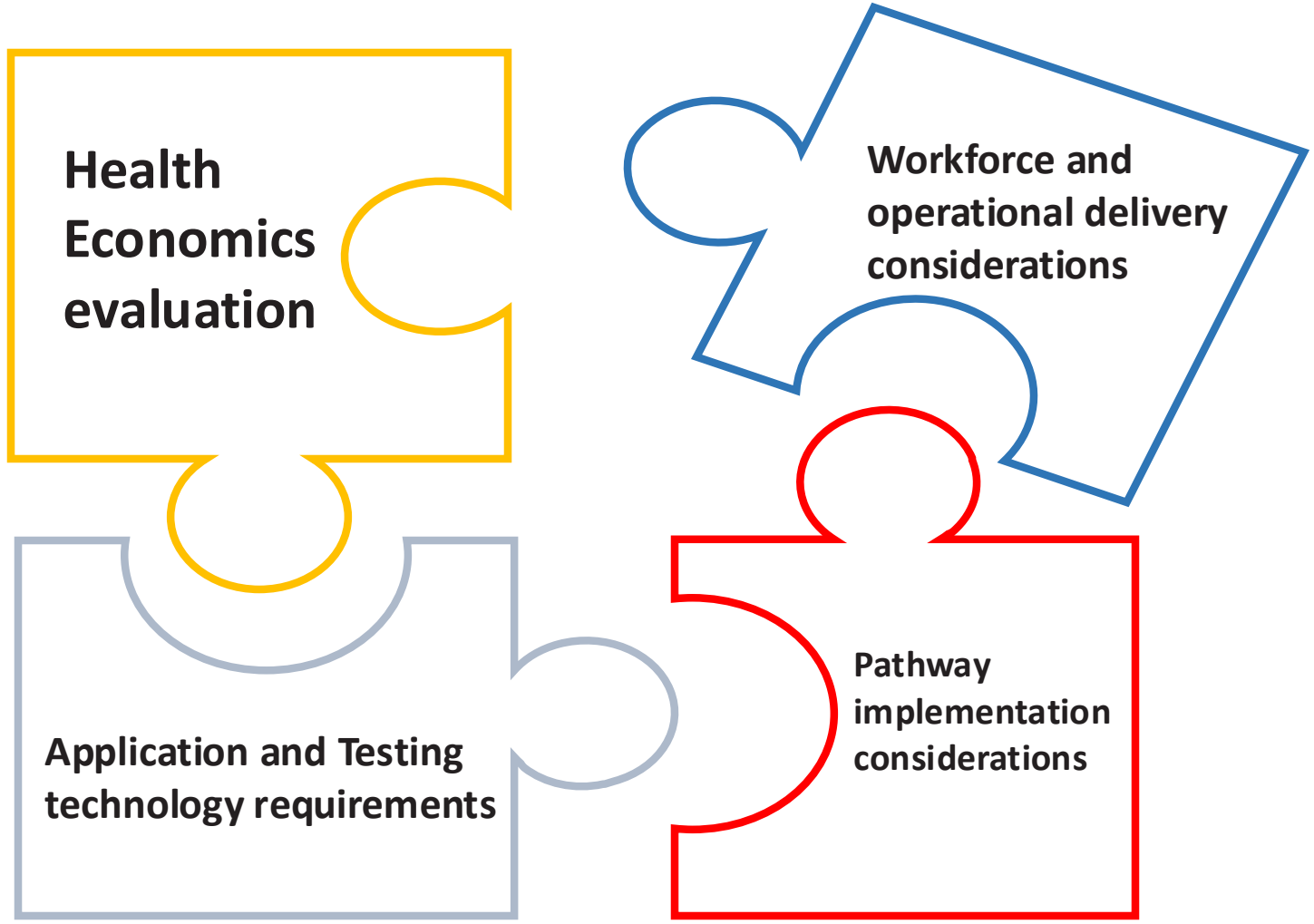
- The framework assembles a collection of key assessment reports for each clinical use pathway to be packaged as an overall evaluation report

- The overall framework for each clinical use case will be presented to the Genomics Unit at NHSE to consider as guidance for decision making purposes on the clinical pathway's suitability for commissioning on the national test directory

- The network is working with NICE, industry partners, academia and NHSE to enhance engagement and partnership working to horizon scan for future drugs linked to liquid biopsy indications and align processes for Test Directory applications

Key Assessments of the network

NHS North West Genomic Medicine Service Alliance



Patient and Public input into all assessments

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Launch of national ESR1 testing

Breast ESR1 testing was a clinical use case being assessed in the network of excellence

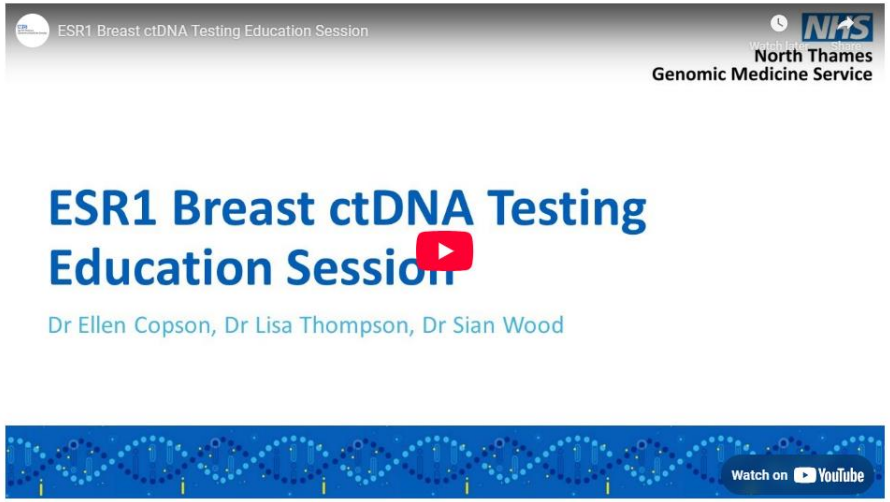
In December 2024 NICE published its recommendations for the use of elacestrant, a drug used in the treatment of breast cancer.

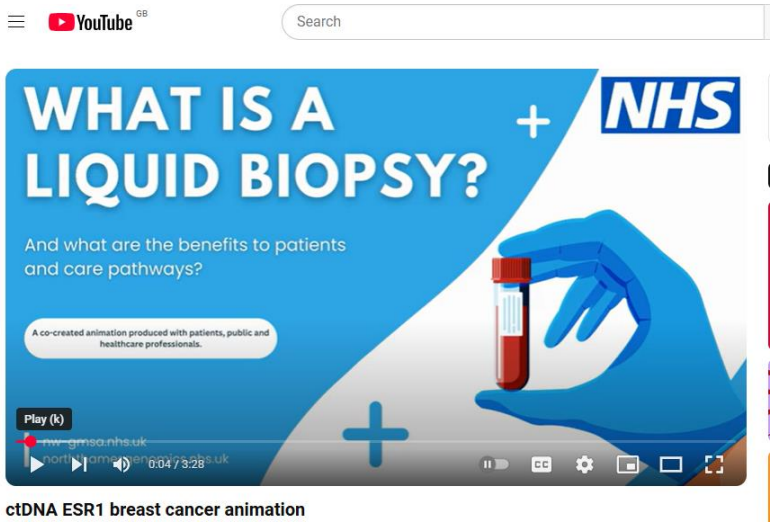
The license for elacestrant requires identification of ESR1 variants from plasma only.

Testing for ESR1 variants in breast cancer requires the genomic test to be performed on circulating tumour DNA (ctDNA) taken from a blood sample rather than tissue.

In January alongside the NW GLH, the NT GLH stood up a service to deliver national ctDNA testing for ESR1.

In less than 4 weeks NT and NW GLH's started testing, delivered education sessions and has since created patient information leaflets and videos.





ctDNA ESR1 breast cancer animation

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The Generation Study

A national research study

The Generation Study, led by Genomics England in partnership with NHS England, will offer whole genome sequencing for newborn babies.

The sequencing identifies 200+ treatable, rare conditions shortly after a baby is born rather than when symptoms might appear later in childhood.

In numbers (as of 27 Feb):

- **27** sites live across **18** NHS Trusts
- **5,814** parents enrolled
- **3,842** samples taken (89% cord blood)
- **3,102** cases sequenced and through our pipeline

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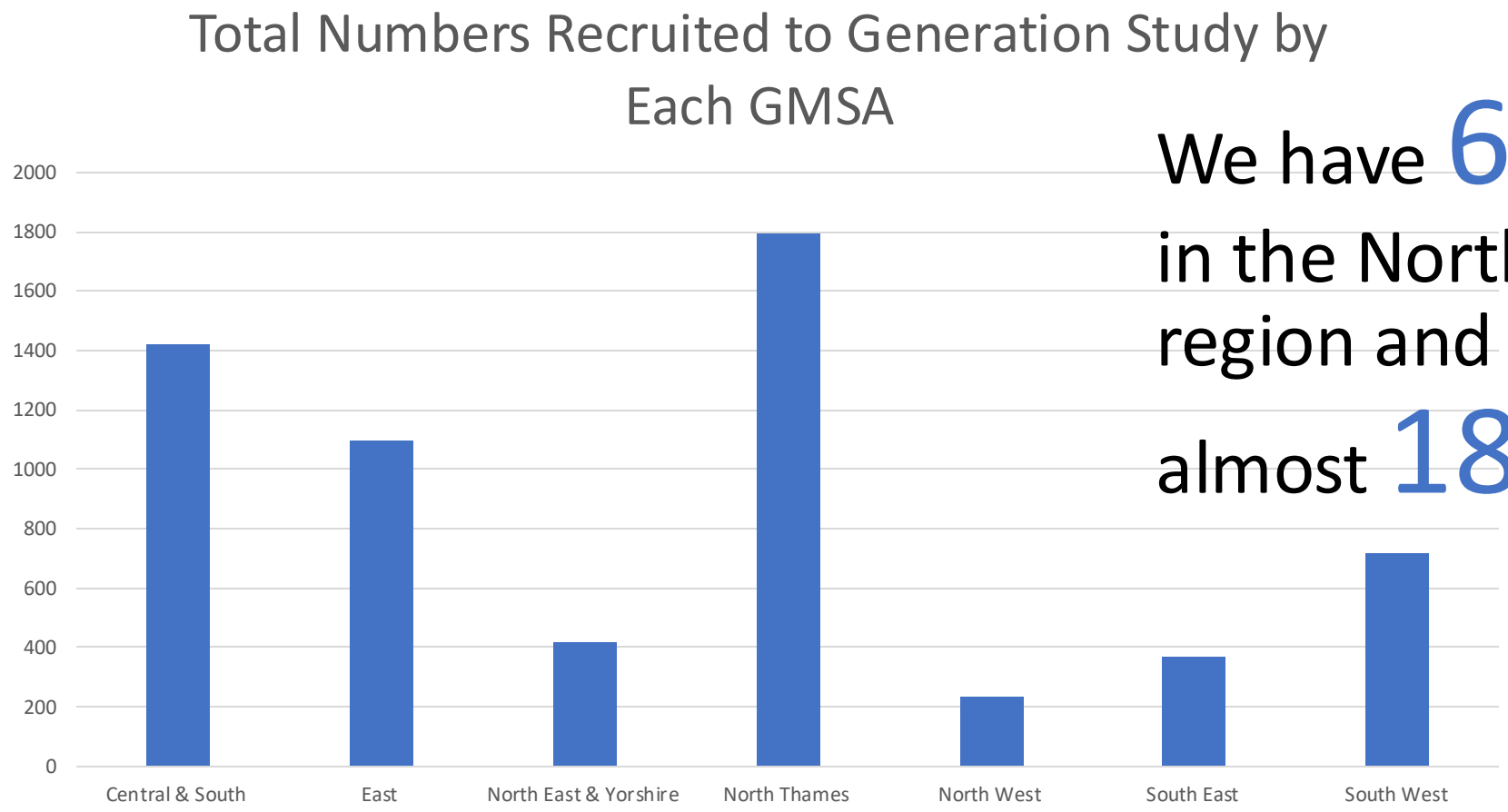
The Generation Study

The North Thames picture



We have 6 recruiting sites in the North Thames region and have recruited almost 1800 families!

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Moving towards automated labs

In 2024 our Royal Marsden laboratory became the first lab in the UK to integrate robotic technology into its cancer genomic testing pipeline, in partnership with Automata Technologies.

The team estimate that the installation will double the laboratory's genomics testing capacity and expand the range of tests it can perform within its existing laboratory space.

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Our digital journey

National Order Comms project – Alpha Phase

A national project to take the genomic test directory digital. Our NT GMS team are taking part in the Alpha Phase, a proof-of-concept testing phase.

Our bioinformatics cloud project

Working with IT teams, Bioinformaticians and Industry Partners to understand how we can move our bioinformatics pipelines onto cloud services.

Admin automation

Our Informatics team are working closely with the Rare & Inherited Disease admin teams to understand how we can use digital solutions to streamline labour intensive parts of the administrative processes.

9:45 – The journey of a genetic sample: Request to result

Session leads – Dr Angela Brady, Consultant Clinical Geneticist, and Liz Bancroft, Chief Nurse

The role of CPGCs – Dr Madhuri Warren, CPGC Pathology Lead – Barts Health NHS Trust

Our Genomic Laboratory Hub teams – Beth Kimpton, NT GLH General Manager

????? GENETIC COUNSELLORS

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Prostate Cancer Genomic Testing: The Testing Journey

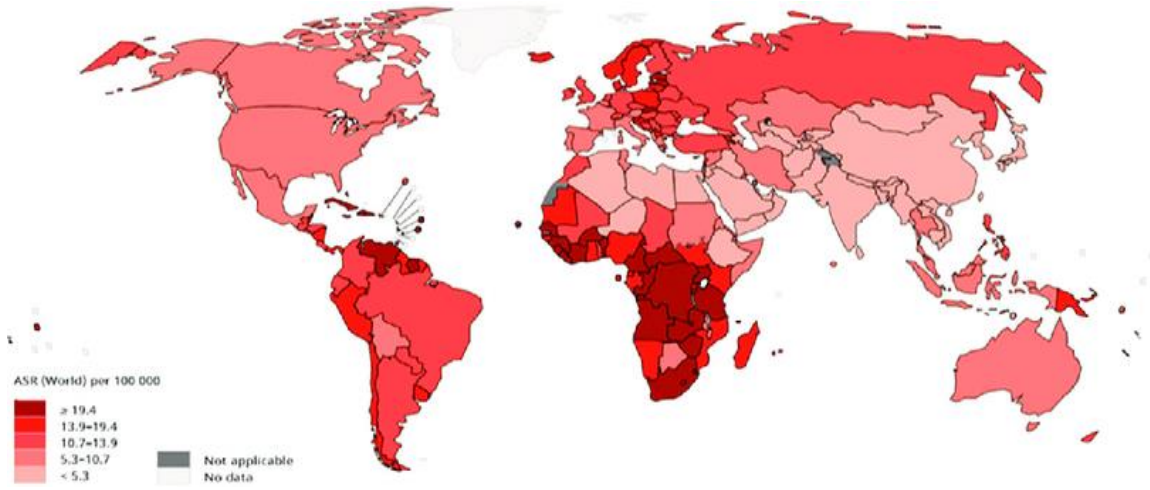
Overview

1. Introduction to prostate cancer testing – Liz Bancroft
2. Test requesting - mainstream pathway - Liz Bancroft
3. Test requesting family history pathway - Angela Brady
4. Role of CPGCs – Madhuri Warren
5. Our GLH team – Beth Kimpton
6. Patient discussion – video from Eddie Blair
7. Role of genetic counsellors – Ailidh Watson
8. Education and training – Liz Bancroft & Angela Brady

Background

Most common cancer in people assigned male at birth in the UK

- Affects 1 in 8 men in the UK by age 80
- >50,000 new cases per year
- >12,000 deaths per year



Deaths from prostate cancer

Risk Factors

Age

Ancestry - highest risk in Black African/Caribbean

- 1 in 4 risk of PrCa
- 2x risk of death from PCa
- More likely to present at a young age

Family history

- Risk increases with **closeness** and **number** of affected relatives

Genetic basis of prostate cancer

- Most cancers are caused by somatic variants acquired during our lifetime.
- ~5-10% are caused by germline variants in rare cancer susceptibility genes

- Prostate cancer is the most heritable cancer
- ~ 60% of prostate cancer is thought to have an inherited component

Established germline genetic factors

- Rare genetic variants
  (eg *BRCA1, BRCA2, Mis-Match Repair genes* and other DNA repair genes)
- Common genetic variants (polygenic risk score)

Genetic predisposition to prostate cancer - rare variants

***BRCA2*:** Prostate cancer risk 4-5 times general population

- Absolute risk is ~**50-60%** by age 85
- Found in ~5% of men with metastatic (advanced) PrCa
- *BRCA2* carriers are diagnosed younger, higher grade disease, significantly worse survival

BRCA1: Prostate cancer risk 2-3 times general population

- Absolute risk is ~**30%** by age 85

Mis-Match Repair genes: *MSH2, MSH6, MLH1*

- **Lynch syndrome** - bowel, endometrial and ovarian cancer
- Evidence of increased PrCa risk (**up to 3-5** times) ~30-35% by age 85
- Reports of predisposition to young onset, more aggressive disease

BRCA1 and *BRCA2*

DNA Repair: *BRCA1/2* genes help protect against cancer by repairing DNA damage.

Prevalence: ~1 in 400 people (0.5%) carry a *BRCA1/2* variant, with higher rates in certain groups (e.g., Ashkenazi Jewish ancestry, Whalsay in Shetland – 1 in 40).

Inheritance: Carriers have a **50% chance** of passing the variant to their children.

Family Testing: At-risk relatives can undergo **predictive testing**.

Impact on prostate cancer management:
For people with metastatic prostate cancer who have either a germline or somatic *BRCA1* or *BRCA2* variant can be treated with PARP inhibitors (e.g., Olaparib).

How does genetic information help with managing prostate cancer / risk

Currently no prostate cancer general population screening programme

PSA screening debate

- What is a ‘normal’ PSA?
- What screening interval?
- Optimal imaging?
- When to biopsy?

Overdiagnosis / overtreatment

Screening high-risk individuals

- Benefit outweigh potential harms?
- Research ongoing internationally

	General Population screening	Screening in men with a Family History	Screening in Black men	Screening in *BRCA2* carriers
American Urological Association	No	Yes from 40 years	Yes from 40 years	Not specified
American Cancer Society	No	Yes from 40-45 years	Yes from 40-45 years	Not specified
European Association of Urology	No	Yes from 45 years	Yes from 45 years	Yes from 40 years
NICE UK	No	Not specified	Not specified	Not specified

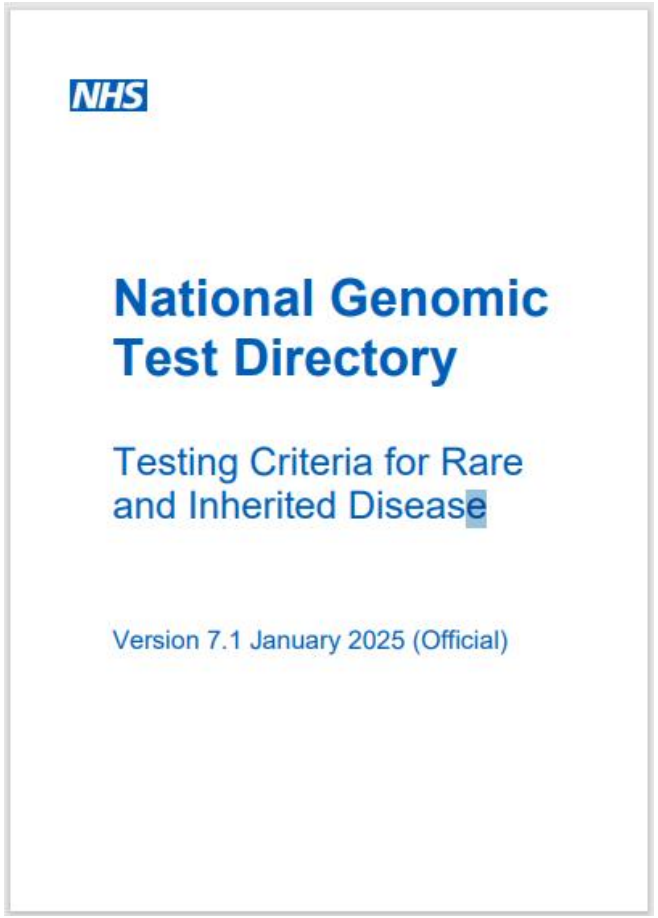
How does genetic information help with managing prostate cancer / risk

- Identifying people with increased cancer susceptibility is important because it offers opportunities for intervention
- For the prostate cancer patient:
  - Precision medicine - targeted treatments

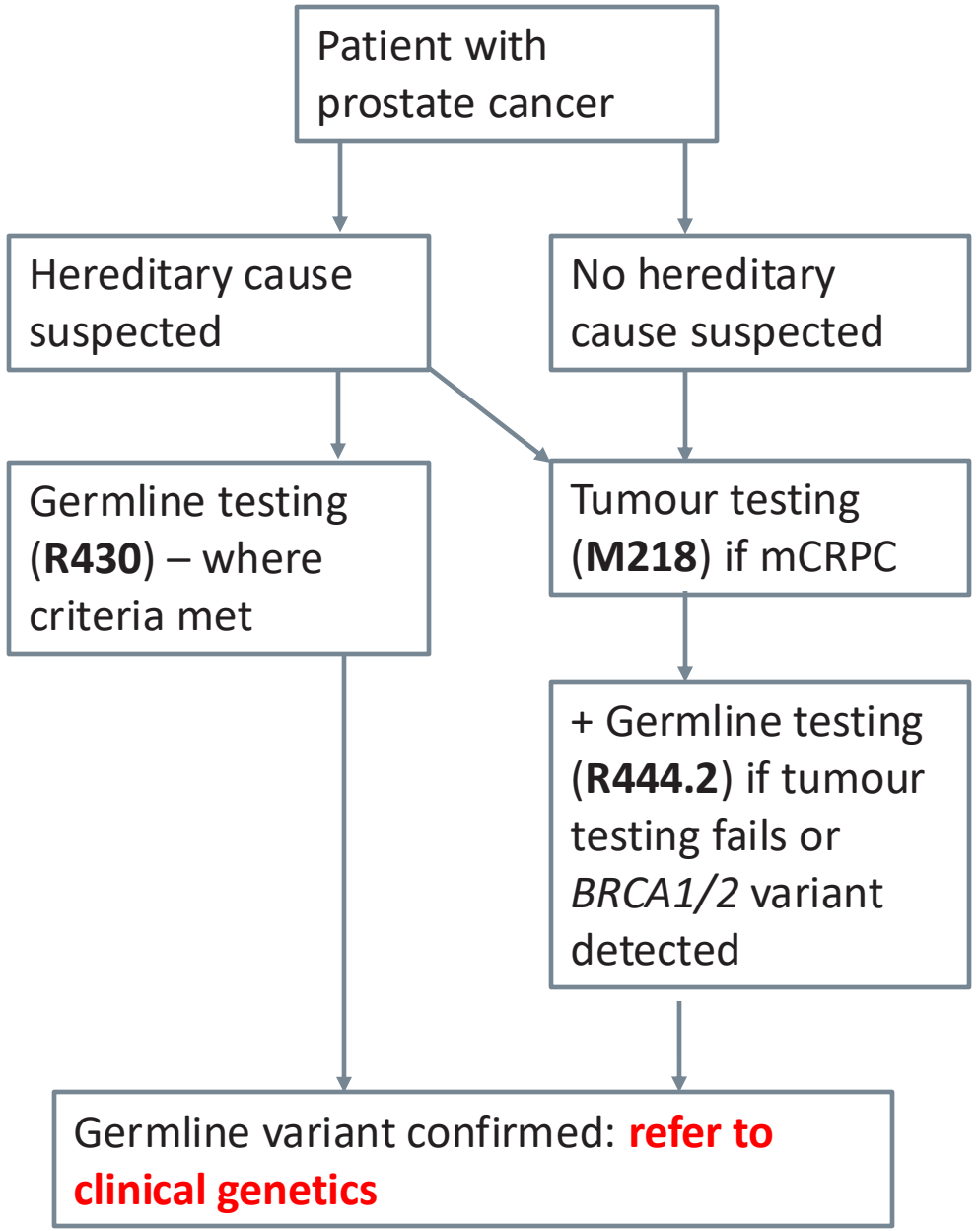
- For their family members:
  - Risk-reducing surgery (eg risk-reducing mastectomy / oophorectomy for female BRCA1/2 carriers
  - Chemoprevention (e.g. aspirin (Lynch Syndrome), tamoxifen (*BRCA1/2*)
  - Intensive surveillance for cancers (eg breast cancer (*BRCA1/2*), colorectal cancer screening (Lynch Syndrome)
  - Modification of lifestyle/non-genetic factors (eg smoking, diet, alcohol intake, exercise)

- **Important for all clinical staff to take a family history and consider whether the pattern of cancer in that family suggests underlying genetic susceptibility and refer for genetic testing where appropriate**

National Genomic Test Directory



https://www.england.nhs.uk/wp-content/uploads/2025/01/rare-and-inherited-disease-eligibility-criteria-V7.1-OFFICIAL-2.pdf



Mainstream Pathway

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NICE approved PARP inhibitor treatment

June 2023: The R444.2 germline test and M218 somatic (tumour) test were introduced for people with metastatic castration resistant prostate cancer (mCRPC) to screen for pathogenic *BRCA1* or *BRCA2* variants to identify those eligible for treatment with PARP inhibitors (e.g. Olaparib).

Olaparib Eligibility Criteria – NICE approved May 2023

Confirmed somatic and/or germline *BRCA1* or *BRCA2* variant.

Hormone-relapsed metastatic prostate cancer (previous ARTA treatment).

Performance status 0-2

R444 NICE approved PARP inhibitor treatment

Testing Criteria

Testing Criteria only applies to patients not meeting R208/R430 criteria AND with current cancer diagnosis for treatment decisions.

R444.2 Prostate Cancer

Metastatic, castration-resistant prostate cancer where somatic tumour testing (M218.1) has failed.

Overlapping indications

- R208 Inherited breast cancer and ovarian cancer
- R430 Inherited prostate cancer
- M3 breast cancer should be used for somatic testing
- M218 prostate cancer should be used for somatic testing

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

At earliest stage, either at primary surgery or after neo-adjuvant chemotherapy

Requesting Specialties

- Clinical Genetics
- Surgery
- Oncology

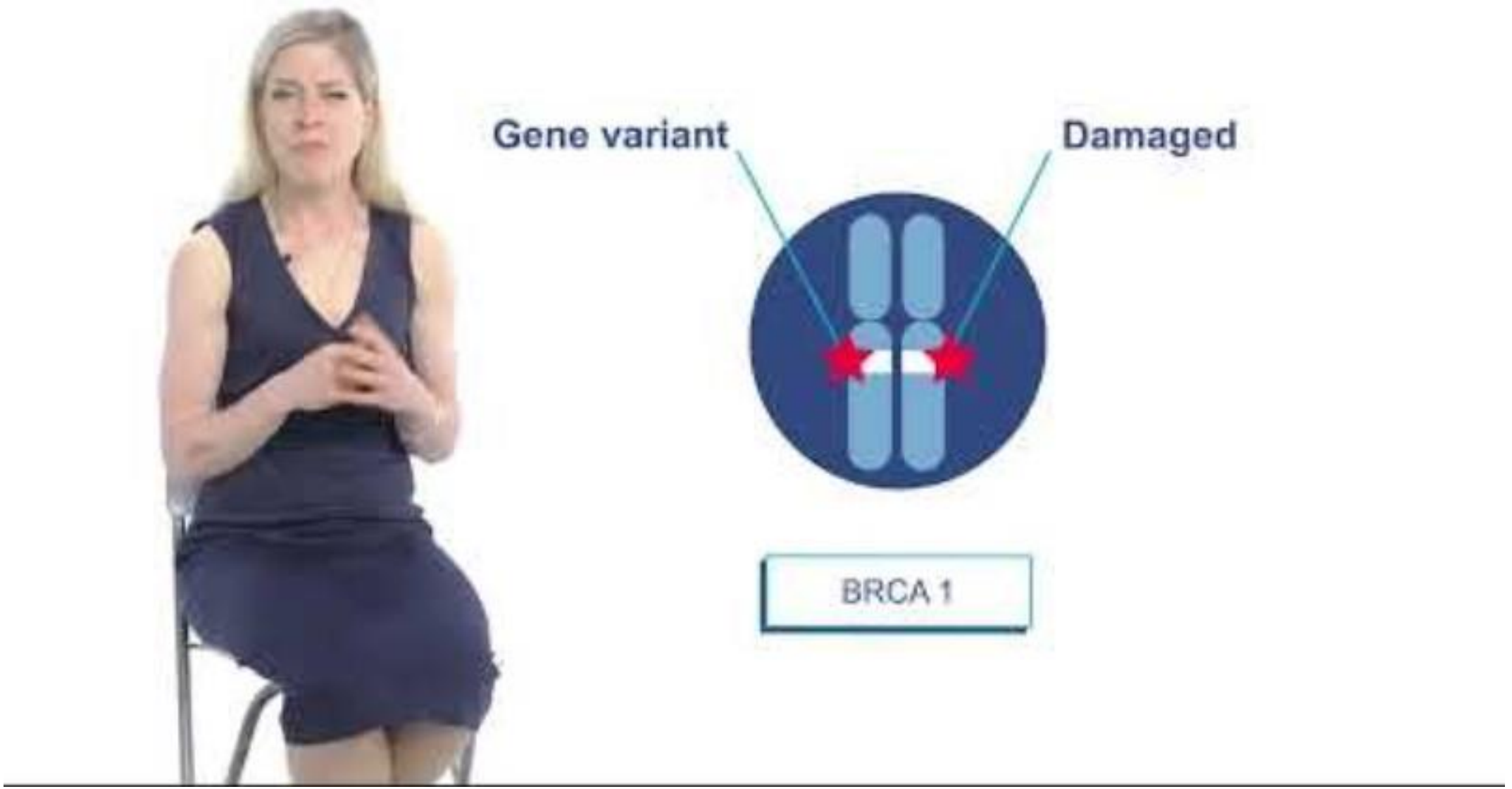
Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R444.1	NICE approved PARP inhibitor treatment – breast cancer	Singleton	Small variants, CNVs	Small panel of genes	BRCA1; BRCA2;	Small panel
R444.2	NICE approved PARP inhibitor treatment – prostate cancer	Singleton	Small variants, CNVs	Small panel of genes	BRCA1, BRCA2	Small panel

Nb (Feb 24) – Olaparib and Abiraterone approved by NICE for mCRPC (no previous ARTA and in whom chemotherapy is not clinically indicated). Regardless of BRCA status.


Gene variant
Damaged
BRCA 1

R430 – Inherited prostate cancer

- **April 2023** - *Inherited Prostate Cancer* panel added to the NGTD for either young onset (<50y) or metastatic prostate cancer (<60y)
- Offers NHS genetic testing to highest risk men / families
- Those who test positive are managed via Clinical Genetics unit

Testing Criteria

- Diagnosed with prostate cancer <50
- Diagnosed with prostate cancer (any age) and of Ashkenazi Jewish ancestry
- ≥1 grandparent from Whalsay (Shetland) and prostate cancer at any age
- Diagnosed with metastatic prostate cancer <60
- Diagnosed with prostate cancer and a strong FH of prostate / other cancers (needs to have a 10% chance of finding a pathogenic variant)

R430 Inherited prostate cancer

Testing Criteria

- Proband diagnosed with prostate cancer at <50 years
- Ashkenazi Jewish ancestry and prostate cancer at any age
- ≥1 grandparent from Whalsay (Shetland) and prostate cancer at any age
- Proband diagnosed with metastatic prostate cancer <60 years
- Proband diagnosed with prostate cancer with a family history of prostate cancer where estimated likelihood of identifying a pathogenic variant in the relevant target genes is at least 10%

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present.

Overlapping indications

- R208 Inherited breast cancer and ovarian cancer - Proband affected with prostate cancer who has a personal/family history of other BRCA related cancers see R208 (BRCA related cancers = breast, ovarian, pancreatic, prostate).
- R210 Inherited MMR deficiency (Lynch syndrome) - For prostate cancer with personal/family history of other Lynch related cancers see R210 (See list of Lynch related cancers in R210).
- R444 NICE approved PARP inhibitor treatment
- M218 prostate cancer should be used for somatic testing

Referrals for testing will be triaged by the Genomic Laboratory; testing should be targeted at those where a genetic or genomic diagnosis will guide management for the proband or family.

Where in Pathway

At presentation

Requesting Specialties

- Clinical Genetics
- Oncology
- Urology

Specialist Service Group

- Core

Associated Tests

Code	Name	Optimal Family Structure	Scope(s)	Target Type	Target Name	Method
R430.1	Inherited prostate cancer	Singleton	Small variants, CNVs	Small panel of genes	Inherited prostate cancer (1223)	Small panel

Genes Tested: *BRCA1, BRCA2, MSH2, MSH6, MLH1, CHEK2, ATM, PALB2*

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R208 – Inherited breast cancer and ovarian cancer

Testing Criteria

Living affected individual with prostate cancer AND a family history of breast/ovarian/pancreatic cancer with a pathology adjusted Manchester score of ≥ 15/CanRisk score of 10%

Genes Tested: *BRCA1, BRCA2, PALB2, ATM, CHEK2, RAD51C and RAD51D*

R208 Inherited breast cancer and ovarian cancer

Testing Criteria

1. **Living affected individual (proband)** with breast* or high grade ovarian cancer where the individual +/- family history meets one of the criteria. The proband has:
   a. Breast cancer (age <40 years), OR
   b. Bilateral breast cancer (age < 60 years), OR
   c. Triple negative breast cancer (age < 60 years), OR
   d. Assigned male at birth and affected with breast cancer (any age), OR
   e. Breast cancer (age <45 years) and a first degree relative with breast cancer (age <45 years), OR
   f. Combined pathology-adjusted Manchester score ≥15 or single gene pathology adjusted score of ≥10 or BOADICEA/CanRisk score ≥10% OR
   g. Ashkenazi Jewish ancestry and breast cancer at any age
   h. ≥ 1 grandparent from Westray (Orkney) or Whalsay (Shetland) and breast cancer at any age
2. **Living affected individual with pancreatic cancer** AND family history of breast*/high grade ovarian/prostate cancer with a pathology adjusted Manchester score of ≥ 15/CanRisk score of 10%.
3. **Living affected individual with prostate cancer** AND a family history of breast/ovarian/pancreatic cancer with a pathology adjusted Manchester score of ≥ 15/CanRisk score of 10%.
4. **Deceased affected individual** with breast* or high grade ovarian cancer with:
   a. A previously stored constitutional DNA/ blood sample is available, AND i.) Eligibility Criteria 1, 2 or 3 are reached AND ii). No living affected individual is available for genetic testing
   OR
   b. If no stored constitutional DNA/blood sample is available, but appropriate tissue is available (tumour or normal) AND i.) Criteria 2 are reached OR Pathology-adjusted Manchester score ≥17 or BOADICEA/CanRisk score ≥15% , for affected deceased relative AND ii) No living affected individual is available for genetic testing
5. **Living unaffected** individual with:
   a. first degree relative affected by breast* or serous ovarian cancer, AND
   b. Combined pathology-adjusted Manchester score ≥20 or BOADICEA/CanRisk score of ≥20% for affected relative or BOADICEA/CanRisk score of ≥10% for unaffected relative AND
   c. No living affected individual is available for genetic testing, AND
   d. No deceased affected individual with tumour material available for testing

   Note for living unaffected individuals:

   Where more than one family member may be eligible for unaffected testing, the residual probability of a causative pathogenic variant in the family should be considered, taking into account prior normal unaffected tests.

NOTES

- ***Breast cancer definition includes high grade DCIS, LCIS is not included.**
- **The proband's cancer and majority of reported cancers in the family should have been confirmed**
- **The pathology adjusted Manchester score involved incorporation of pathology data for the tested proband alone, i.e. pathology need not be sought for other family members.**
- **Ovarian cancer: Fallopian Tube and Primary Peritoneal cancers can be included**
- **BRCA1/BRCA2 testing should not typically have previously been performed. Exceptions may include, for example, patients who have been tested through the Jewish Community's NHS BRCA-Testing Programme for BRCA1/BRCA2 and not received a molecular diagnosis**
- **Testing of unaffected and deceased individuals can only be offered by Clinical Genetics**

Genetic testing may occasionally be appropriate outside these criteria following discussion at a specialist MDT with a cancer geneticist present

Overlapping indications

- M2 Ovarian carcinoma should be used for somatic testing
- M3 Breast cancer should be used for somatic testing

R210 – Inherited MMR deficiency (Lynch Syndrome)

Testing Criteria

Lynch-related cancers comprise:
Colorectal cancer, Endometrial cancer, Epithelial ovarian cancer, Urothelial cancers, Transitional cell cancer of renal pelvis, cholangiocarcinoma, Small bowel and upper gastrointestinal cancers, Glioblastoma, endocervical cancer, multiple sebaceous tumours, **PROSTATE**, gastric and pancreas

Genes Tested: *MSH2, MSH6, MLH1, PMS2, EPCAM*

R210 Inherited MMR deficiency (Lynch syndrome)

Testing Criteria

All new diagnoses of colorectal and endometrial cancer should have tumour MSI / IHC as outlined in the cancer test directory and the Lynch syndrome handbook for Alliances in order to identify dMMR tumours and additional testing that suggests Lynch Syndrome. This may include BRAF testing in MLH1 deficient colorectal cancers and somatic MLH1 hypermethylation testing in BRAF negative colorectal cancers and all MLH1 deficient uterine cancers. Somatic MLH1 hypermethylation testing is included on the Cancer Test Directory under M1.5.

1. **Clinical Criteria for germline testing in an affected individual**
   The proband has a dMMR tumour where results of additional testing suggest Lynch syndrome. This may include BRAF testing in MLH1 deficient colorectal cancers and somatic MLH1 hypermethylation testing in BRAF negative colorectal cancers and all MLH1 deficient uterine cancers
   a. The affected proband comes from a modified Amsterdam criteria positive family irrespective of the dMMR status of the tumour
   b. Personal or family history suggestive of Constitutional Mismatch Repair Deficiency (CMMRD) with Wimmer score =>3
   c. Deceased affected individual meets criteria and a previously stored constitutional blood/DNA sample is available.

2. **Clinical criteria for MSI /IHC testing on a stored tumour sample prior to germline testing**
   a. Personal/family history of colorectal cancers reaching Modified Amsterdam Criteria (≥ 3 cases of Lynch related cancer over ≥2 generations with ≥1 case diagnosed <50 years) OR
   b. Any lynch-related cancer* <50 years (excluding isolated pancreas, prostate or gastric cancers)
   c. Two Lynch-related cancers (any age, one is colorectal or endometrial), OR
   d. Lynch-related cancer and ≥ 1 first degree relative has Lynch-related cancer (both occurred ≤60 years, one is colorectal or endometrial), OR
   e. Lynch-related cancer and ≥ 2 relatives (first / second / third degree relatives) have Lynch-related cancer (all occurring ≤75years, one is colorectal or endometrial), OR
   f. Lynch-related cancer and ≥ 3 relatives (first / second / third degree relatives) have Lynch-related cancer (occurring any age, one is colorectal or endometrial)

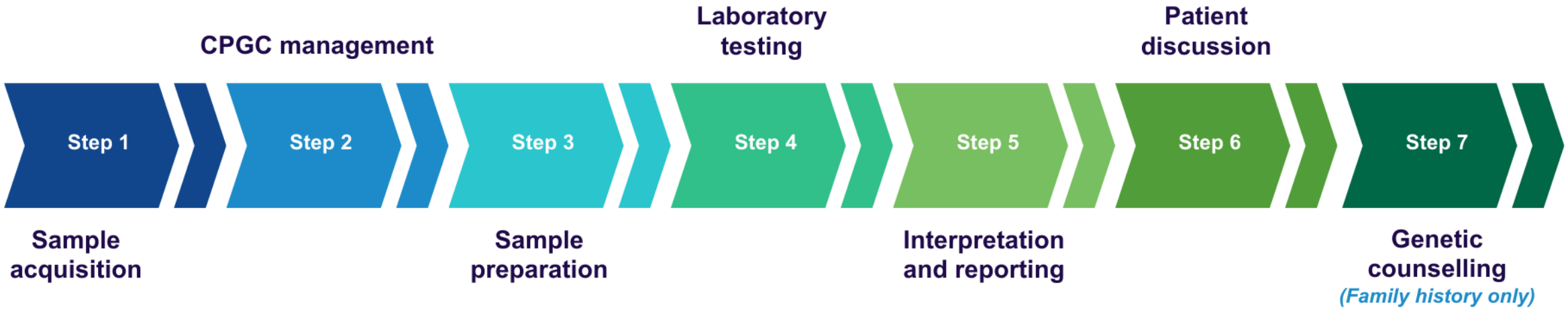
*Lynch-related cancers comprise: Colorectal cancer, Endometrial cancer, Epithelial ovarian cancer, Urothelial cancers, Transitional cell cancer of renal pelvis, cholangiocarcinoma, Small bowel and upper gastrointestinal cancers, Glioblastoma, endocervical cancer, multiple sebaceous tumours, prostate, gastric and pancreas

3. **Clinical Criteria for somatic (tumour) Lynch syndrome panel testing**
   a. Proband has colorectal or endometrial cancer with a dMMR tumour with normal BRAF and somatic MLH1 hypermethylation analysis AND germline testing did not reveal a pathogenic variant OR personal/family pattern of disease whereby demonstration of acquired MMR variants (and therefore exclusion of constitutional MMR abnormality) enables downscaling of surveillance
   b. Deceased affected individual with colorectal or endometrial cancer ≤60 years AND tumour featuring high/intermediate MSI or loss of staining of MMR protein(s) on IHC, AND one first degree relative with Lynch-related cancer ≤60 AND no living affected individual is available for genetic testing.

4. **Clinical Criteria for germline testing in an unaffected individual**
   a. First degree relative affected with Lynch-related cancer, AND
   b. Family history of colorectal cancer/Lynch-related cancers reaches Amsterdam Criteria (≥3 cases over ≥2 generations with ≥1 case affected <50 years) AND
   c. Tumour sample analysis from affected family member has been attempted and is not possible, failed, indeterminate or indicates MMR deficiency (via IHC or MSI), AND
   d. Somatic sequencing is not possible, or failed, AND
   e. No living affected individual is available for genetic testing

5. **Criteria for germline MLH1 promoter methylation**
   a. Families where MLH1 promotor methylation has been identified in tumour tissue in >1 affected individual with colorectal cancer ≤ 60

NOTE: The proband's cancer and majority of reported cancers in the family should have been confirmed



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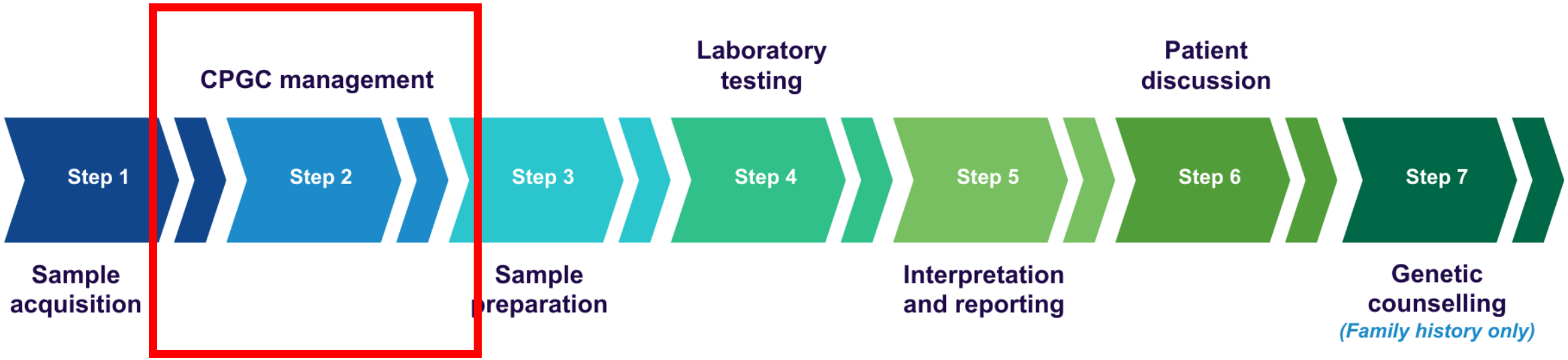

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Barts Health CPGC & GCIP Initiatives

Dr. Madhuri Warren

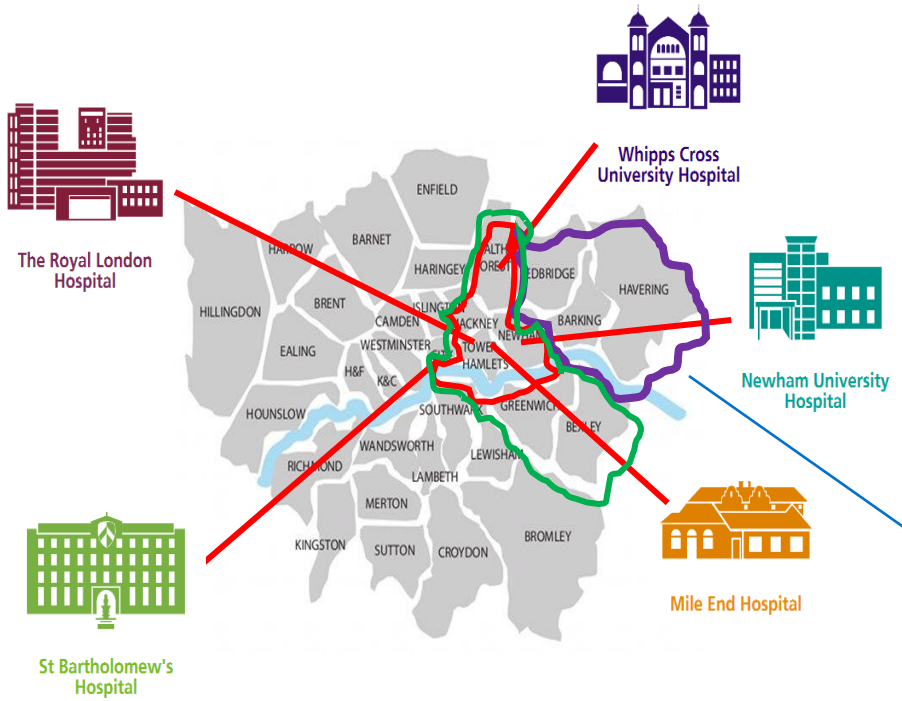
Consultant Histopathologist

CPGC Pathology Lead,

Barts Health NHS Trust

Barts Health NHS Trust configuration and local population demographics

Our core catchment area spans 6 local authorities:



We are part of the NE London ICB and cancer alliance along with BHRUT

Barts Health NHS Trust and Lewisham and Greenwich hospitals form part of the East and South East London Pathology partnership (ESEL)

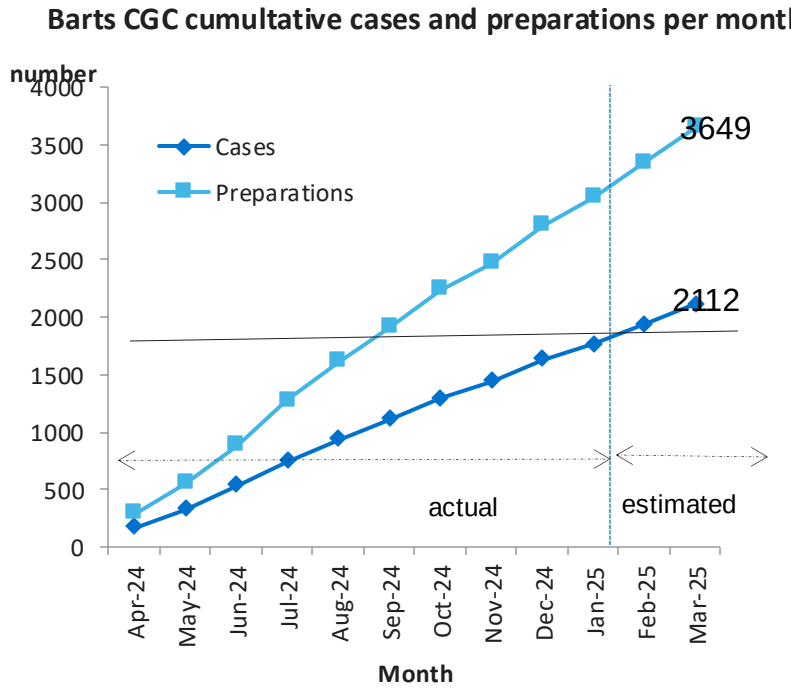
<u>Local population statistics</u>:

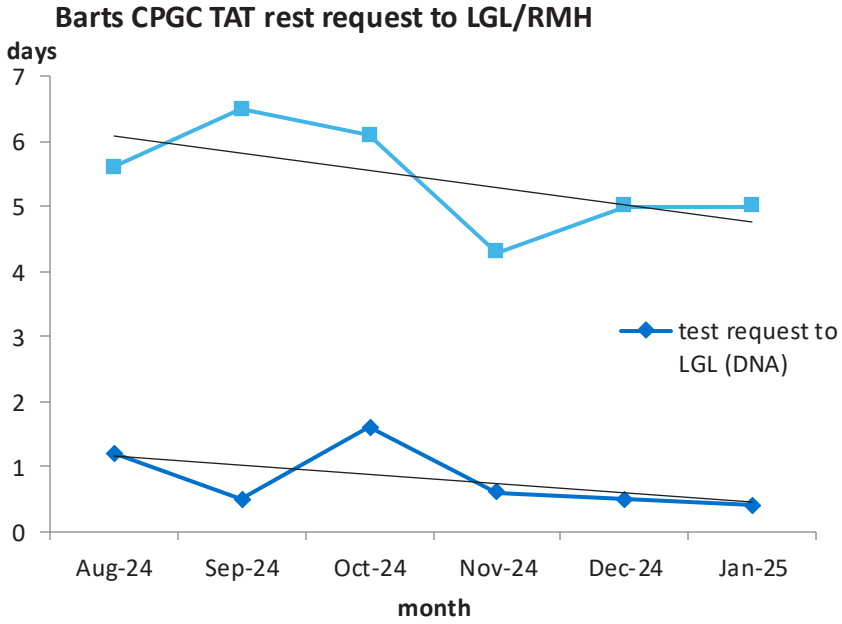
Total population 1.31 million
Population growth rate: 15% per annum (one of highest in UK)
<u>Healthy life expectancy (HLE):</u>
Tower Hamlets worst female HLE in London
Hackney 2nd worst male HLE in London
Percentage of smokers in Tower Hamlets = 20%
Uptake of bowel screening: 43-50%
Uptake of breast screening: 36%
Uptake of targeted lung health check 59.1%

Cancer statistics	Cancer incidence per annum NEL (% of pan London)	London wide cancer incidence per annum
lung	888 (20.1%)	4,405
colorectal	790 (19.8%)	4,000
prostate	1119 (19.1%)	5,840
endometrial	187 (18.0%)	1,036
melanoma	197 (15.5%)	1,272
breast	1173 (19.8%)	5,895

It is imperative to focus on improving diagnosis and access to cancer treatments in our region since our population contributes ~20 % of cancer cases in London

Barts CPGC history and achievements to date





Historic figures:

2022/23:

estimated new cancers* in local population = 2,325
number of solid tumours sent for genomic testing = 1,600
percentage of potentially eligible cancers tested = **68.8%**

CPGC (Jan -Dec 2024)

estimated new cancers* in local population = 2,813
number of solid tumours sent for genomic testing = 2,490
percentage of potentially eligible cancers tested = **88.5%**
(21.7% improvement)

Genomic testing TAT:	2022 (IHC lab instead of CPGC) (days)	Aug –Dec 24 (days)	Improvement (days)
Genomic test request to receipt at CPGC*	0	0	0
Genomic test request to CPGC dispatch	6.3	4.3	2
CPGC dispatch (to GLH) to receipt at GLH	2.5	1.2	1.3
Genomic test request to receipt at GLH	9.8	5.5	4.3

* Cancers include lung, colorectal, endometrial, melanoma, lymphoma

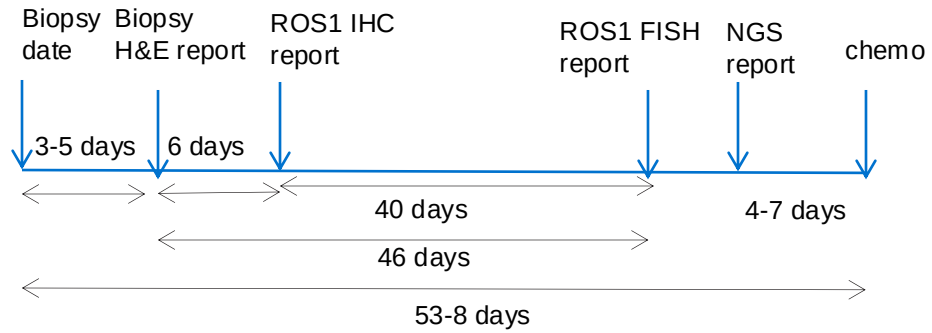
37% improvement in cellular pathology TAT since CPGC set up

Barts CPGC QI TAT improvement project Oct 24 -Mar 2025

Improving TAT for molecular testing of lung adenocarcinoma

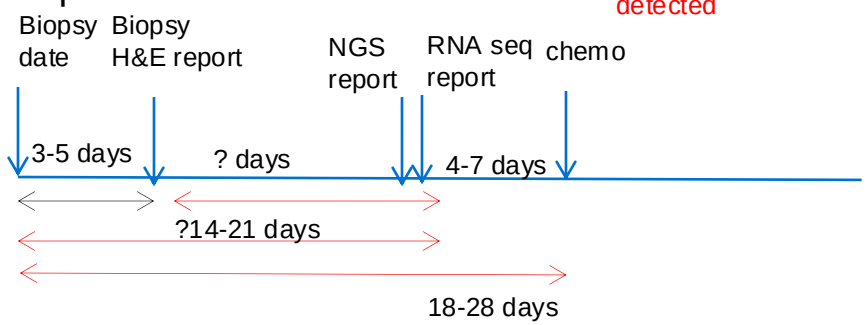
Barts Health NHS Trust

Historic timeline:



Proposed timeline:

Also ALK, NTRK fusion proteins detected



Audit Results:

step in pathway	turnaround times (days)	
	mean	minimum
pathologist sequencing request to sections cut	1	0
sections to pathologist ->H&E review -> sections back to lab-> sent to RMH	7	2
sent to RMH to booked in at RMH	2	0
RMH RNA sequencing TAT	17	11
RMH Result on O&V downloaded by Molecular and e-mailed to oncologist	1	0
TOTAL PATHWAY TIME (TAT pathologist receives request to report sent to oncologist in days)	28	13

2024:
RNA sequencing request -> result to oncologist: mean TAT 28 days
ROS1 fusion detection rate = 2.3%.
RNA sequencing failure rate = 4.7%.
ROS1 IHC positive rate = 34%
False positive IHC rate = 32%
PPV 5.5%

2022/23:
Historic ROS1 FISH TAT = 40 days;
ROS1 IHC to FISH TAT= 46 days;
Failure rate = 31%;
Positive FISH detection rate = 0% (annual positive FISH detection rate = 1.3 %) ;
ROS1 IHC positive rate = 26%
False positive IHC rate = 25%
PPV 11%

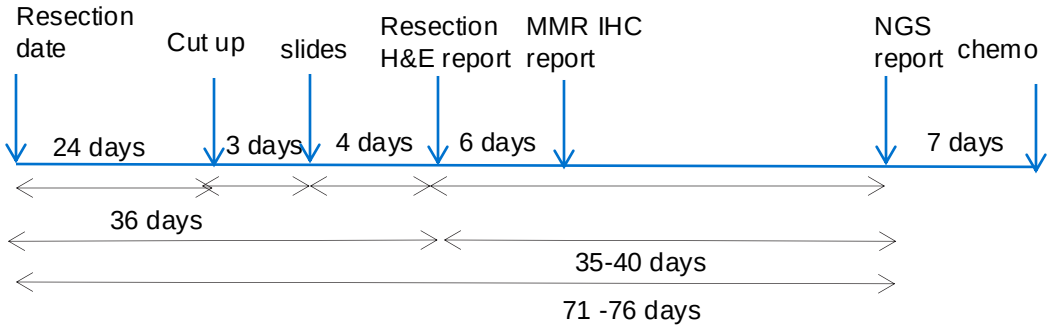
Key Improvements:
TAT improvement = 12 -18 days
Failure rate reduction = 28%
Detection rate increase = 200%

Barts CPGC QI TAT improvement project Oct 24 -Mar 2025

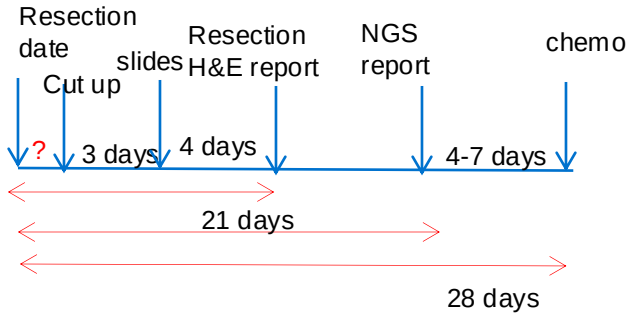
Colorectal Carcinoma Audit Results (2)

Barts Health NHS Trust

Historic timeline:



Proposed timeline:



Audit Results:

step in pathway	TAT (days) 2022 mean	Retrospective 2024 mean		2024 minimum	Prospective 2024 mean	Prospective 2024 minimum
Specimen transport local hospital to RLH*	2.63	1.11		0	0.6	0
Specimen cut up	overall 16	Overall	11.2	0	3.5	0
		Biopsy	2.6	0	3.1	0
		Resection	23.7	1	4.2	0
Sign out from lab ->H&E authorisation	4.14	4.17		0	5	0
Overall TAT specimen date to HE report	overall 27	Overall	20.3	3	13	0
		Biopsy	9.3	3	10	2
		Resection	35.9	8	16.7	6
MMR request to authorisation	6.7	4.0		1	6.4	1
Pathologist request MMR + sequencing to authorisation	26	26.4		6	19	15
% tumour content assessed	31%	89%			95%	

2024 retrospective audit:

% of cancers ST3/4 = 88%
MMR failure rate = 0%
MMR detection rate = 9.5%
NGS failure rate = 1.6%
NGS detection rate = 12.6%

Key Improvements:

Resection cut up TAT =19.5 days

Specimen date->H&E report=19.2 days

MMR request to authorisation =2.7 days

Increase in % of samples with tumour content assessment = 64%

NHS
Barts Health
NHS Trust

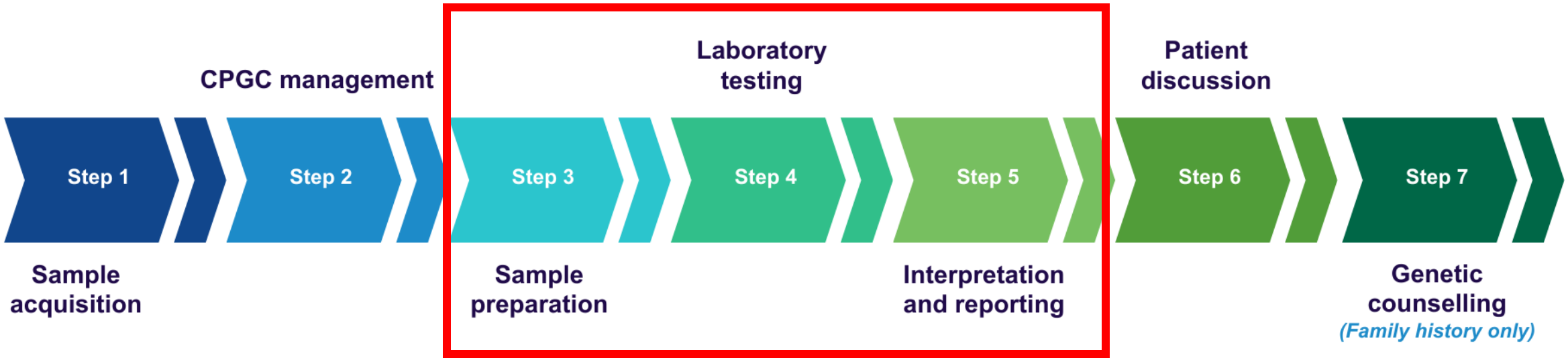
Acknowledgements

Barts CPGC Management Team

- Stephen Rodgers – CPGC & IHC Operational Lead, Cellular pathology
- Jamie Hughes – CPGC / CVLP Associate Manager, Cellular Pathology
- Marianne Grantham – Head of Cytogenetics and Molecular Pathology, Barts Health NHS Trust
- Toby Hunt, Divisional Manager, Barts Health NHS Trust
- Tom Butler, Medical Director, ESEL Pathology Partnership

Barts Audit Teams

- Lung adenocarcinoma audit team: Dr K Giaslakiotis, Dr M Warren, Dr T Farooque, Prof L J Jones, S Thiruvengatham
- Colorectal carcinoma audit teams: Dr L Beltran, Dr M Rathbone, Dr M Liaquat, Dr V Sheshappanavar, S Thiruvengatham



NHS
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Genomic Medicine Service

Sample testing – our genetic technologists

Our technical team process samples in each of our labs, they operate testing equipment in the lab and have specialist knowledge of each testing process.

We have over 170 technologists working across our labs in the North Thames Genomic Medicine Service.

NHS
North Thames
Genomic Medicine Service

Analysis pipelines – our bioinformaticians

Bioinformaticians work closely with teams across the GMS to build analysis pipelines for all the genomic data we generate.

We now have 14 bioinformaticians within the North Thames GMS!

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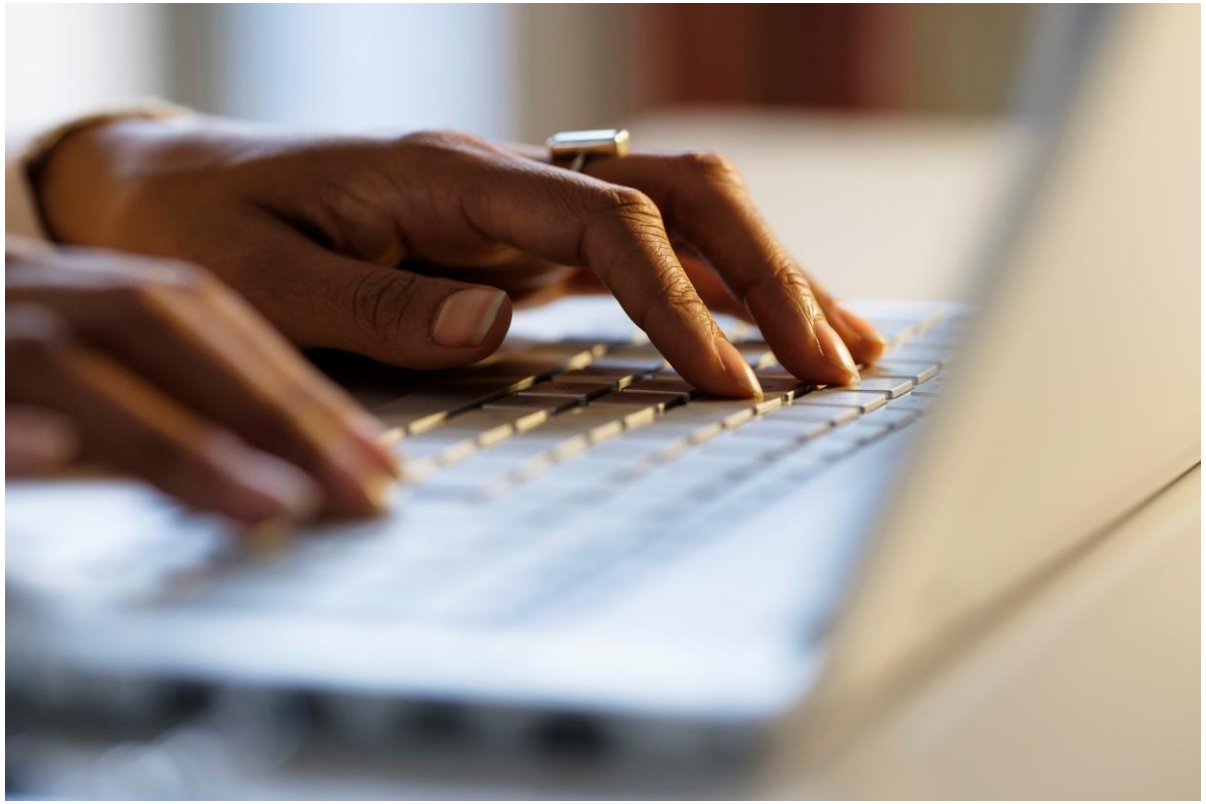
Genomic Medicine Service

Interpretation and reporting – Our clinical scientists

Clinical scientists provide expert knowledge to the genomic service-users. They handle referrals, request tests, analyse results, and also write reports.



Over 170 clinical scientists across the North Thames GMS work to provide testing results to clinical teams.

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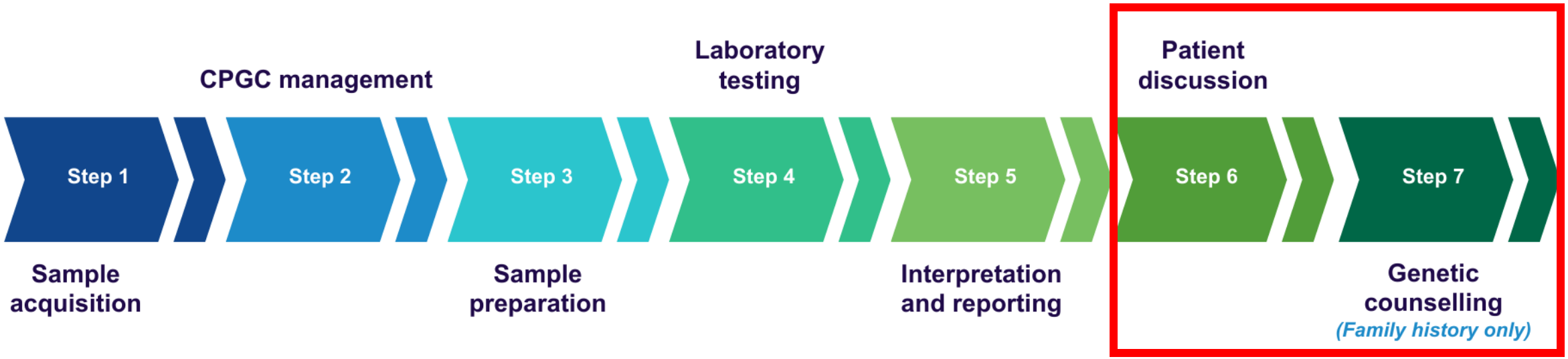
Genomic Medicine Service



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NHS
East Genomics

NHS
North Thames
Genomic Medicine Service

Genetic Counselling

What happens when we find a germline variant that highlights a predisposition to cancer(s)?

Genetic Counselling

For the patient:

- Referrals for screening/management
- Psychosocial impact (positive and negative) and support
- Implications for family planning/reproductive choices
- Disclosure of genetic results - impact on insurance

For family members:

- Results may affect relatives
- Access to testing/management
- Importance of sharing results
- Discuss strategies e.g. ‘to whom it may concern’ letters
- Refer for genetic counselling

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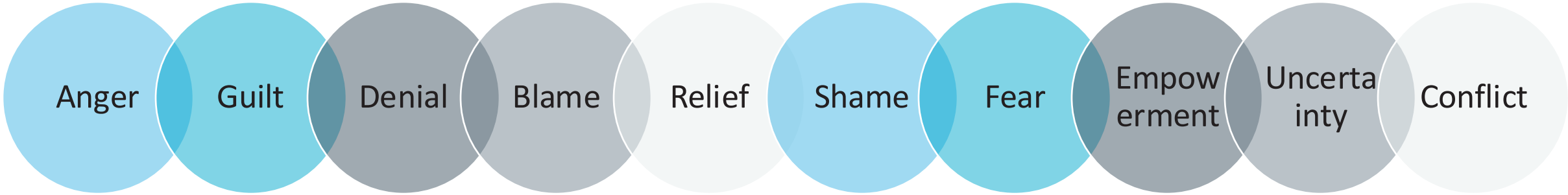
Genetic Counselling

"How/where can we learn more about this?"

"What does this mean for future children?"

"Is this my fault?"

"Are there any treatments or preventative measures that can be taken?"



"What do we know about this gene?"

"Can we fix the gene?"

"What does this mean for my other children/family members?"

"What does this mean for my/my child's future?"

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North Thames
Genomic Medicine Service

Education and Training

Fundamentals in Human Genetics and Genomics

- Up to 6 weeks
- Accredited
- Part Time
- Blended learning

Find out more

Genomics 101: Genomics in Healthcare

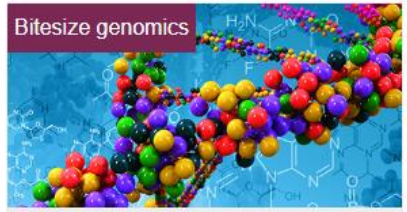
- 30 minutes
- Certificate of completion
- Part Time
- Online

Find out more

Introduction to the Counselling Skills used in Genomic Medicine

- Up to 6 weeks
- Accredited
- Part Time
- Blended learning

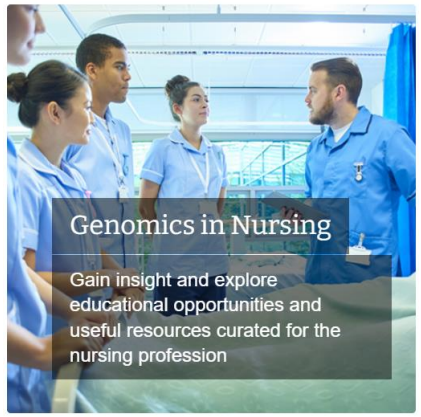
Find out more

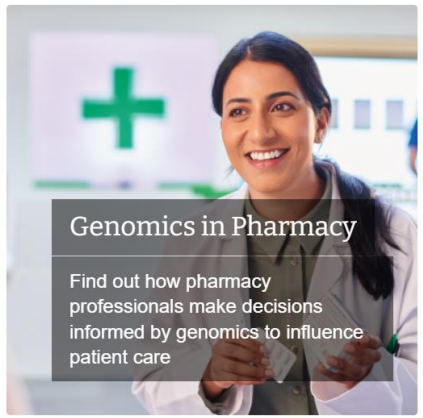


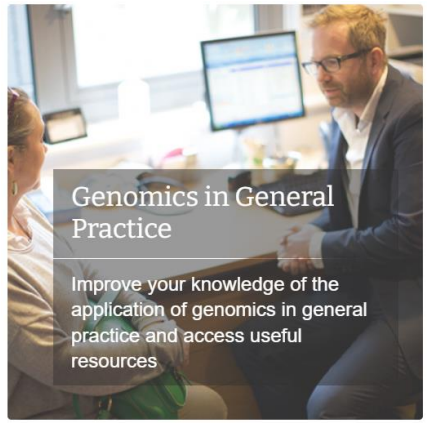
What is genomics?

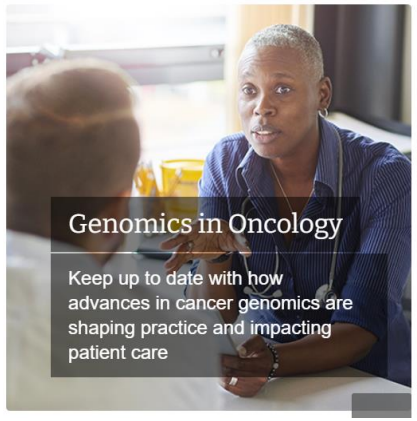
- 10 minutes
- Multimedia

Find out more









Genomics Education Programme: https://www.genomicseducation.hee.nhs.uk/

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Prostate Cancer Genomic Testing Mainstreaming Event

Educational event for healthcare professionals involved in the care of individuals with prostate cancer wanting to learn more about genomic testing.

CONFIRMED SPEAKERS

- Mr Eddie Blair
- Dr Terri McVeigh
- Dr Alison Reid
- Mr Ben Lamb
- Dr Mikel Valgañón
- Professor Gert Attard
- Professor Ros Eeles
- Dr Anju Kulkarni
- Dr Vishakha Tripathi
- Dr Thomas Charlton
- Dr DoraidAlrifai
- Dr Kenrick Ng
- Dr Marianne Grantham

20 June 2025, Friday

9am-5pm

Woburn House Conference Centre,
20-24 Tavistock Square,
WC1H 9HQ

Healthcare professionals involved in the care of individuals with prostate cancer

Only 80 spots available!

REGISTER NOW

norththamesgenomics.nhs.uk

Join us on 20th June for an education day focussed on prostate cancer genomic testing –

Registration opening soon!

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We are taking a short break

We will be back at 11:30

14:00 – What I want my healthcare professionals to know about genomics

Dr Fiona Calvert

Comms and Engagement Lead

Pooja Dasani

Genetic Counselling Lead

Jason Dunlop

Patient and family representative

Amber Dobinson-Evans

Patient and family representative

Harri Pessoa de Araujo

Patient and family representative

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We are breaking for lunch!

We will be back at 14:00

14:00 – Equity: Meeting real world needs

Developing the NT GMS Equity Strategy

- Dr Shazia Mahamdallie, Equity Lead

Equity and community: local change makers East London Foundation Trust Mental Health Services

- Dr Nick Bass, Mental Health Lead

Equity and workforce: spotlighting Genomic Associates

- Arti Patel, Senior Genomic Associate

Equity and data: NTGMSA Equity of Access Dashboard

- Megan Luker, Data and Performance Analyst
- Balbir Lehto, Information Analyst

Equity and research: can the Generation Study do better?

- Dominic Studart, Regional Results Coordinator
- Yvonne Muwalo, Regional Results Coordinator

North Thames
Genomic Medicine Service

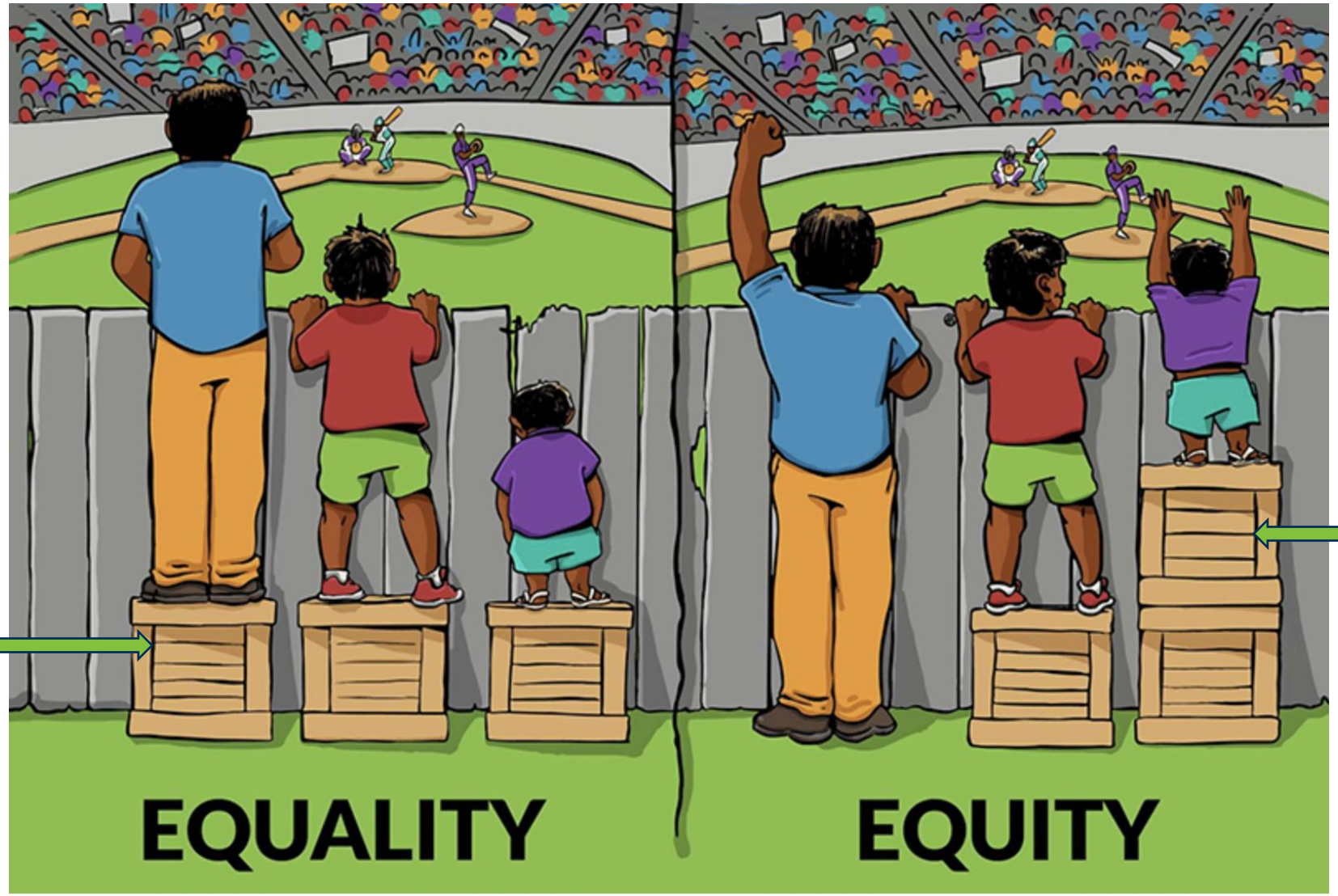
NT GMS Equity Strategy – bitesize!

Tomorrow's genomic medicine together

NTGMS 2025 Showcase

Dr Shazia Mahamdallie, Health Equity Lead, NTGMS

Evenly/equal distributed tools, resources and information



Custom tools, resources and information that address inequality

Tailoring support to ensure equal, opportunity to access, and delivery of the Service

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Genomic Medicine Service

Inequity is at the core of genomic medicine

Inequity is experienced by the communities we serve - we are leaving population groups behind - leading to missed diagnoses and misdiagnoses, and thus disparities in care.

Genomic research:

Ethnic biases persist in genomic research methodologies and databases.

- GWAS studies (2016) 81% of European bio-geographical ancestry, but Europeans are 16% of the global population.
- gnomAD (2023) 77% European vs 5% African or South Asian ancestry.

- Under-representation > VUSs + reduced biological understanding of disease > misdiagnoses/reduced drug efficacy (PMC5292722).
- Recruitment into genomic databases can favour **cost-effectiveness and convenience sampling over representation**. Targets of numbers rather than time hinder inclusive conversation.

Genomic Healthcare:

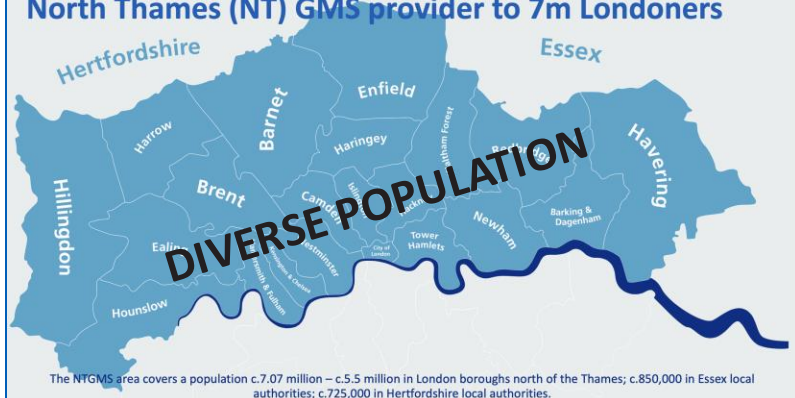
Ethnic minority groups, marginalised communities face challenges in accessing genomic services – **language and mistrust.**

Developing the strategy in two slides!

Elements of a strategy

Vision	Purpose	Principles
Pillars	Priorities	Phases

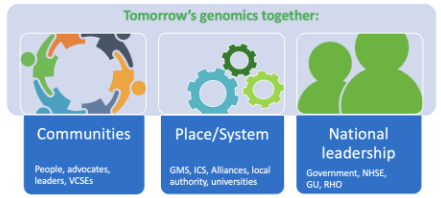
North Thames (NT) GMS provider to 7m Londoners



The NTGMS area covers a population c.7.07 million – c.5.5 million in London boroughs north of the Thames; c.850,000 in Essex local authorities; c.725,000 in Hertfordshire local authorities.

NTGMS additionally covers cancer genomic services for Kingston, Merton, Richmond, and Wandsworth.

…by working better together in neighbourhoods, recognising the importance of both the message and the messenger



Community-first approach

Working together and within existing relationships/representatives

Community leadership

Partner with VCSEs

Collaborate with ICSs, Alliances

Support for Primary Care

10-YEAR HEALTH PLAN

'Working within neighbourhood footprints is not new. Neighbourhood working harnesses the assets valued in a local area, with services' operating models proactively wrapping around those communities and their needs.'

Working within 'neighbourhoods' does not necessarily mean integration, instead involves building trust with people, communities and their organisations and representatives.

NHS Confederation in Oct 2024 published a 'case for change' exploring the nature of the relationship between statutory services, neighbourhoods and communities, to provide a chance of sustaining our health and care systems, closing the gap on growing population inequalities, and achieving our bigger aspirations for a better society.'

Source: NHS Confederation Oct, 2024

NTGMS has equity deliverables

GLHs and GMS Alliances are responsible for actively contributing to the NHS Genomics Ethics, Equity and Legal Advisory Group and considering the recommendations of the group.

NHS GMS Alliances are responsible for developing strategies and actions to support the NHS GMS in their geography to reduce inequities in access and to use genomics to reduce health inequalities. NHS GMS Alliances are responsible for identifying and prioritising cohorts of individuals at higher risk populations for genomic variants, for example BRCA variants in the Ashkenazi Jewish and South Asian populations. NHS GMS Alliances are responsible for identifying and prioritising cohorts of individuals, for example those with protected characteristics e.g. black, Asian and minority ethnic groups; disabled; LGBTQ+ to actively engage with the NHS GMS and potentially socially excluded cohorts e.g. inclusion health groups such as rough sleepers, the homeless; asylum seekers and Gypsy, Roma and Traveler groups.(Core 20+5)

NHS GMS Alliances are also responsible for ensuring patient and public involvement is built into their plans, service development and delivery, and increasing patient and the public and clinical awareness of NHS GMS through their engagement campaigns and engagement events across their geography, considering urban, rural and coastal inequalities.

GMS DELIVERABLES

GMSA Business Plan key deliverables:

1. Deliver and Extend Transformation Projects
2. Evaluate and Report Outcomes
3. Enhance Genomic Service Models
4. Expand Whole Genome Sequencing
5. Address Genomic Health Equity
6. Enable Precision Medicine & ATMPs
7. Support Pharmacogenomic Testing

The NTGMSA is hosted by GOSH, which has two frameworks:

GOSH [workforce] Diversity and Inclusion 2020 – 2022:

1. Opening-up external recruitment;
2. Creating internal career paths and opportunities;
3. Creating a more inclusive work culture for all;
4. Creating channels and safe spaces which amplify the employee voice.

Tackling [patient] health inequalities at GOSH:

Working groups:

1. Experience
2. Outcomes
3. Access
4. Awareness
5. Digital exclusion

NTGMS represented

NHS North Thames Genomic Medicine Service

Our legal obligations under the UK equality framework

The Human Rights Act 1998 and Equality Act 2010 both focus on the UK legal anti-discrimination position, outlining public sector duties and legal protections.

Public Sector Equality Duty (which includes the NHS) that public bodies to consider how their policies and decisions can:

- Remove or minimise unlawful disadvantages suffered by people due to their protected characteristics [Tackle discrimination]
- Take steps to meet the needs of people who share a particular protected characteristic, where those needs are different from the needs of those who do not share that protected characteristic [Tailor our approach - basis of equity vs equality]
- Encouraging people with particular protected characteristics to participate in public life or in other activities* where their participation is disproportionately low [* i.e., Research.]

Ensure our approach is inclusive, we engage at a neighbourhood-level]

LEGAL

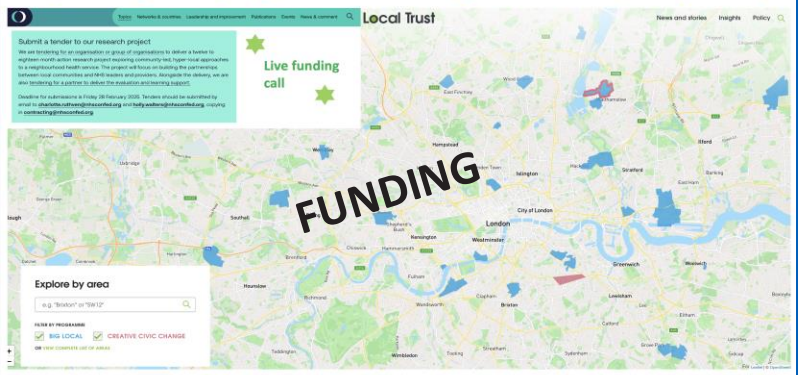
Workforce

Service & Community

To comply with this legal mandate the Department of Health and Social Care Equality Objectives 2023-2027 include five areas to integrate equality considerations into operations:

1. **Attracting, developing, and retaining diverse talent**: Ensuring the workforce reflects the communities served.
2. **Creating a welcoming and inclusive workplace**: Encouraging staff to bring their authentic selves to work.
3. **Enhancing leadership capabilities**: Promoting a culture of diversity and inclusion through empowered and accountable leaders.
4. **Engaging with diverse stakeholders and the public**: Incorporating varied perspectives in policy design and service delivery.
5. **Promoting awareness and understanding of our Public Duty and health disparities**: Embedding equity considerations in all departmental work.

…by seeking funding e.g., NTGMS has "Big Local" areas (blue patches)



FUNDING

What do the people of NTGMS want?

NTGMS ENGAGEMENT

Health EDI landscape – KOL have paralleling recommendations

Workforce | service | community | research

Marmot, M. et al. 2020. Health Equity in England: The Marmot Review 10 Years On. London: Institute of Health Equity. This report provides an analysis of health inequalities in England and offers several key recommendations to address these disparities. These include: **(1)** Improve education and employment; **(2)** Strengthen health services; **(3)** Enhance community engagement; **(4)** Address systems of inequality. See notes for more explanation.

The overall aims of health equity approaches should be to… redress current patterns and reduce the magnitude of health inequities…

Morris, L. and Robertson, R. 2024. Tackling health inequalities: seven priorities for the NHS. The King's Fund. This report identifies seven key priorities for the NHS to tackle health inequalities. These include: **(1)** Equip staff; **(2)** Local decision making; **(3)** Empowering communities; **(4)** Support local organisations; **(5)** Address discrimination. See notes for more explanation.

Bains, M. et al. 2024. Ethnic inequities in genomics and precision medicine. The NHS Race and Health Observatory and University of Nottingham. This report emphasises the need for tailored public health education to increase understanding of genomics and the potential benefits of precision medicine for all communities. Recommendations made include: **(1)** Workforce diversity and training; **(2)** Improve access to genetic services; **(3)** Public engagement and trust; **(4)** Increase representation in research; **(5)** Ongoing monitoring and accountability. See notes for more explanation.

RECOMMENDATIONS

Health and genomic improvement recommendations

The National Healthcare Inequalities Improvement Programme (NHSE), 2021, from which the CORE20+ was an output aims to "deliver exceptional healthcare for all; ensuring equitable access, excellent experience and optimal outcomes"

National priorities and success [illegible] for 2025/26

Address inequalities and shift to prevention

Increase the % of patients with hypertension treated according to NICE guidance, and the % of patients with GP recorded CVD, who have their cholesterol levels managed to NICE guidance

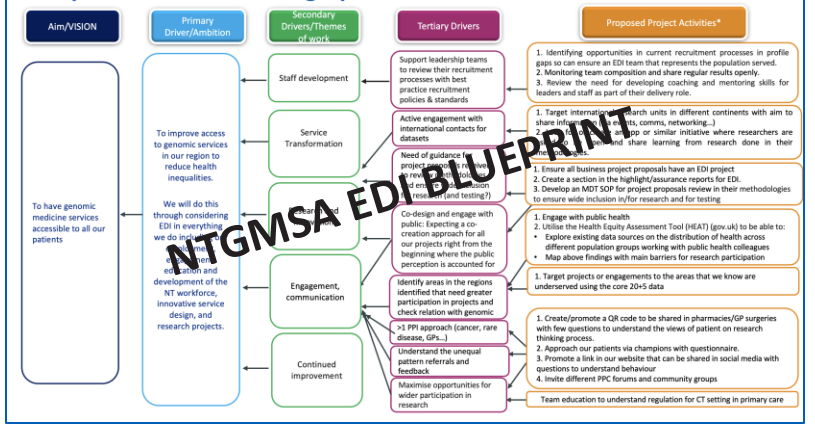
NHS Race & Health Observatory and CORE20+5 recommendations:

- Define target populations – protected characteristics. [Equity]
- Identify clinical areas requiring improvement. — service
- Community engagement. — community
- Tailored/equitable interventions — community
- Monitoring equity of access in GMS — service
- Workforce training needs. — workforce
- Diversify research — research

NHS North Thames Genomic Medicine Service

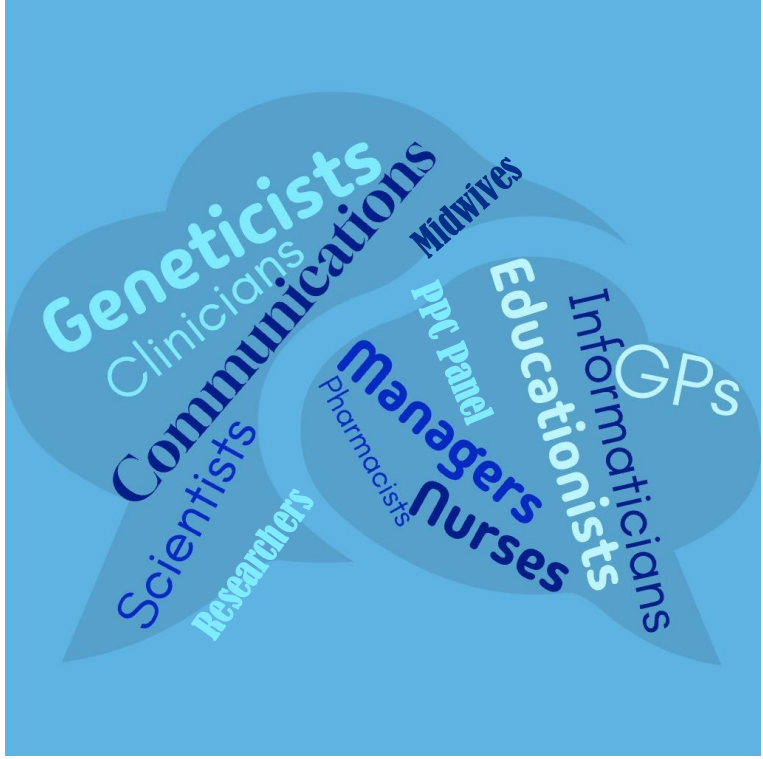
NHS PLANNING GUIDANCE

Blueprint: GMSA EDI strategic plan v2.0 2022



NTGMSA EDI BLUEPRINT

Collaborators Thank you



Author:
Dr Shazia Mahamdallie, Health Equity Lead, North Thames Genomic Medicine Service (NTGMS)

Support by NTGMS Senior Leadership Team:

- Dr Angela George, Co-Medical Director, NTGMS
- Dr Sophia Varadkar, Co-Medical Director, NTGMS
- Paul Ryves, Programme Director, North Thames Genomic Medicine Service Alliance
- Anthony Sullivan, Chief Operating Officer, North Thames Genomics Laboratory Hub

Thanking the time and contributions of:
NTGMSA PPC Panel; Moses Adegoroye; Cynthia Amo-Ameyaw; Elizabeth Bancroft; Dr Nick Bass; Leanne Barrett; Cheryl Berlin; Dr Angela Brady; Simon Burn; Dr Fiona Calvert; Dharmisha Chauhan; Adele Corrigan; Dr Faye Dannhauser; Pooja Dasani; Natalie Ellery; Demetra Georgiou; Merrie Gowie; Denzil James; Professor Anwar Khan; Monika Kosicka-Slawinska; Balbir Lehto; Megan Luker; Bethany Lumborg; Yvonne Muwalo; Dr Marie Nugent; Arti Patel; Tina Prendeville; Ravinder Sehra; Dr Dania Shoeb; Dominic Studart; Dr Shereen Tadros; Dr Tosin Taiwo.

>30 hours of conversation

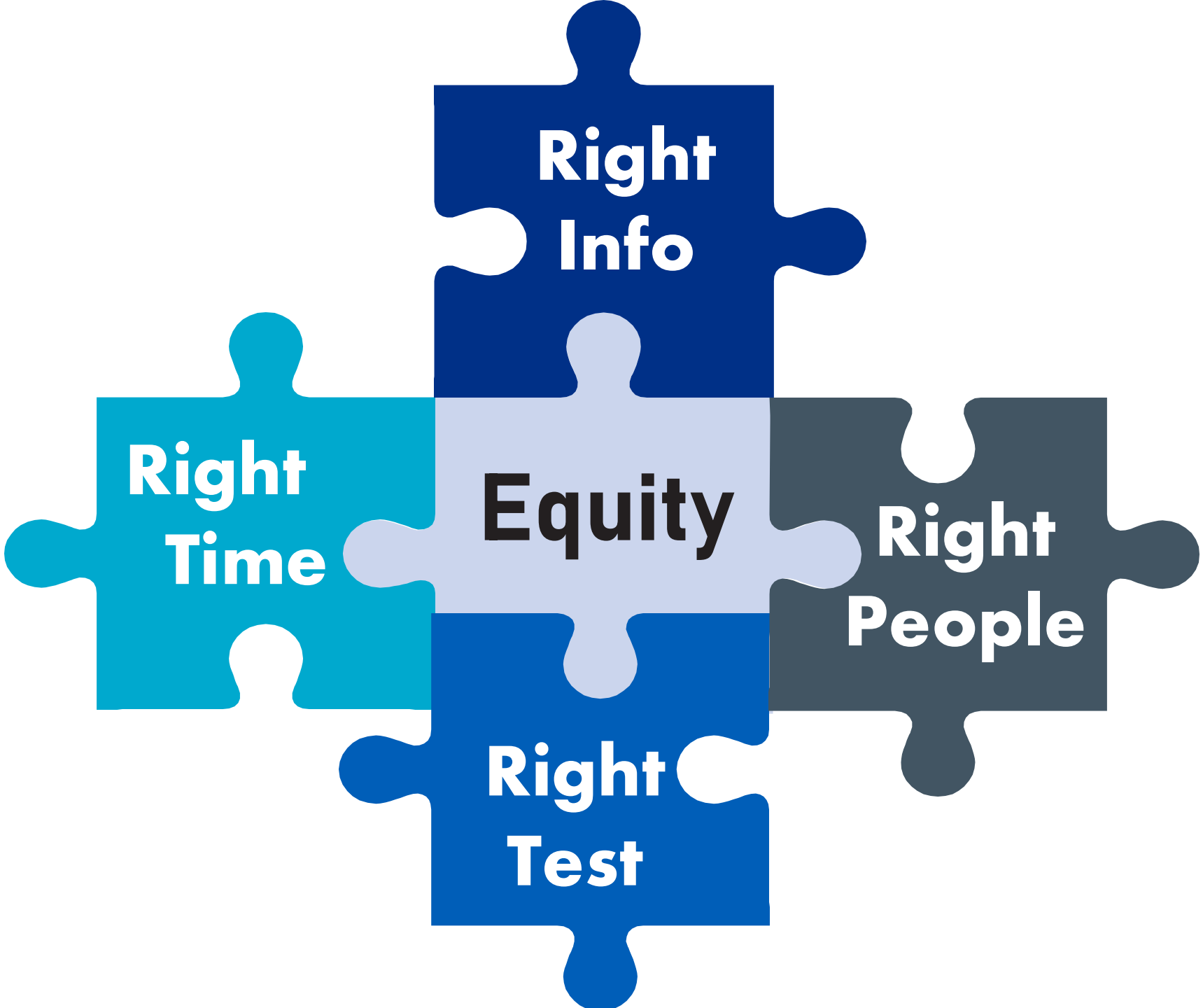
Imperial
GOSH
RNOH
NW Thames Regional Genetics Service
NE Thames Regional Genetics Service
N Thames GPs
RMH
UCLH

NHS
North Thames Genomic Medicine Service

>30 hours of conversation

Listening – what do the people of NTGMS want?


To consider equity in all current and future initiatives within the NTGMS, benefiting both the workforce and the health of the population we serve.
Write lay summaries and disseminate them, for all our research findings.
Provide all people with what they need, making sure they are guided to the right places and resources with less delays.
To better understand what the barriers to [genetic] testing are.
Empower people to be able to ask questions.
Is it equity of access? I want to see equitable benefits.
'Closing the loop' as a standard; we must always feedback to the communities we work with.
Equal, fairer access to careers in genetics; attracting, developing, and retaining a diverse workforce to better serve our [NTGMS] diverse populations.
Empower the workforce and communities to reach equity
Earmarked and sustainable resourcing for equity.
I want the NTGMS to be a fairer and aspirational place to work, and to be anchored in the community, sharing knowledge confidently and sensitively, so we can ask questions. Let us be a genome service that is for everyone, at their time of need and provided in a way that makes sense.
Equity means engagement and we need to do more of this.
Improved upfront community engagement.
Change targets for consent conversations; resourcing time and targets will help improve equity.
To promote a holistic understanding of societal factors impact health, recognising intersectionality, and addressing health inequity through equal quality education so everyone can navigate the system, access services, understand their health and ask questions.
I want the next generation to see people like me and know that they, too, can become scientists.
To improve how we work through stronger integration between the workforce and service users.
We have, and link ethnicity data, across health records.
Challenge if we have a fair and transparent recruitment process, and make the needed changes.
Equal, fairer access to careers in genetics; attracting, developing, and retaining a diverse workforce to better serve our diverse populations.
Provide guidance or a framework of how research can be more representative of our population.
I want to see leadership roles reflect the diversity of our population. This can bring equity, as decisions can be informed by lived experiences rather than relying on extrapolation.
Every clinical staff member across the NTGMS can use the [Equity of Access] dashboard to analyse patient demographics relevant to their testing activity at key points in the pathway. This functionality will support analysis in equity of access/accessibility, enabling a deeper understanding of testing pathways and prioritising interventions to deliver equitable genomic testing.
Improve awareness of the benefits of genomic testing, for patients and staff.



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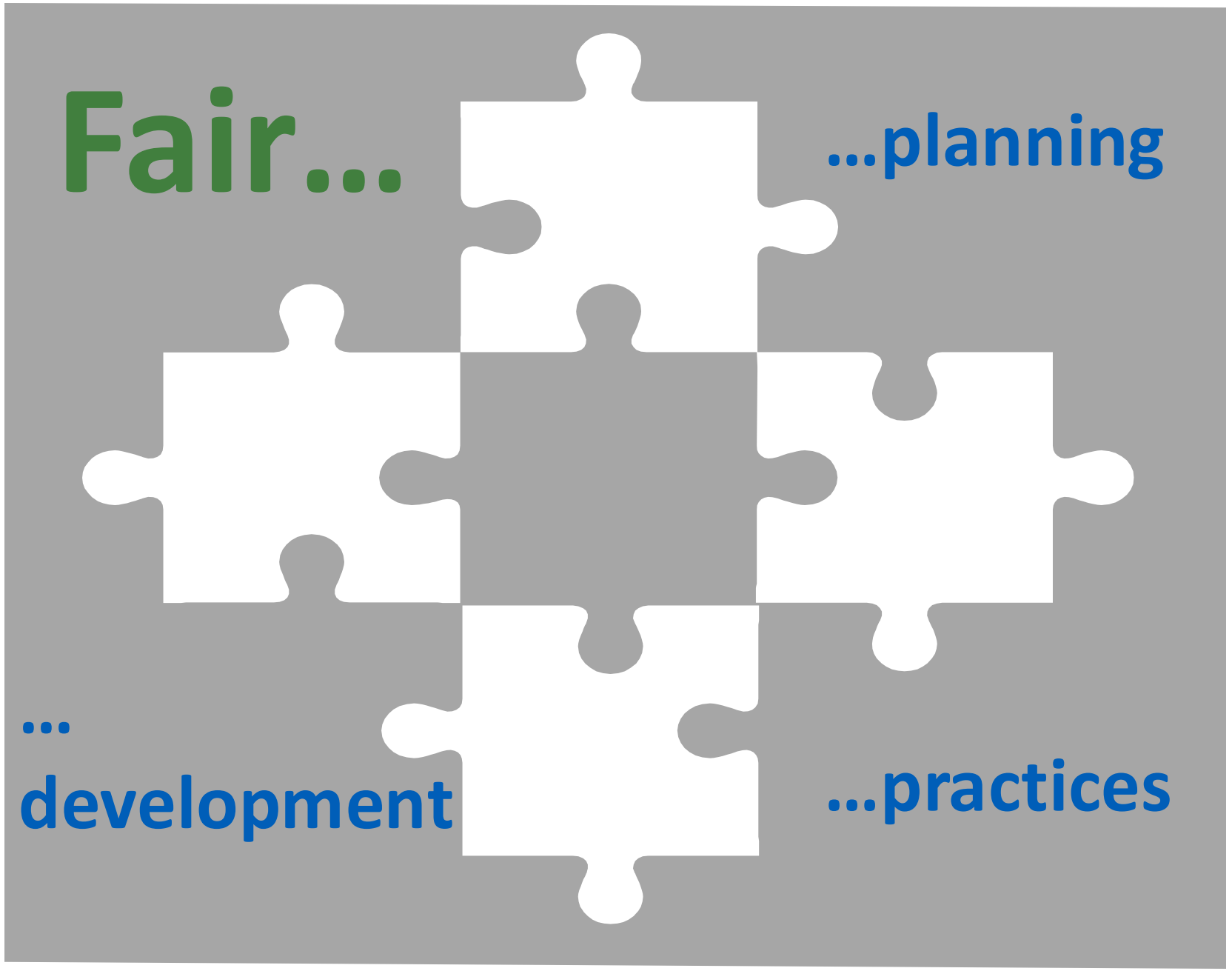

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Pillars

Initial activities were outlined during the development of the 2022 strategy and follow-up of over **30 hours of stakeholder engagement** conducted between December 2024 to date. Pillars are defined through landscaping, activities and which groups sit together to deliver, as:

Community

Together within neighbourhoods

Understand neighbourhood-level experiences, to create collaborative resources that help to ask questions and make informed decisions, bringing equity into the work we do.

Workforce

Workforce for all

Support equity across the workforce through motivating, fairer workforce planning, development and practices.

Service

Accessible service for all

Improve aspects of data, structure and processes, to guide and equip equitable service delivery

Research

Representation in research

Embed equity into all research projects and programmes.

Framework/guidance > pilots > iteration > implementation > share & rollout > policy

Types of projects – will be contingent on partnership building, listening to people and patient-facing funding

Elements of a strategy

NTGMS Equity Strategy Workshop
Charles West Board Room (Level 2, Barclay House, GOSH)

NTGMS Equity Strategy Workshop

Monday, 31 March 2025 from 12:00 to 17:00
5 hours

Charles West Board Room (Level 2, Barclay House, GOSH)

Join Teams Meeting | Chat with participants

15 minutes before

Meeting Details | Meeting Insights (1)

Dear all,

Please accept this invitation to the NTGMS Equity Strategy Workshop.

This workshop will be held **in person at GOSH on March 31st from 12–5 PM. Lunch and afternoon tea will be provided.**

The workshop's goal is to finalise the core components of the NTGMS 5-year Equity Strategy and collaboratively brainstorm potential workstream activities.

The strategy is still evolving (thank you to all that have already inputted) as I engage with various groups and individuals across NTGMS over the next few months. But, I wanted to get this date in your diaries as early as possible. Further details, including the agenda and supporting materials, will be shared near the time.

Please accept or decline, so we have an idea of numbers. If you are unable to make it, but would like someone else to come along, let me know. Also, if you know anyone who would like to input into the strategy, please feel free to share their contact details and I can arrange a time to connect with them.

I'm looking forward to seeing you all on the day and working together to shape and implement the strategy.

Thanks and best wishes,
Shazia

Join in – Workshop

MARCH 31st
12-5
F2F
@BARCLAY HOUSE

shazia.mahamdallie@gosh.nhs.uk

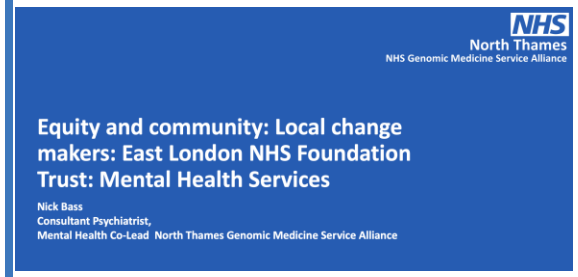
Reimagine

Equity

Today’s speakers followed by Q&A

Community

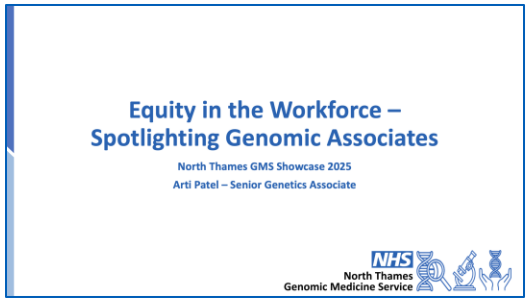
Together within neighbourhoods



Dr Nick Bass

Workforce

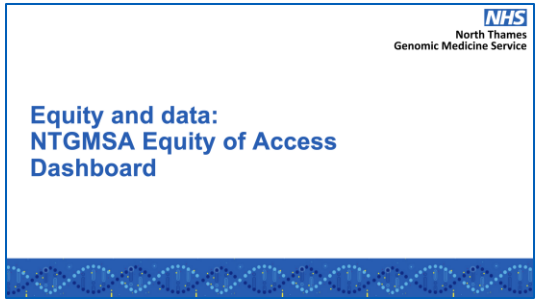
Workforce for all



Arti Patel

Service

Accessible service for all



Megan Luker &
Balbir Lehto

Research

Representation in research

Yvonne Muwalo &
Dominic Studart

Thank you

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Equity and community: Local change makers: East London NHS Foundation Trust: Mental Health Services

Nick Bass
Consultant Psychiatrist,
Mental Health Co-Lead North Thames Genomic Medicine Service Alliance

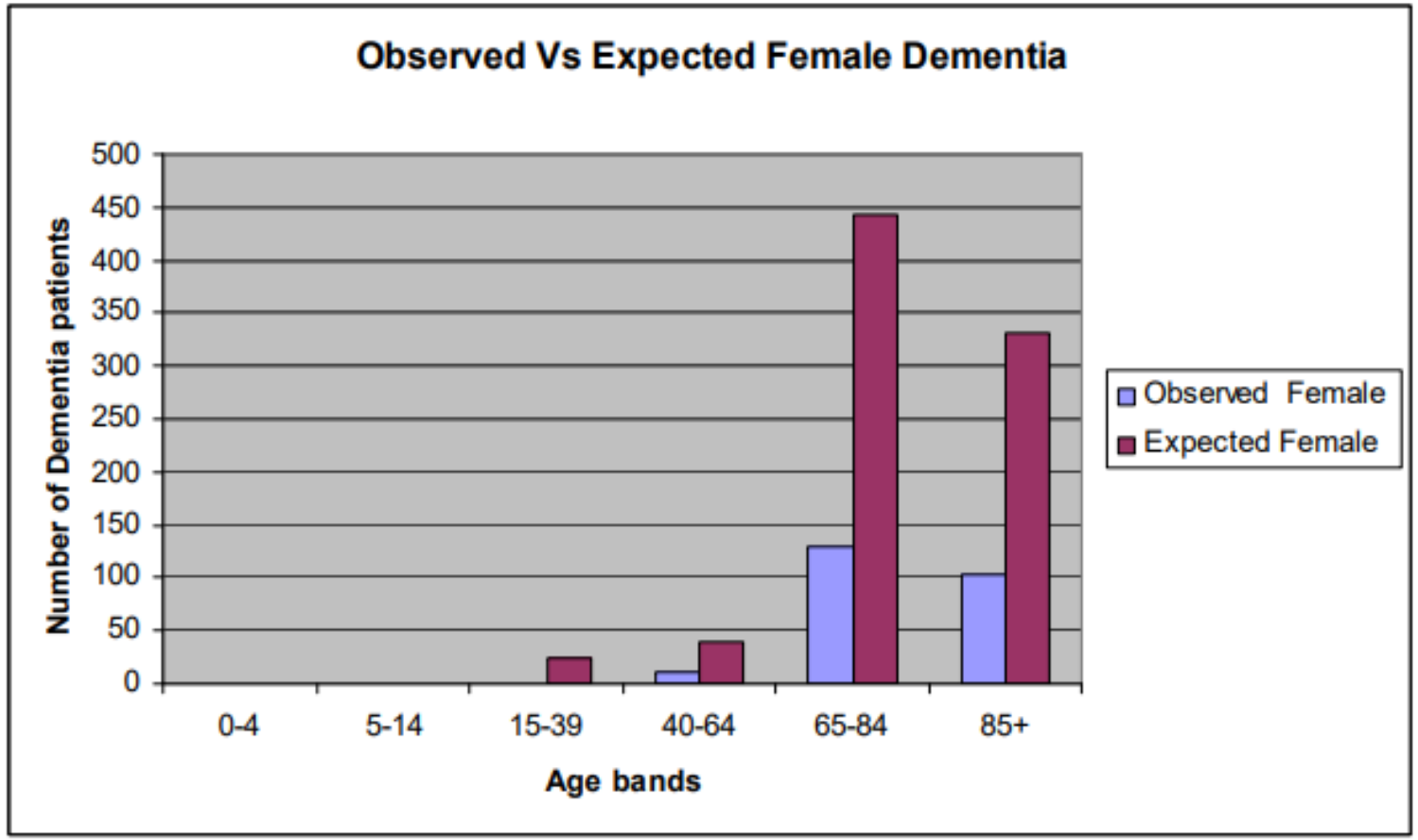
Hosted by NHS Great Ormond Street Hospital for Children NHS Foundation Trust

Tower Hamlets Memory Clinic: East London NHS Foundation Trust

Tower Hamlets 2008: Poor dementia KPIs

Only 33% of expected numbers of dementia patients are on GP registers

Figure 10: Observed and expected female dementia numbers in Tower Hamlets 2008



Dementia diagnosis and ethnicity: Identifying inequity

Table 9: Observed count of dementia by ethnicity 2007/08

Ethnicity	Male	Female	Total
Bangladeshi	36	39	**75**
Black	21	13	**34**
Incomplete	1	0	**1**
Mixed	1	1	**2**
Other Total	2	3	**5**
Not stated	0	4	**4**
Other Asian	2	5	**7**
White	94	160	**254**
Not Recorded	14	17	**31**
Grand Total	**171**	**242**	**413**

Source: CEG

Older People's Mental Health Needs Assessment For Depression, Dementia and Severe Mental Illness, October 2009

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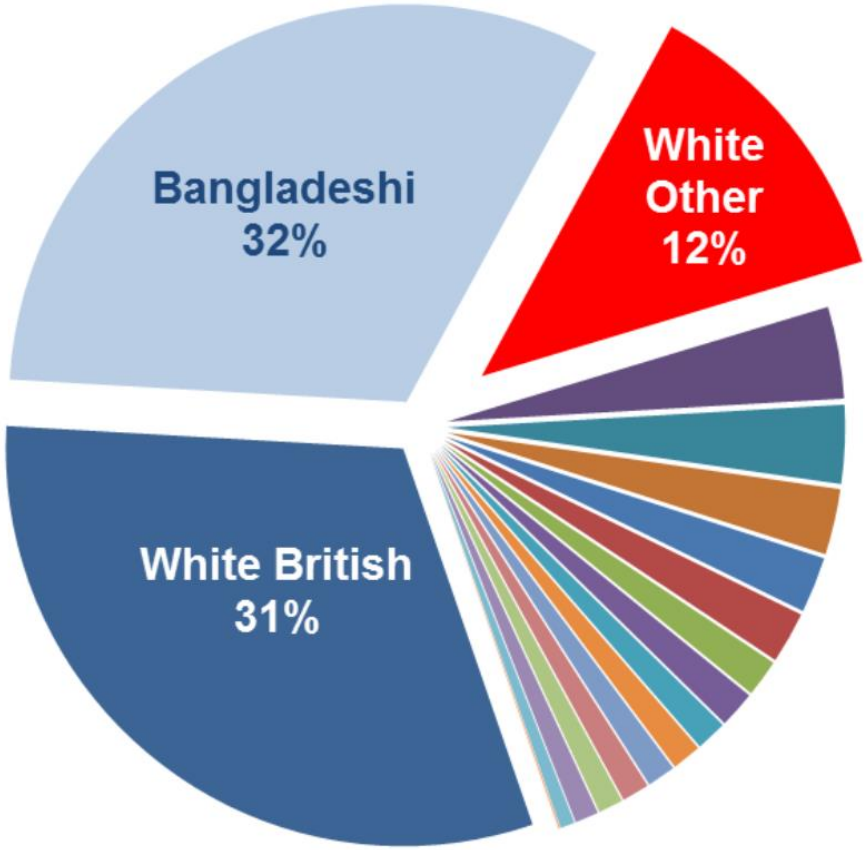
NHS
Great Ormond Street Hospital for Children
NHS Foundation Trust

Figure 2. Population by ethnicity, Tower Hamlets, 2011



2011 Census population = 254,096

White Other residents = 31,550

Source: 2011 Census (KS201EW).

Ethnic elders and late/non presentation to services

South Asians have similar (Bhatnagar and Frank 1997) or higher (McCracken et al. 1997) prevalence compared to the White British population

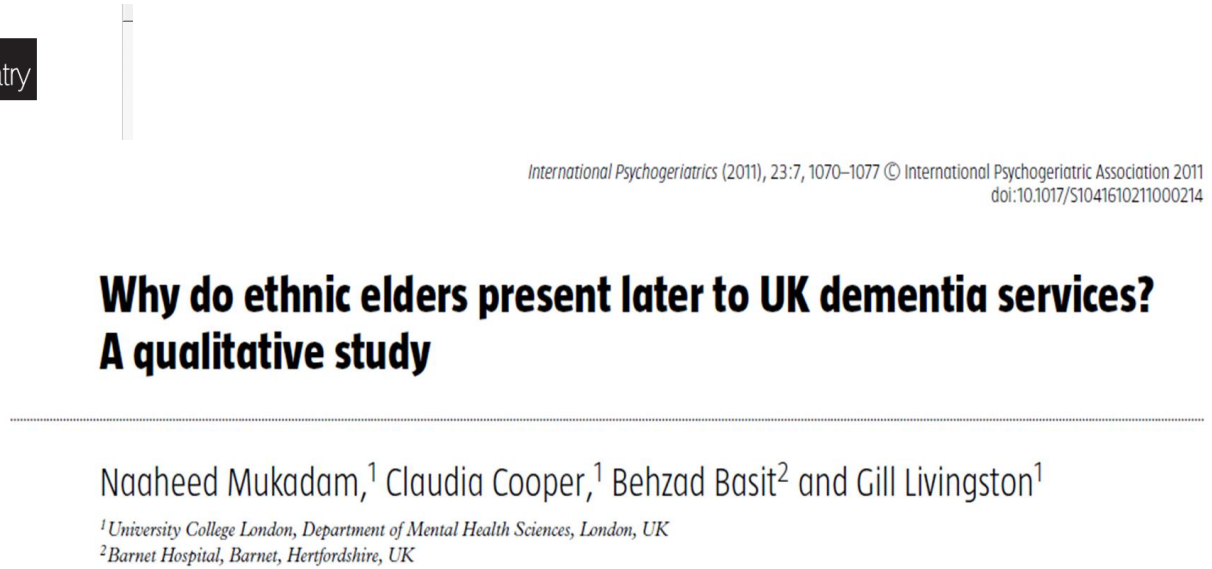
REVIEW ARTICLE

International Journal of Geriatric Psychiatry

A systematic review of ethnicity and pathways to care in dementia

Naaheed Mukadam, Claudia Cooper and Gill Livingston

Int J Geriatr Psychiatry 2011; 26: 12–20.



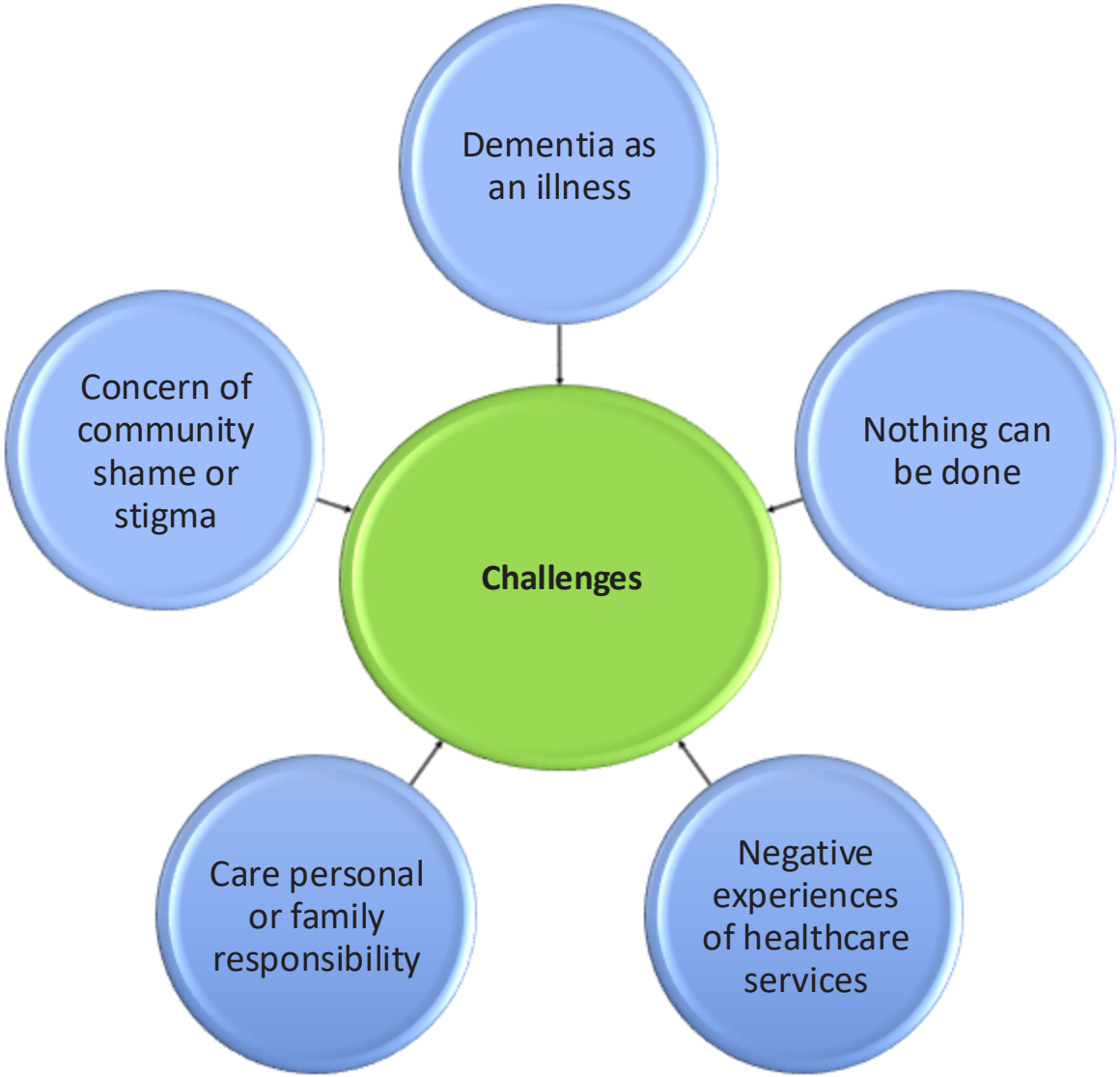
International Psychogeriatrics (2011), 23:7, 1070–1077 © International Psychogeriatric Association 2011
doi:10.1017/S1041610211000214

Why do ethnic elders present later to UK dementia services? A qualitative study

Naaheed Mukadam,[1] Claudia Cooper,[1] Behzad Basit[2] and Gill Livingston[1]

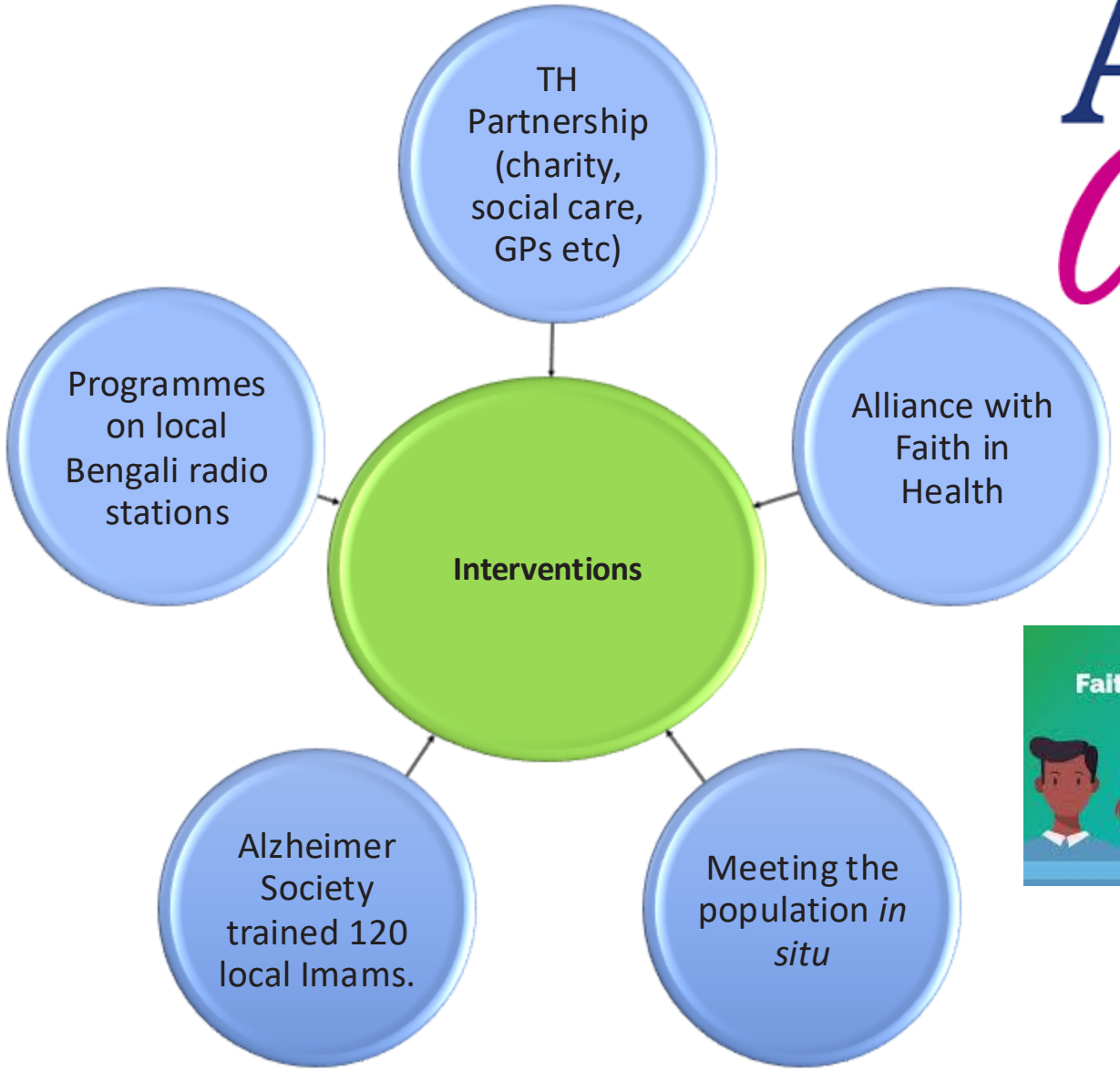
[1]*University College London, Department of Mental Health Sciences, London, UK*
[2]*Barnet Hospital, Barnet, Hertfordshire, UK*

Barriers to accessing services



Targeted community interventions: Partnerships and education

Alzheimer's Society



AGE Concern

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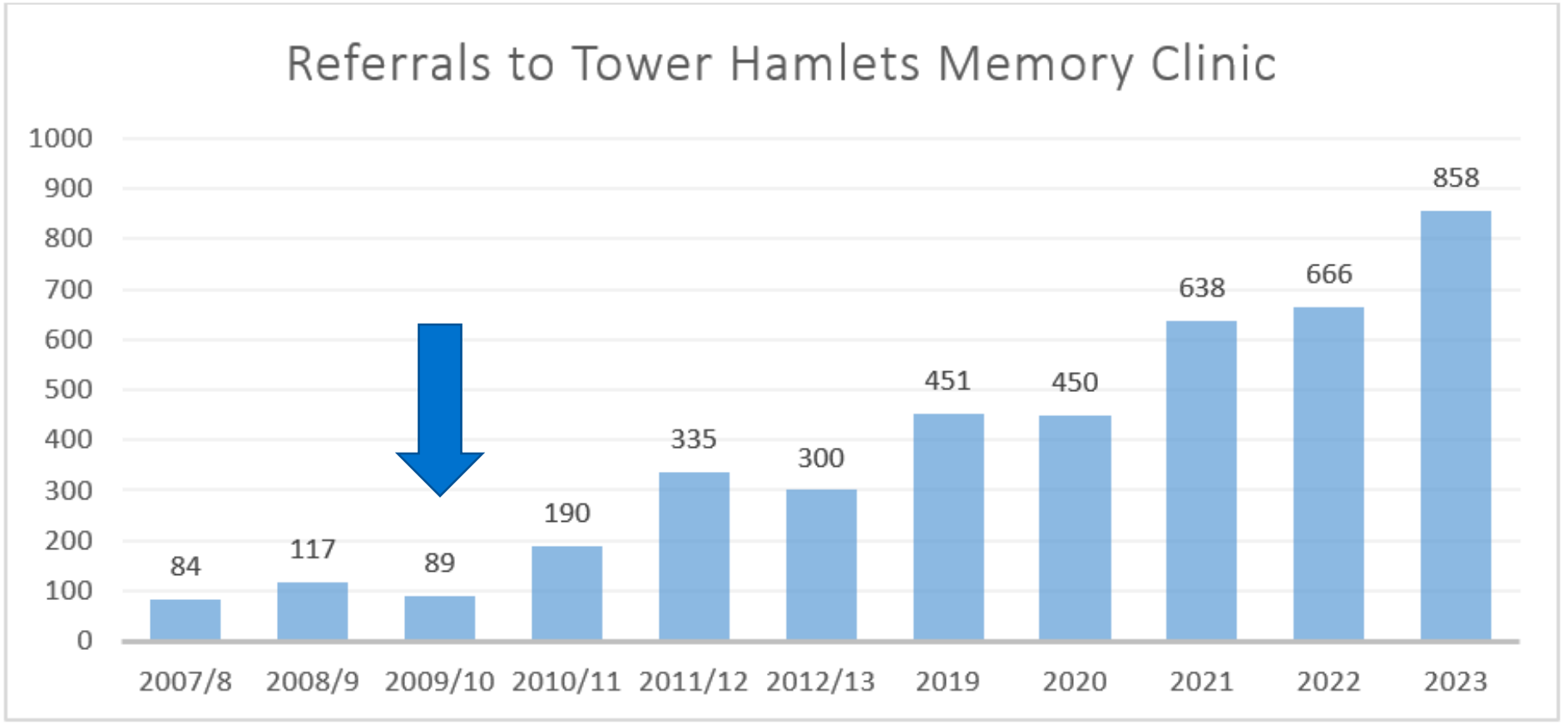
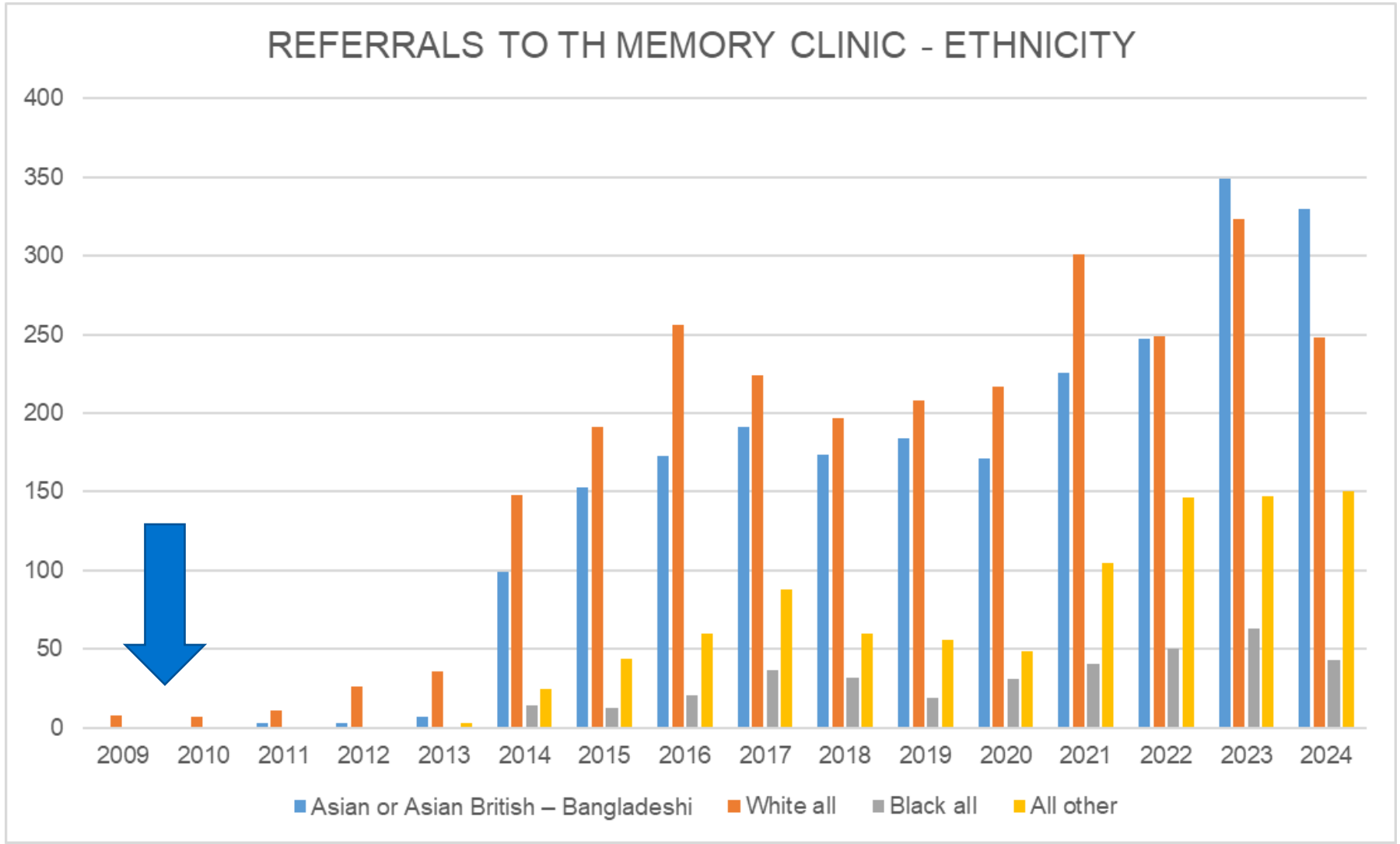
Hosted by NHS Great Ormond Street Hospital for Children NHS Foundation Trust

Impact: Overall referrals

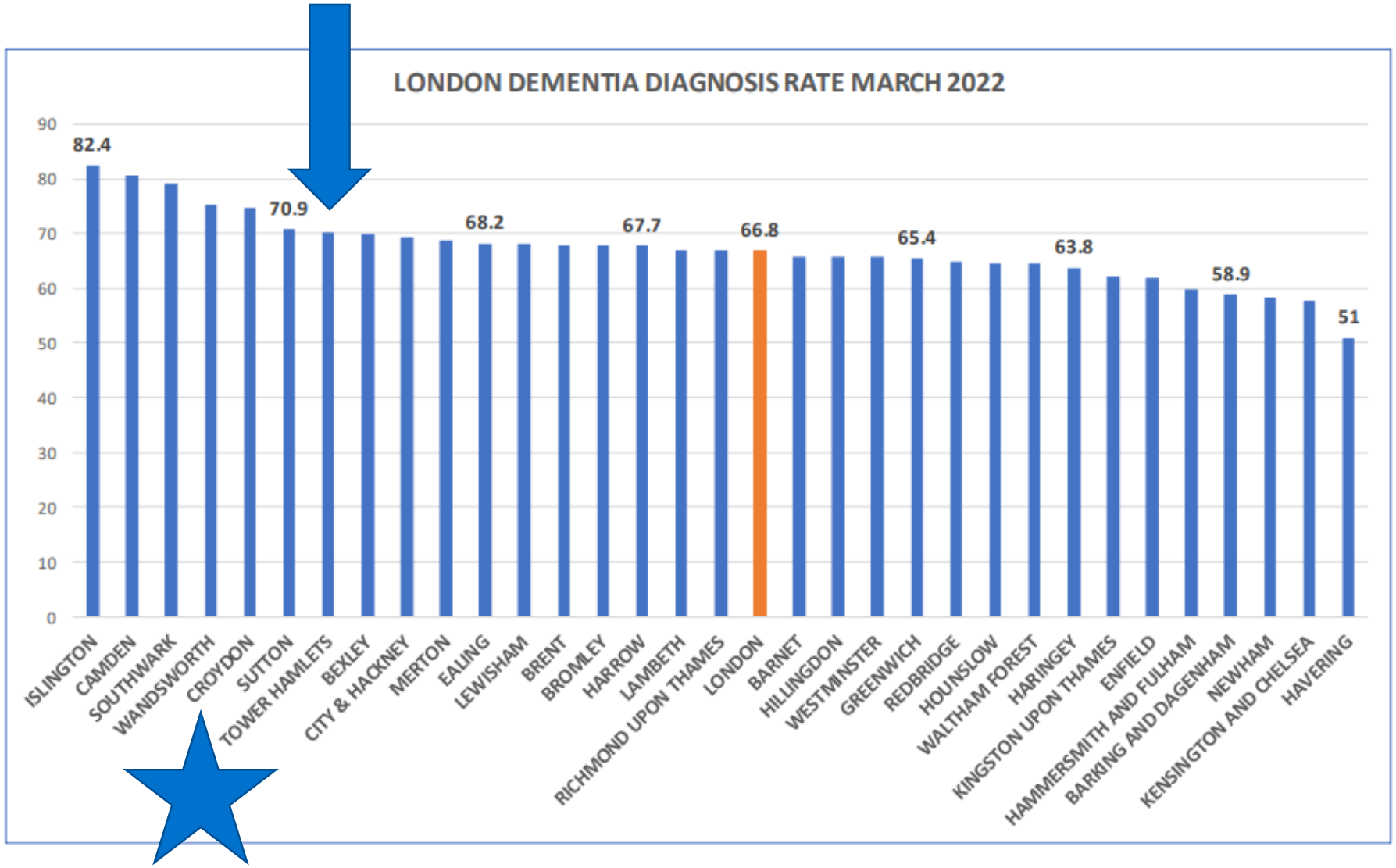
2007-2023



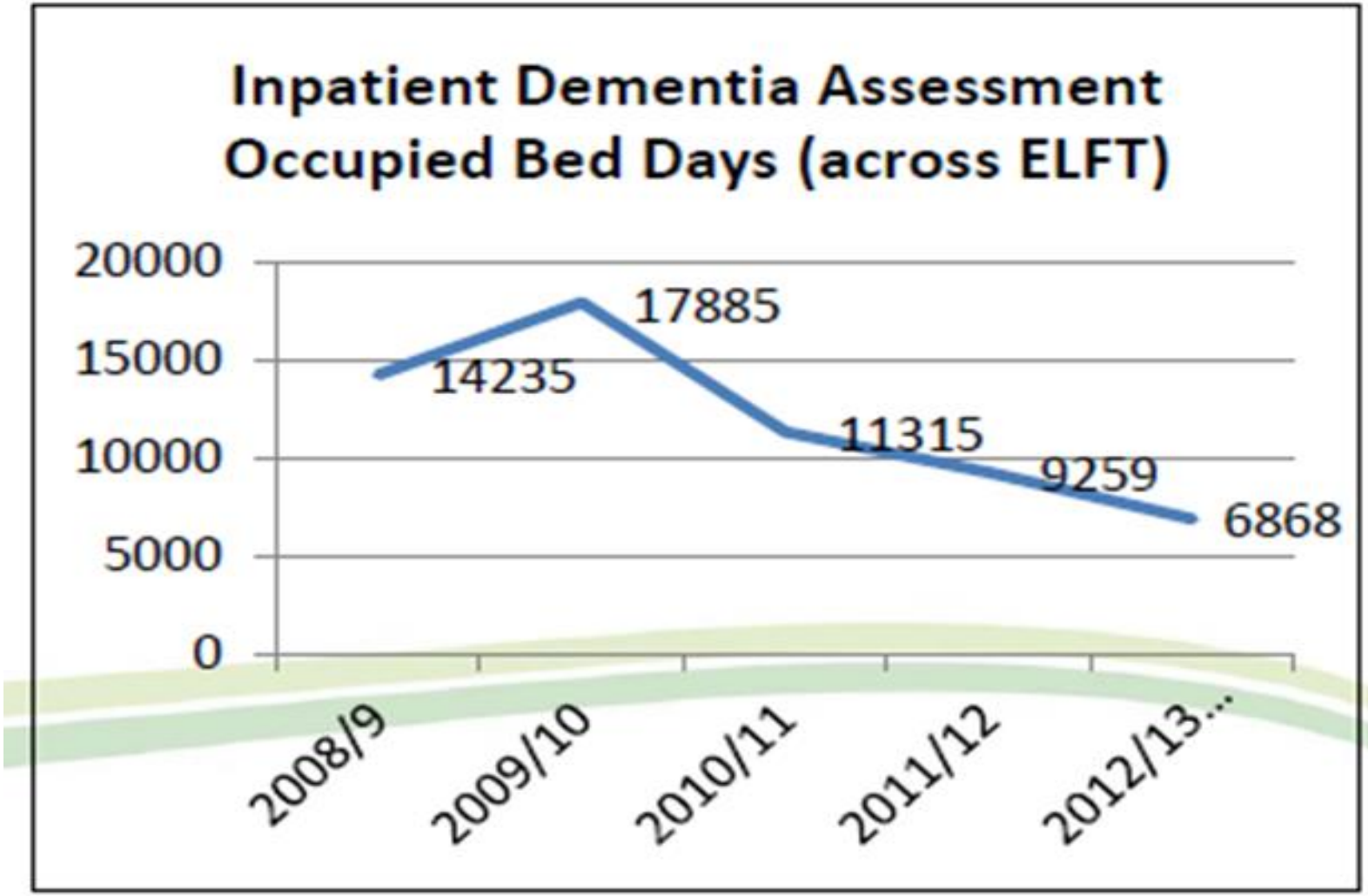
Impact on referrals from Bangladeshi community



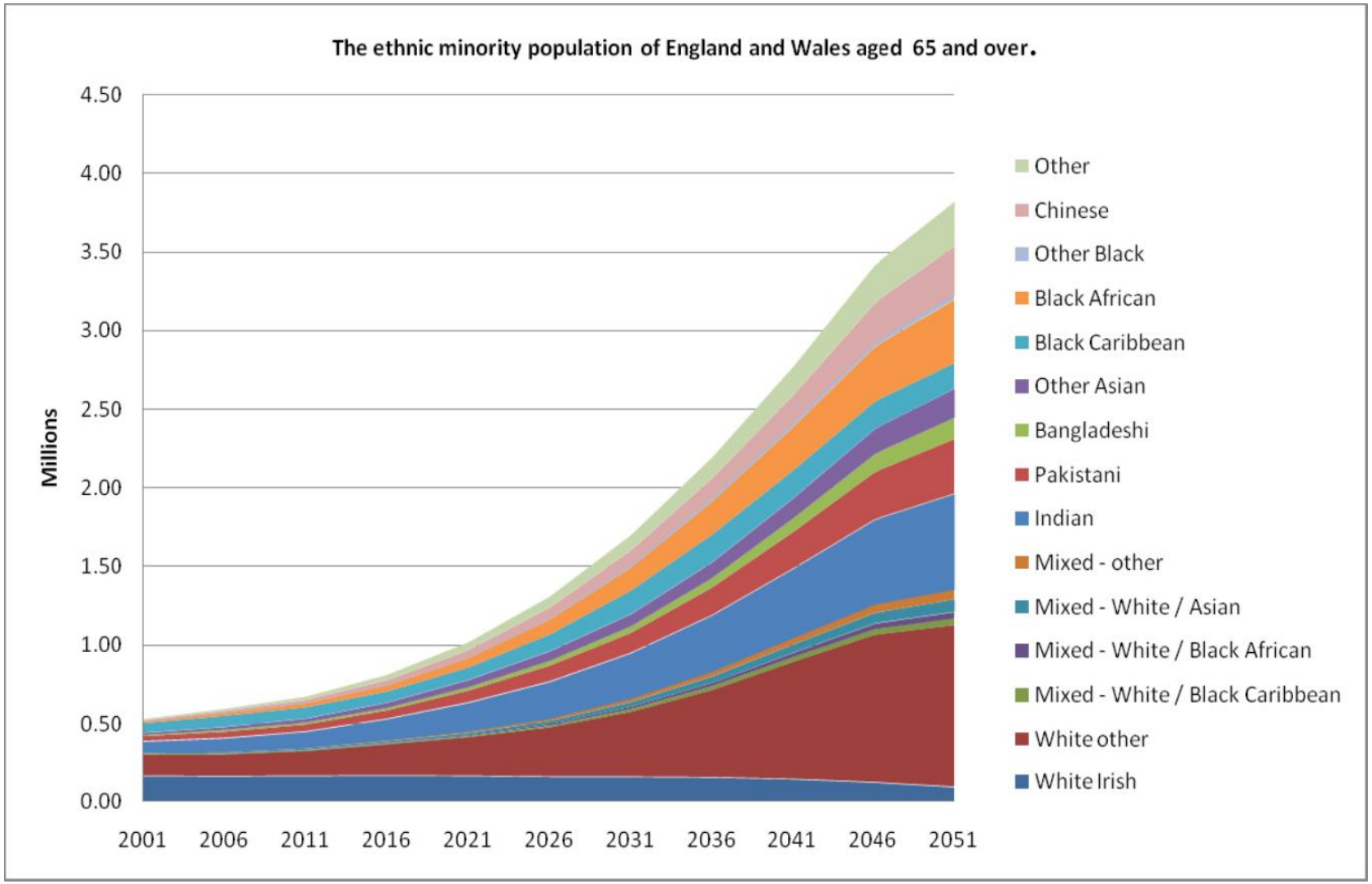
Dementia Diagnosis Rates – March 22



Impact on wider system?



Beyond the East End



- ~ 25,000 people from BME groups with dementia, ~ 172,000 by 2051
- Overall number of people in the UK with dementia projected to double by 2051
- Number of people in UK with dementia from BME groups projected to increase sevenfold
- Population as a whole will be more diverse as BME people move from inner city to suburban and rural area

Recommendations

Systems should:

- have **clear pathways to dementia assessment**
- have a **dedicated cultural worker** at primary care level to support referrals
- **audit** referral patterns, challenge are reflective of local demographics
- assessments and interventions that are **culturally appropriate**
- **cultural and linguistic skill provision**
- review access to **interpretation services** aligns to local language needs
- ensure GP practices adhere to **contractual requirements** of ethnicity data collection and provide additional guidance and resource to support this.

Observations

- Partnerships (Alliances) key
- Can’t just stay in the clinic
- Impact persists

None of this was my work!

Local Government Chronicle Award for Health and Social Care Partnership 2012

Corinne Drummond
Fiona Day
Norman Poole

Equity in the Workforce – Spotlighting Genomic Associates

North Thames GMS Showcase 2025

Arti Patel – Senior Genetics Associate

NHS
North Thames
Genomic Medicine Service

Introduction – My Journey

- My background: From patient advocacy to genomics
- The transition into the **Genomic Associate (GA) role**
- Why workforce equity matters in genomics
- My passion: **supporting patients with rare and undiagnosed conditions**

The Role of a Genomic Associate

- GenPAN – Genomic Practioners/Associates/Nurses
- **A hybrid role**: combining administrative, scientific, and patient support functions
- Key responsibilities:
  - Supporting **Whole Genome Sequencing (WGS) referrals**
  - Managing **WGS consent appointments**
  - Tracking **samples and results**
  - Liaising with **clinicians, labs, and families**
  - How we contribute to **patient care and diagnosis**

Supporting Patients with Rare and Complex Conditions

- Many families struggle for years to get a diagnosis – **diagnostic odyssey**
- **Genomic testing** can provide long-awaited answers
- The GA role in supporting these patients:
  - Ensuring **informed consent** and addressing concerns
  - Providing **clear explanations** about testing and possible results
  - Helping families **navigate the system**
- Equity challenge: **Not all patients access testing equally!**

Why Workforce Equity Matters

Workforce equity ensures:

- **Diverse perspectives** in patient support
- **Better understanding** of patient needs
- **Fair access to roles, training, and progression**

Current barriers:

- **Limited awareness** of GA roles
- Inconsistent **training and career pathways**
- **Progression challenges** – Where do GAs go next?

My Challenges & Barriers

- **Career transition** – Moving into genomics from a non-clinical background
- **Limited structured training** – Learning on the job vs. formal training
- **Progression uncertainty** – Lack of defined next steps
- **Equity in training** – Access to funded courses vs. self-directed learning

Good Practice & Positive Change

NT GMS initiatives:

- Structured **WGS referral training**
- Supporting **mentorship and networking**
- Encouraging **multi-disciplinary collaboration**

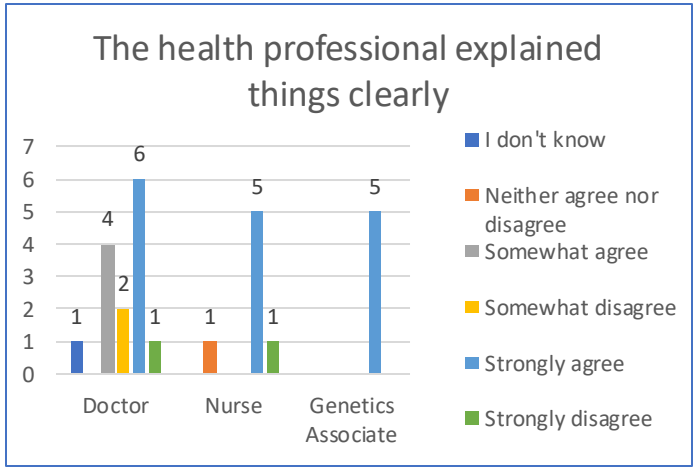
Broader initiatives:

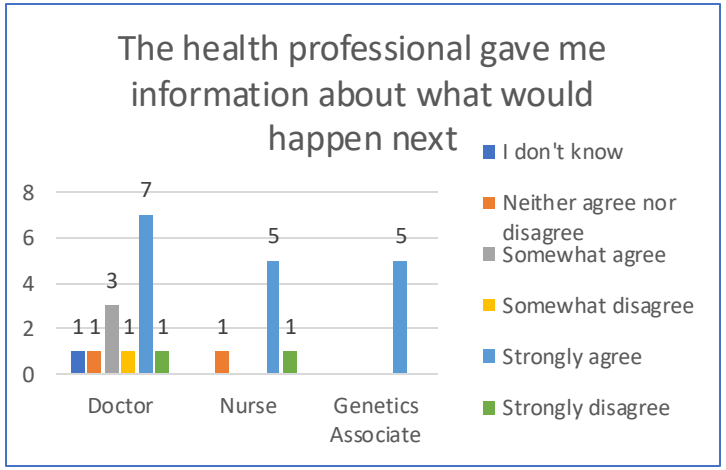
- National discussions on **career progression for GAs –** AGNC
- **Increased visibility** of GA roles in workforce planning

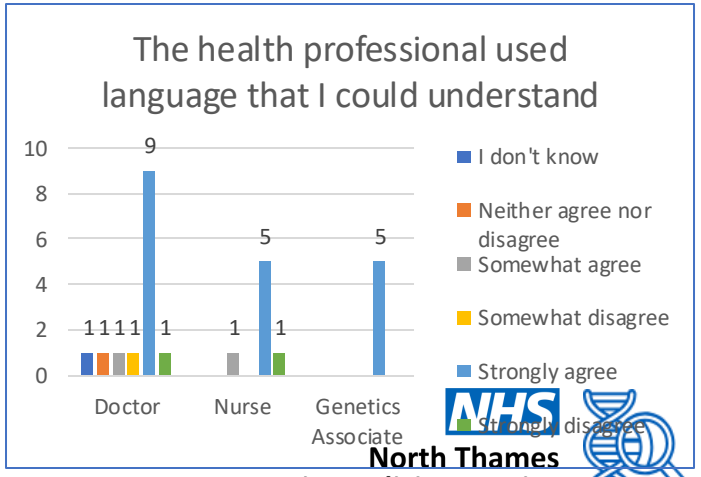
User feedback

Survey about Whole Genome Sequencing (WGS) consent process at NT GLH in 2022.

- The surveyed patients who were consented by Genetics Associates experienced a **more thorough WGS discussion**.
- Team could be used both to **facilitate consenting** of WGS and **training** of other healthcare professionals.







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Mapping Career Pathways – The Next Steps

- Reviewing entry-level access and increasing **awareness of GA roles**
- Standardising **training pathways** across GMS
- Identifying internal and external opportunities for training
- Facilitating **CV enhancement & skill-building** aligned with national job descriptions

Addressing Barriers & Achieving Equity

What needs improvement?

- **Clear career ladders** for progression beyond GA
- **Recognition of the GA role** in genomics workforce planning
- **Funding & access to training** – making development **inclusive**
- Embedding **equity and diversity principles** into workforce planning

My vision for the future:

A workforce that is:

- **Diverse** – reflecting the patient communities we serve
- **Supported**- with structured training & development
- **Valued** – as essential contributors to genomics services

Ensuring all patients, regardless of background, have equitable access to genomic services

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Conclusion & Call to Action

Equity isn’t just about access—it’s about empowerment.

We must:

1. Open doors to diverse candidates
2. Standardise training and career pathways
3. Invest in Genomic Associates as a long-term workforce solution

Let’s work together to build a fairer, more inclusive genomics workforce!

Thank you!

Arti Patel – Senior Genetics Associate

arti.patel@gosh.nhs.uk

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Equity and data: NTGMS Equity of Access Dashboard
Using PLCM and Population data for Equity of Access

19th March 2025

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Summary

- Introduction to Patient Level Contract Monitoring (PLCM), population data sources and the North Thames GMS Equity of Access dashboard – Megan Luker NT GLH Data & Performance Analyst
- Using the dashboard in the GMSA – Balbir Lehto NT GMSA Information Analyst

NT Equity of Access dashboard

Data Sources:

- Patient Level Contract Monitoring (PLCM) genomic testing activity data
- Index of Multiple Deprivation (IMD) – GOV.UK
- Mid-year population estimates – Office for National Statistics (ONS)
- Regional Ethnic Diversity publication – GOV.UK
- Household Language Data – Census 2021

Data sources – Genomics Patient Level Contract Monitoring (PLCM) dataset

Laboratory service providers

- Receive referral (electronic, paper, internal/external to Trust)
- Perform genomic activity (Prep, Test, Report) and record in LIMS
- Submit PLCM extract in line with NHSE Reporting Specification to GLH via Azure

North Thames GLH

- Process and store PLCM extracts from service providers
- Send collated North Thames dataset to NHS England for monthly statutory submission
- Analyse data for:
  - Turnaround Time Performance monitoring
  - Activity monitoring
  - Clinical Indication testing pathways – equity of access

Genomics Unit (NHS England)

- Publish activity data
- Monitor data quality, activity, finance and performance
- Cost and volume tariff payments

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North Thames Genomic Laboratory Hub - Providers

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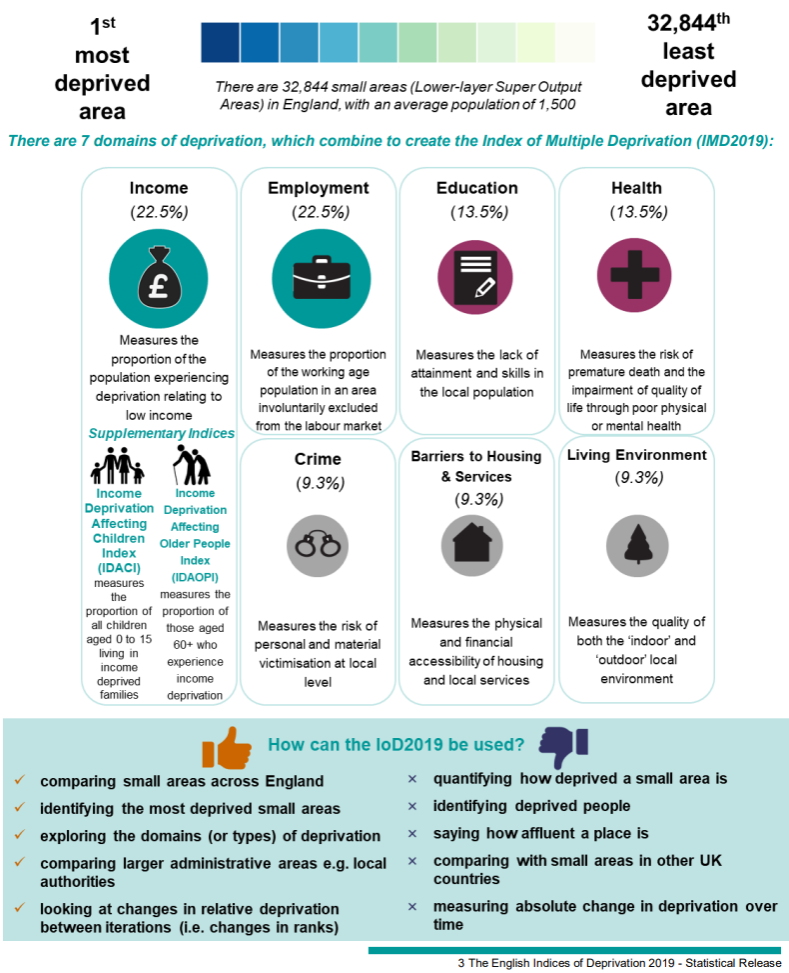
Data sources – Genomics Patient Level Contract Monitoring (PLCM) dataset

- Activity stage (wet lab/analysis)
- National Genomic Test Directory code (including clinical indication)
- Test method
- Patient demographics (age, postcode, ethnicity, gender)
- Ordering Trust
- NT GLH service provider
- Turnaround times

Index of Multiple Deprivation (IMD)

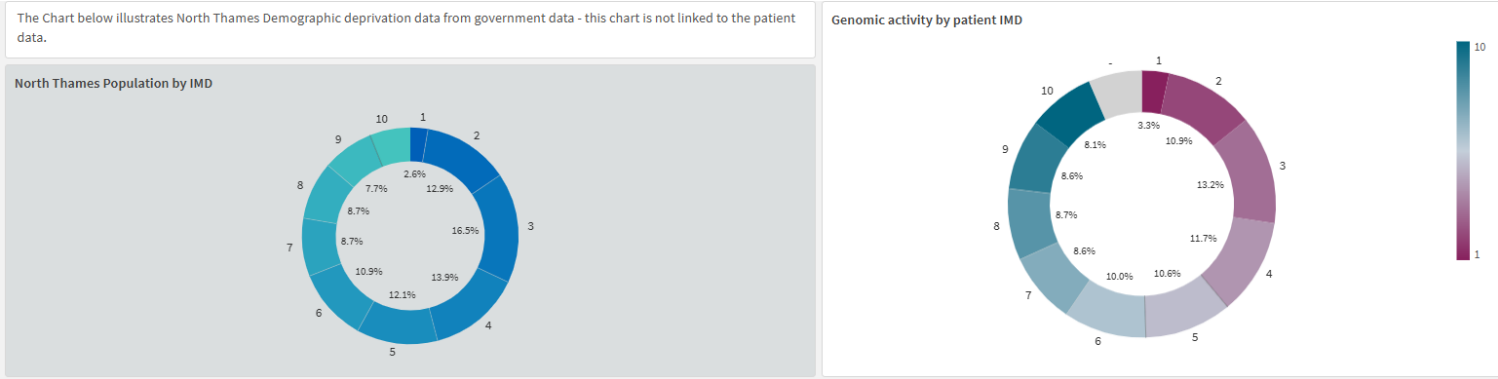
- Official measure of relative deprivation in England published by GOV.UK, based on 39 indicators, organised across seven domains of deprivation which are combined and weighted to calculate the IMD.
- Each small statistical area (LSOA) is ranked and assigned a decile. Each LSOA has a population of approx. 1,000 – 3,000 individuals. There are 33,755 LSOAs in England.
- The deciles are grouped from 1 (most deprived) to 10 (least deprived).



Further information here: [English indices of deprivation 2019 - GOV.UK (www.gov.uk)]

NT Equity of Access dashboard

- Interactive Qlik Sense dashboard displaying PLCM genomic testing activity data alongside North Thames population demographic data.
- Ability to filter by Test Code, Time Period, Ordering Trust, Patient Demographics (as IMD decile, resident borough)
- Patient demographics:
  - Age group, gender, ethnicity as reported in the PLCM
  - IMD Decile and resident borough, derived from demographic datasets using patient postcode in PLCM



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Data Quality Limitations

PLCM:

- NHS Number/Local Patient Identifier is not 100% complete. When counting patients, only approx. 93% of activity can be counted.
- Patient postcode is ~93% complete and valid.
- Ethnic group is ~30% complete.

Lack of information with referral, or complexities of data recording and reporting in LIMS.

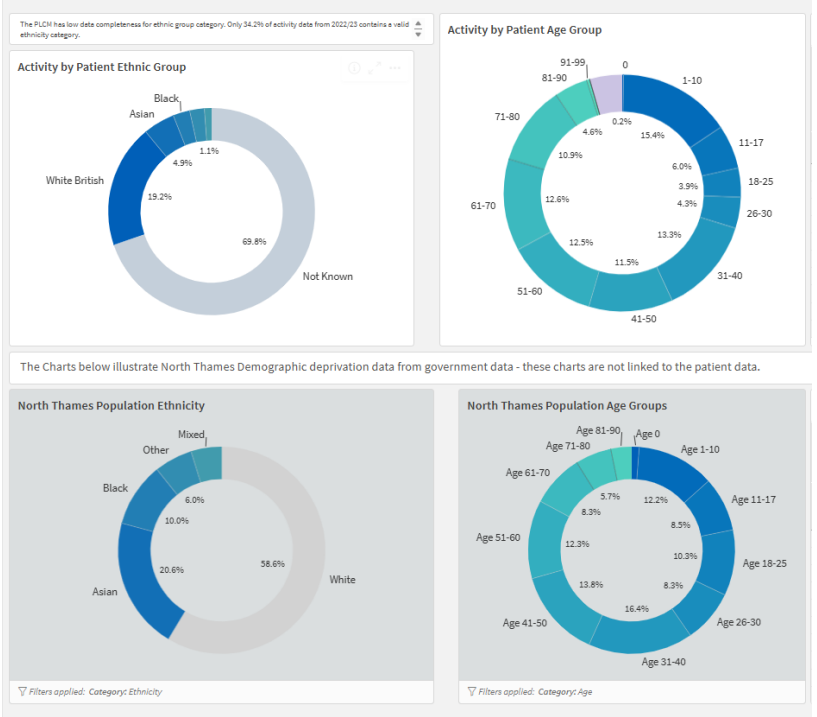
GLH Data Quality Improvement working group meets with each laboratory service provider monthly to ensure data quality issues are being addressed where possible.

North Thames Demographics:

Defining North Thames population for Equity of Access:

a) Patients living in boroughs within North Thames region

b) Patients referred from North Thames Trusts



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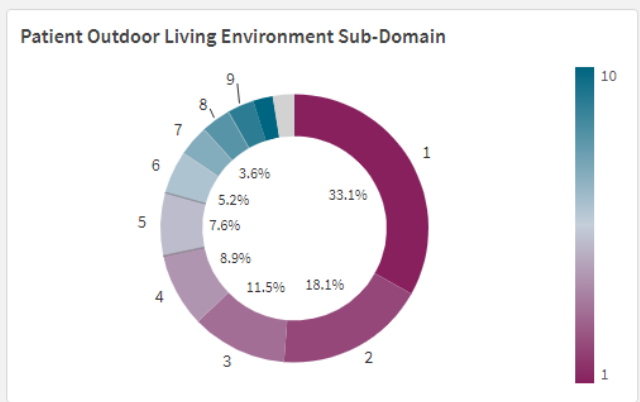
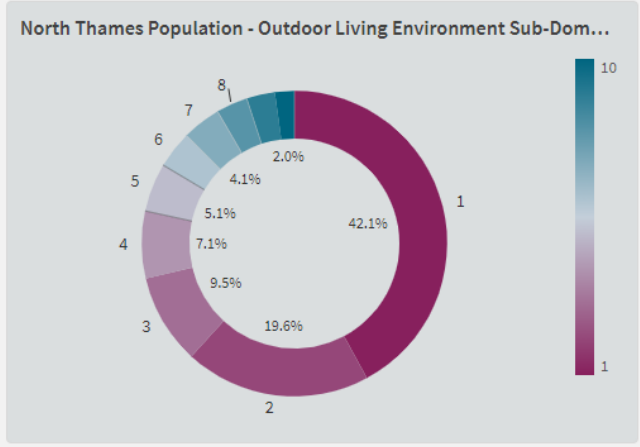
Scenario A: Patients receiving M4 non-small cell lung cancer testing

- Analysis request from Genomic Pharmacist: Number of M4.1 and M4.2 tests performed and deprivation index for the patients tested vs index of general local population.
- Outdoor living domain is a measure of air pollution and particulates.
- Data showed smaller (~10%) but similar percentage of patients in most deprived areas as the general NT populace
- What does this tell us?





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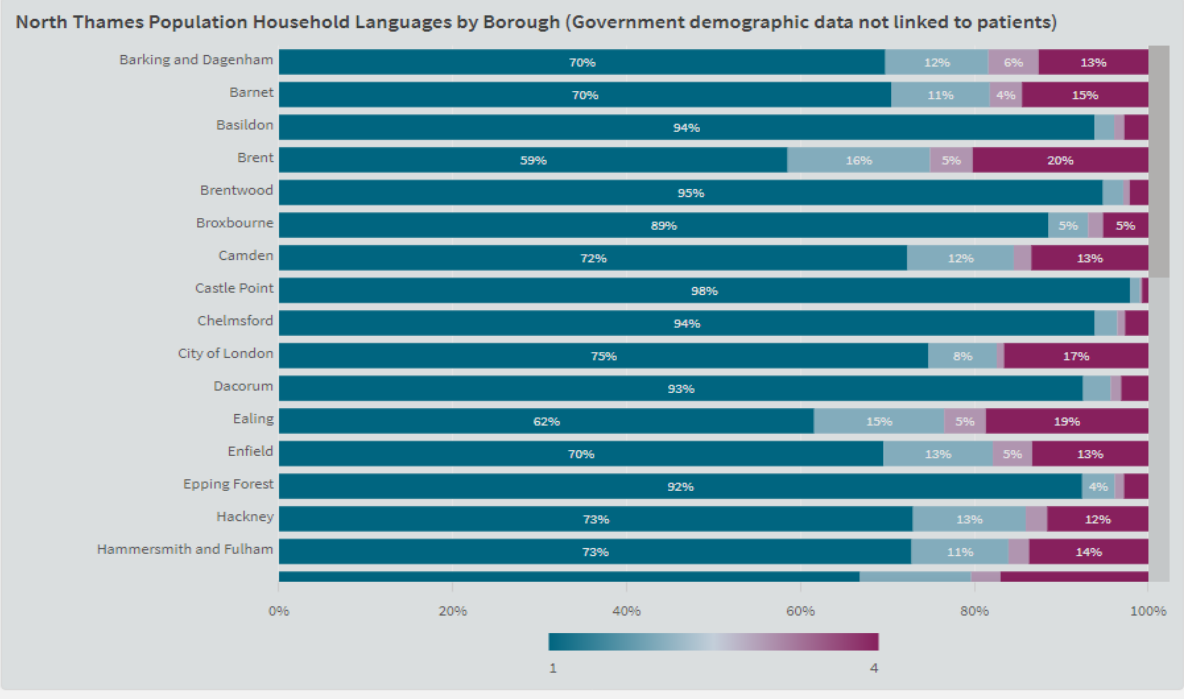
Scenario A: How did Genomic Pharmacist use this data

The data was used to understand the following:

- The level of testing conducted within different areas
- Does socioeconomic impact help provide answers e.g., do more deprived areas mean greater number of smoking related lung cancer
- The data will be used against a local service evaluation to understand number of tests requested verses the number of patients accessing treatment
- To enable non genomic testing data to be cross referenced with PLCM data to enrich the information obtained from a local level vs regional vs national data sets

Scenario B: Education and language demographics of North Thames population



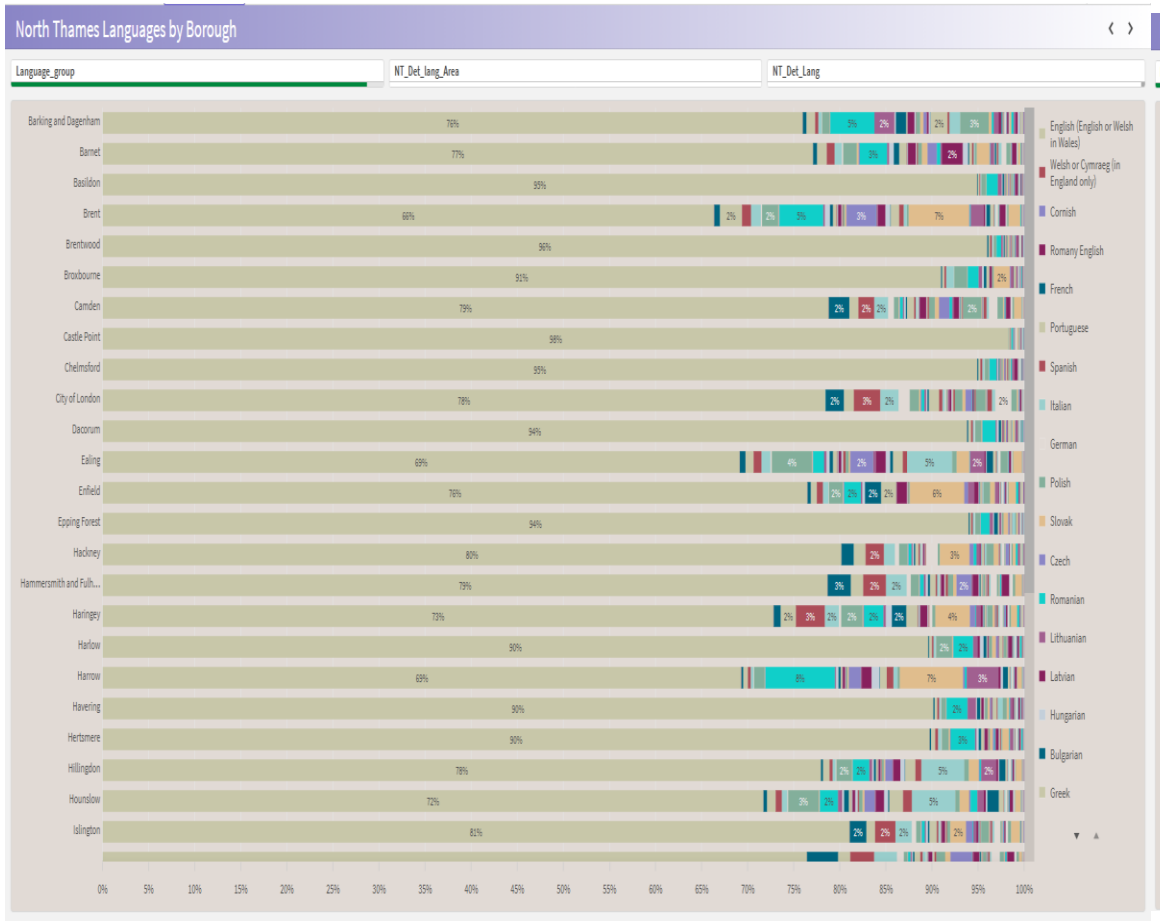
This stacked chart shows the proportion of Households that fall into one of the Language categories defined below:

The Household language categories are defined as:
1 = All adults in household have English in England, or English or Welsh in Wales as a main language
2 = At least one but not all adults in household have English in England, or English or Welsh in Wales as a main language
3 = No adults in household, but at least one person aged 3 to 15 years, has English in England or English or Welsh in Wales as a main language
4 = No people in household have English in England, or English or Welsh in Wales as a main language

This data is taken from The 2021 Census data (Household language - Office for National Statistics (ons.gov.uk))

- English Language household skills by borough (all adults, 1 adult, a child, no one)
- We can use this data to target patient outreach more effectively

North Thames Languages by Borough



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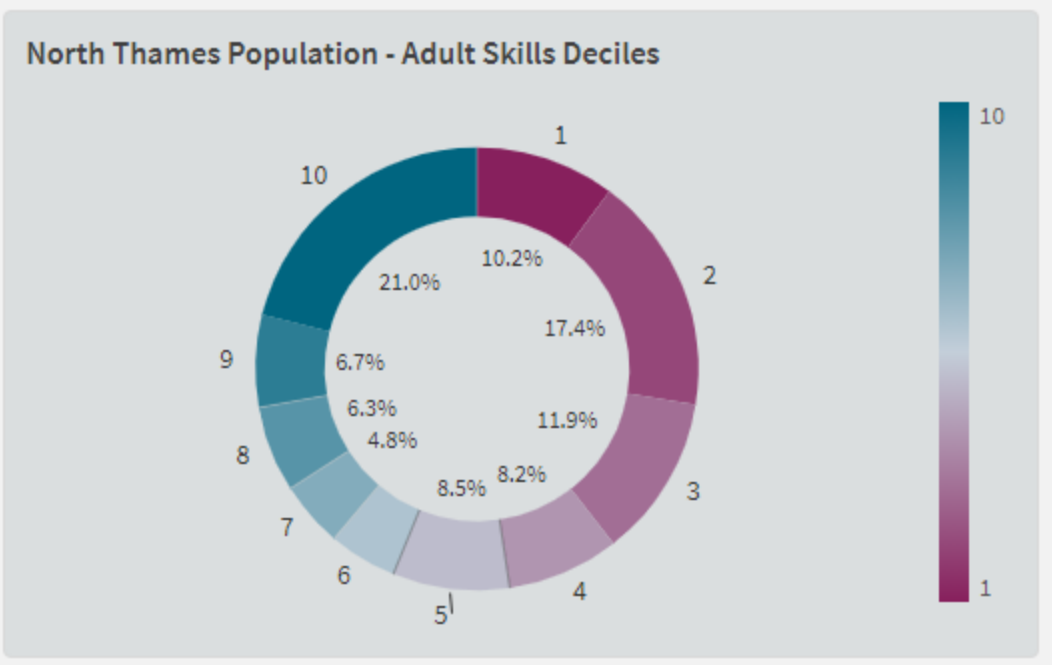
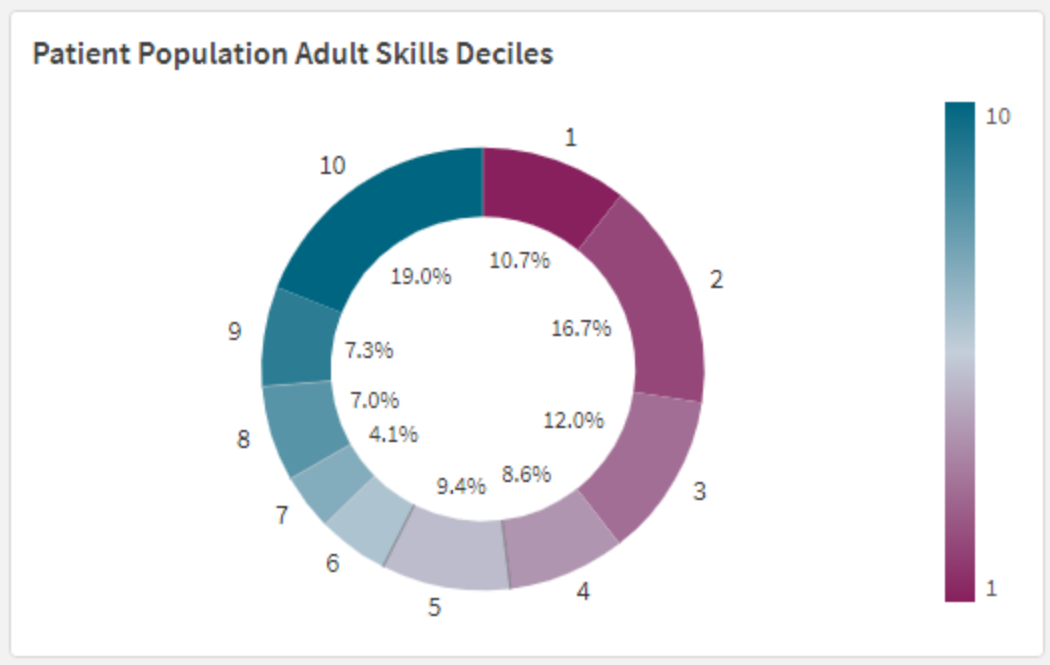
Tower Hamlets– Adult skills deciles

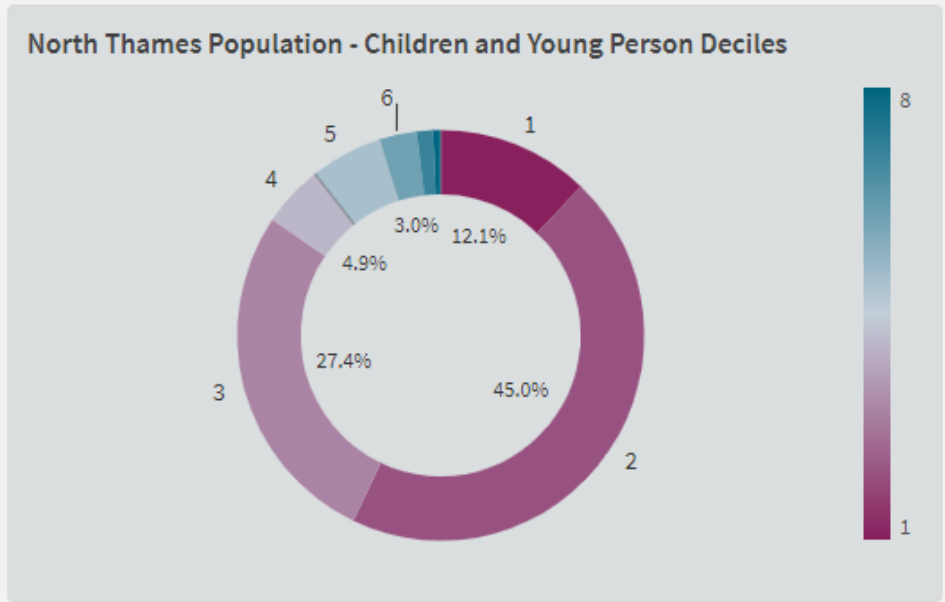


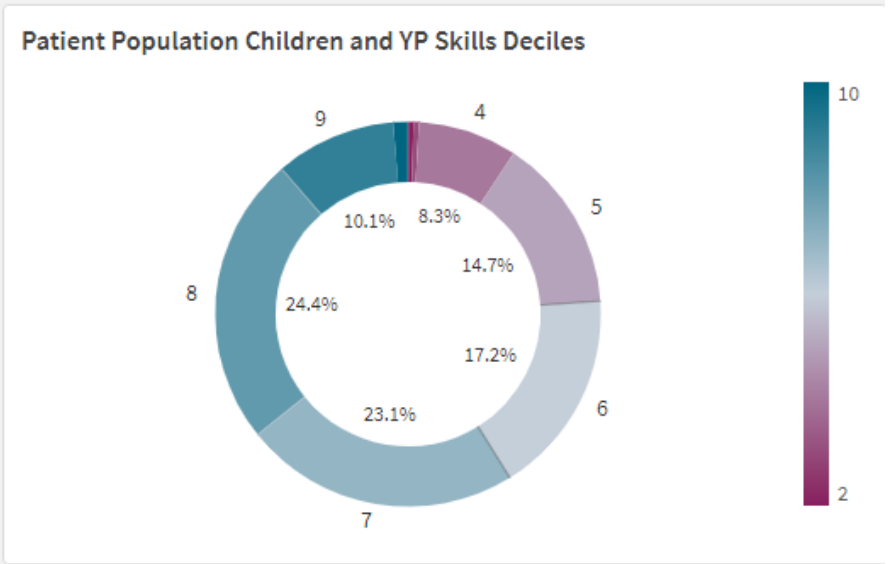


- In this case the patient population deciles are evenly represented in comparison the local population demographics – is more data needed?

Tower Hamlets: Young person Education skills and attainment

- Use to guide how education may be provided to the population
- Is there under representation in testing for young people in lower skills deciles?





Education, Skills and Training Deprivation Domain

The Education, Skills and Training Deprivation Domain measures the lack of attainment and skills in the local population. The indicators fall into two sub-domains:

1.relating to adult skills:

-The adult skills indicator is the proportion of working-age adults (women aged 25 to 59 and men aged 25 to 64) with no or low qualifications. The English language proficiency indicator is the proportion of the working-age population who cannot speak English or cannot speak English 'well'.

2.relating to children and young people:

-The indicator measures the proportion of young people not staying on in school or non-advanced education above age 16, based on receipt of Child Benefit. Shrinkage has been applied to this indicator.

-The indicator measures the proportion of young people aged under 21 not entering higher education.

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Using EoA app for EDA

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Genomics England | Generation Study

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Equity in Research: Can the Generation Study do better?

Yvonne Muwalo & Dominic Studart

Regional Results Co-Ordinators, North Thames GMSA

What is the Generation Study?

The Generation Study

- A long-term research study

- Aims to understand if we can improve how we diagnose and treat genetic conditions by looking at the DNA of newborn babies

- Involves collecting a blood sample after birth to read a baby's genome.

Genomics England

HS
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About Genomics England

- Owned and funded by the Department of Health and Social Care
- Sponsor and coordinator of the study

Mission

To support an evolution in genomic healthcare

To accelerate genomic research

Genomics England

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JCB0

Current NHS Newborn Blood Spot (NBS) Screening Programme

Newborns can currently be screened for nine conditions via a blood spot test.

There is a 97% uptake of newborns screening in the UK

> "There is a clear potential for genomics in the testing for many of the conditions currently included in the blood spot test."
>
> **Generation Genome**

- Sickle cell disease
- Cystic fibrosis
- Congenital hypothyroidism
- Phenylketonuria
- Medium-chain acyl-CoA dehydrogenase deficiency
- Maple syrup urine disease
- Isovaleric acidaemia (IVA)
- Glutaric aciduria type 1
- Homocystinuria
- In service evaluation for SCID in 2/3rds of England)

NHS screening currently only looks for these conditions, rather than screening the baby's genome. We are testing a broader approach.

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Conditions we test for

200+ rare genetic conditions

- Usually appear in the first few years of life
- Can be improved if found early
- Have treatment through the NHS

Learn more:
https://www.genomicsengland.co.uk/initiatives/newborns/choosing-conditions

The locations of our study

NHS sites **throughout England**

Recruitment will be in stages

- Start with 3-5 trusts
- Increase to 25-40 trusts

How we choose locations depends on

- Birth volume
- Diversity of people who use the hospital
- Maternity department performance

Is genomics research equitable?

Acknowledge longstanding issues in genomics, healthcare and research

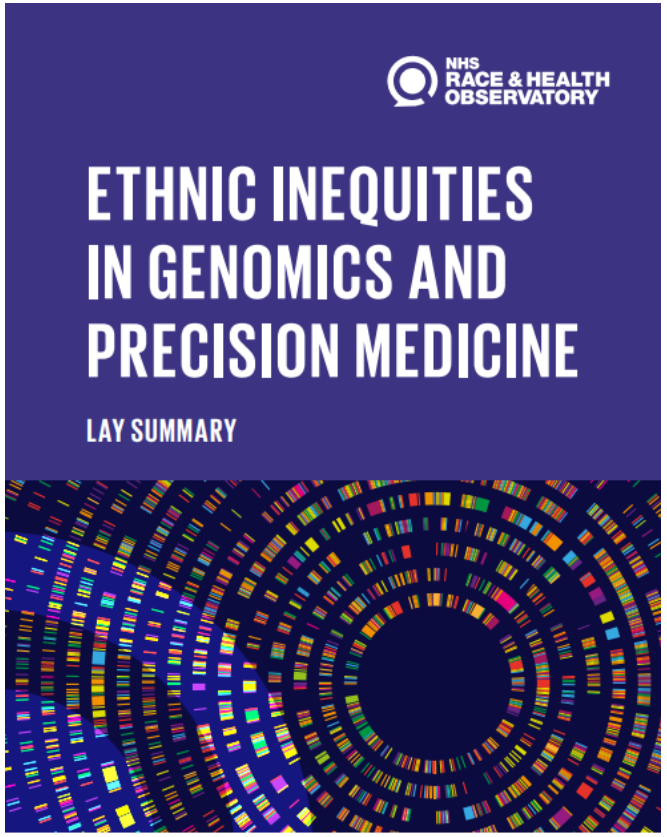
What are the longstanding issues?

- Stigma around health and disease
- Language barriers
- Health and genomics literacy
- Lack of representation
- Cultural awareness
- Lack of trust due to historical mistreatment – genomics and eugenics
- Institutional mistrust
- Not understanding the health system and that research is part of the health system
- Not appreciating that all healthcare is based on research

Inequity in Genomic Healthcare

"ethnic minority groups are hugely underrepresented in precision and genomic medicine research, which has negatively impacted health outcomes"

- GWAS studies (2016) 81% of European bio-geographical ancestry, but Europeans are 16% of the global population.
- gnomAD (2023) 77% European vs 5% African or South Asian ancestry.



RHO-Genomics-Report-Lay-Summary-June-2024.pdf

NHS Race & Health Observatory Equity in Genomics Recommendations:

- When researchers engage with the public and patients, their ideas and concerns should be considered to make taking part in research more accessible.
- Involving people from ethnic minority groups in genetic research and services requires financial, resource and personnel investment.
- Clear plans which suit each community should be made and these should be assessed regularly. These plans need to be sustainable and scalable to improve engagement with ethnic minorities.
- It is important to take time to reflect about past events to build trust with individuals and communities to break down barriers. These barriers usually arise from previous mistrust, discrimination, fear, and bad experiences.
- For these barriers to be addressed, decision-makers, researchers and healthcare professionals need to openly listen so that they can be more aware of the challenges experienced by ethnic minority communities.

How is the Generation Study aiming to improve representation in research?

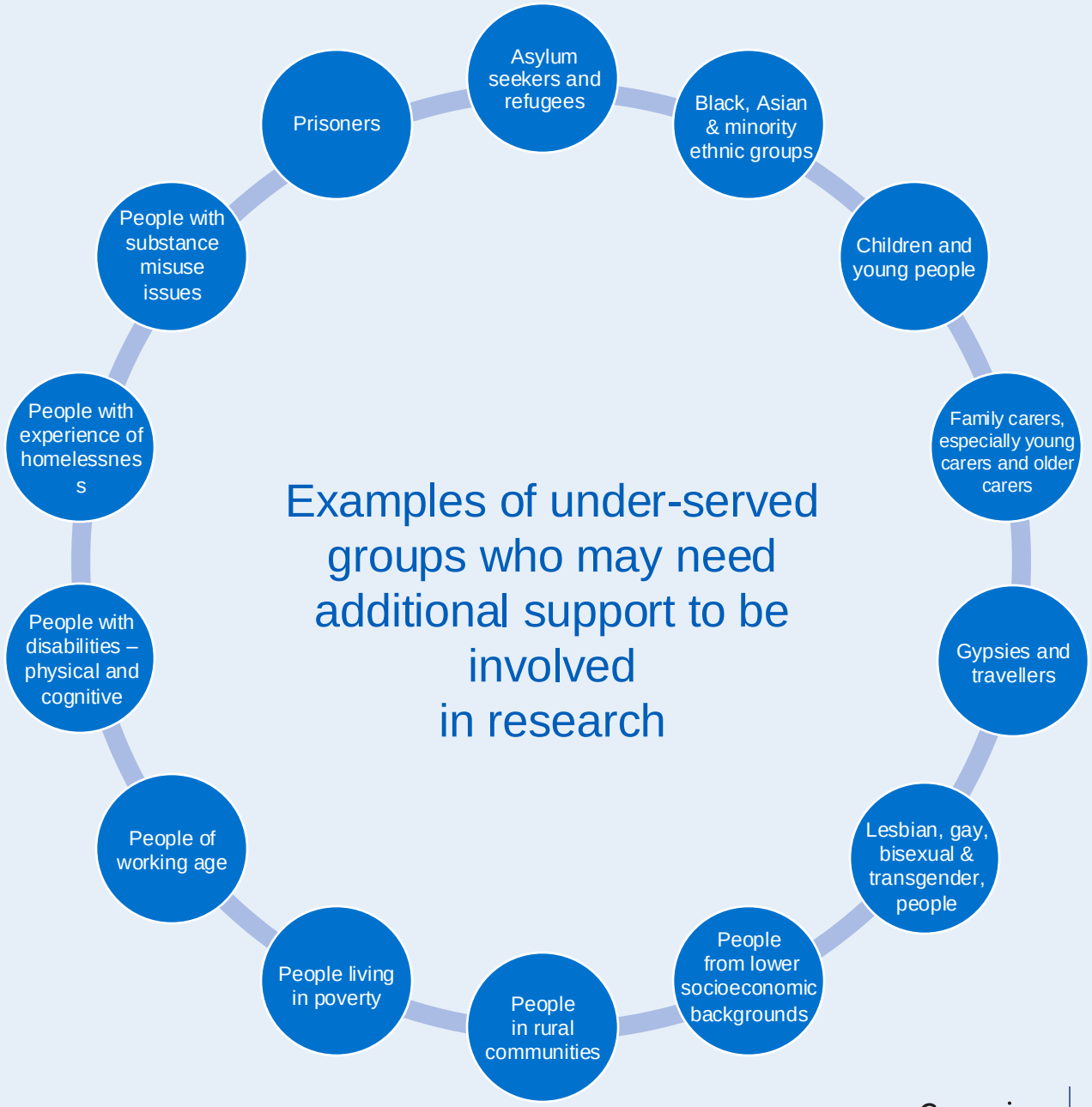
An approach driven by co-design, ethics and engagement

- **Strong governance** including NHS England, the UK National Screening Committee and Department of Health & Social Care
- **Expert working groups** supporting study design, including Recruitment, Ethics, Conditions, Education and Training, Evaluation
- **Public dialogue** and engagement initiatives focussing on:
  - Condition selection
  - Discovery research
  - Research participation in diverse communities
  - Implications of storing a baby's genome over their lifetime
- **User research** with 145 parents and a range of healthcare professionals to inform study design and continue through delivery

Equitable participation within the Generation Study

Under-served groups:

- Are less included in research than expected based on population estimates.
- Healthcare needs are not matched by the amount of current research occurring for them.
- Have important differences in how they respond or engage with health care interventions.



Key Messages

Generation Study Approach

- Aspire to build equity into the study at every opportunity.
- Acknowledge longstanding issues in genomics, healthcare and research.
- Understand that we cannot single-handedly rectify these issues.
- Endeavour to create opportunities to improve equity in health research, reducing inequalities where we can, and not further impacting disparities already present.

Supporting Equitable Recruitment

How was this embedded during the design of the study

Eligibility Criteria

Facilitating access for those particularly vulnerable, experiencing homelessness, and/or asylum seekers, and refugees, to still be able to participate

Interpreters

Available via local sites to communicate the recruitment materials

Translated Materials

Available in 11 written languages

Accessible Language

To avoid excluding those who have low health literacy, or are from lower socioeconomic backgrounds, including a 4-minute explanatory video of the study on our website.

Travel

Parents are not required to undertake additional travel to consent or provide samples, and reimbursement provided to attend initial consultation after condition-suspected result

Planned Pilots

*this work on-going and happening in real-time so may change in-line with insights gathered

National level

Developing a community champions network of black mothers

- Working with the motherhood group and starting with 5 champions as a pilot.
- Building trust and awareness and understanding of the study.
- Well connected with the birthing population.

Regional level

Understand the experience of recruitment for the black mothers in London

- SE GMSA in partnership with London Inspire.
- Workshops/focus groups.
- Using data to explore positive and negative experiences about the experience of recruitment and how they want to hear about the study.

Local level

Exploring the use of a specific engagement methodology - Peer and Audio-Visual Engagement (PAVE) in supporting underserved communities

- Focusing on the Muslim population in Birmingham
- Exploring the use of PAVE to see how different audio and visual material about genomics and the Generation Study are engaged with.

Current availability of translated materials

- 10 professionally translated PIS's on the website and available in print
- Website translates into over 150 languages via Google Translate
- QR code sheet directs users to translated PISs
- YouTube's subtitles can be applied to the video in over 150 languages
  - We acknowledge there are some limitations with the auto-translate functions on Google and You Tube

NHS Race & Health Observatory Equity in Genomics Recommendations:

- When researchers engage with the public and patients, their ideas and concerns should be considered to make taking part in research more accessible.
- Involving people from ethnic minority groups in genetic research and services requires financial, resource and personnel investment.
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- For these barriers to be addressed, decision-makers, researchers and healthcare professionals need to openly listen so that they can be more aware of the challenges experienced by ethnic minority communities.

Can the Generation Study do better?

Is this what equity looks like?

No clear initiatives for recruitment to reflect the populations:

- No incentives for equitable recruitment
  - Funding based on number of samples received
- Not all languages covered in translated materials
  - Does not account for genomic literacy within spoken language
  - Does everyone read an information leaflet?
- Study elevator pitch
  - Takes far longer to explain a study through an interpreter
  - Much easier to recruit English speakers to achieve targets

What do we think could be improved and how?

What could be better?

What could be built into a **research framework** for future studies:

- Funding should support all recruitment activity
- Specific funding to support equity
- Inbuilt funding for interpreter services
- An equity ‘weighting’ for funding – funding currently standard nationally regardless of regional and local population demographics
- Standardised screening process to make data auditable
- Equity subgroup now in place. But an expert working group on equity should be in place at the start of the study design.

North Thames Equity work

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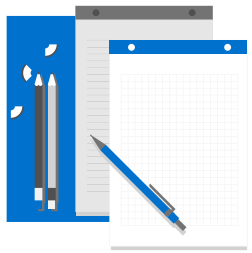
North Thames Generation Study Equity Strategy

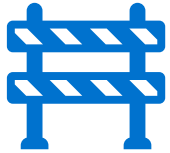


Plans that suit each community

Openly listen so that they can be more aware of the challenges

Identify concerns

Identify resources



Break down barriers and build trust

North Thames Data

To support equitable access, we need baseline data

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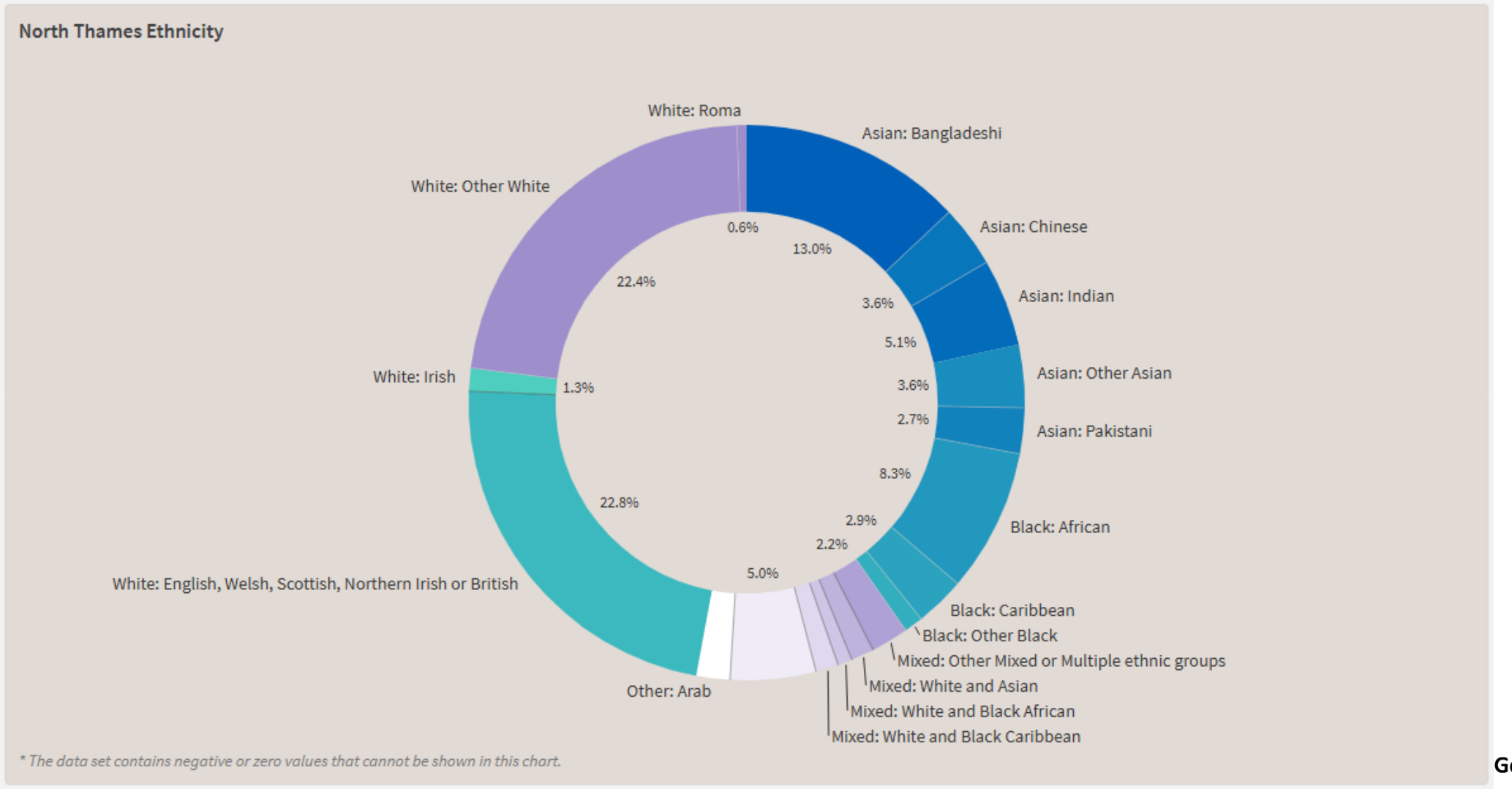
North Thames Ethnicity: Females aged 16 to 50



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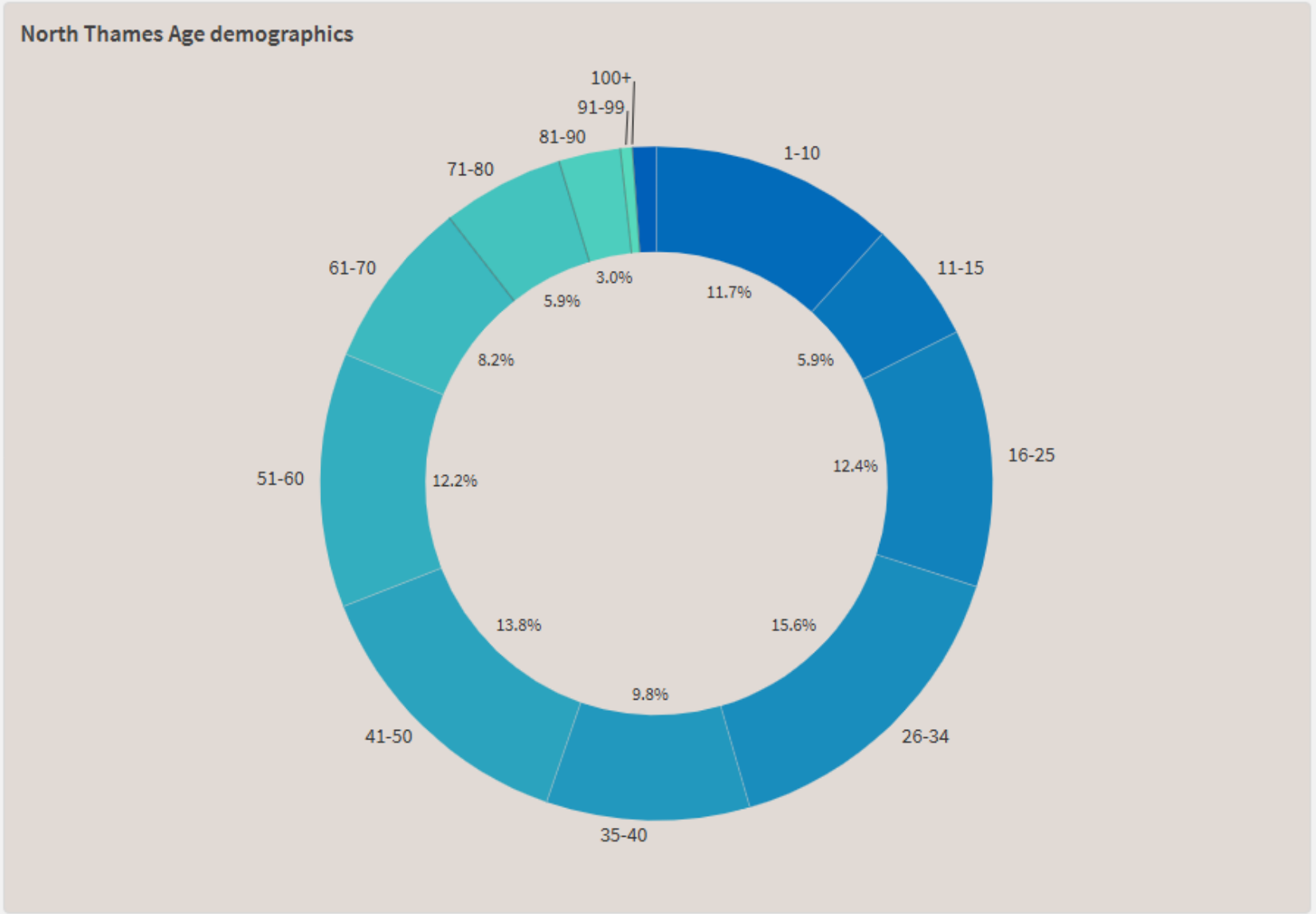
North Thames: Age Females



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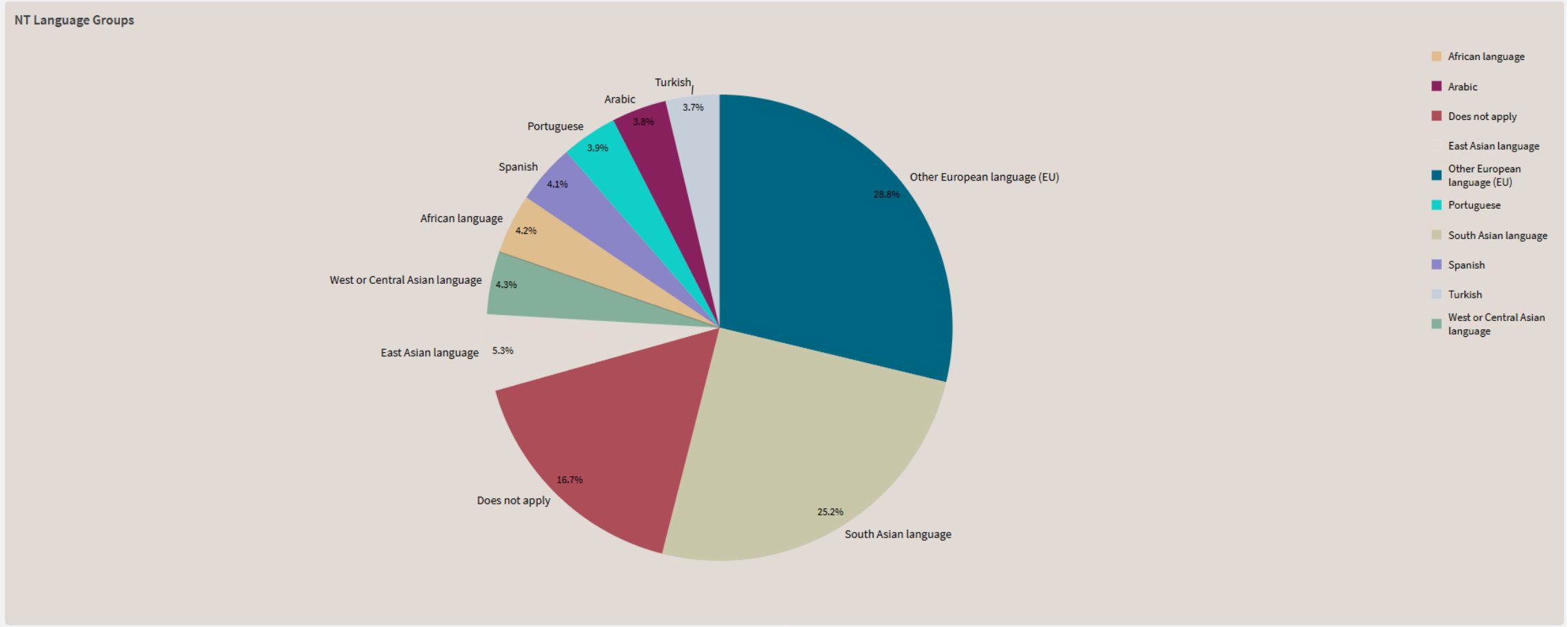
North Thames: Languages



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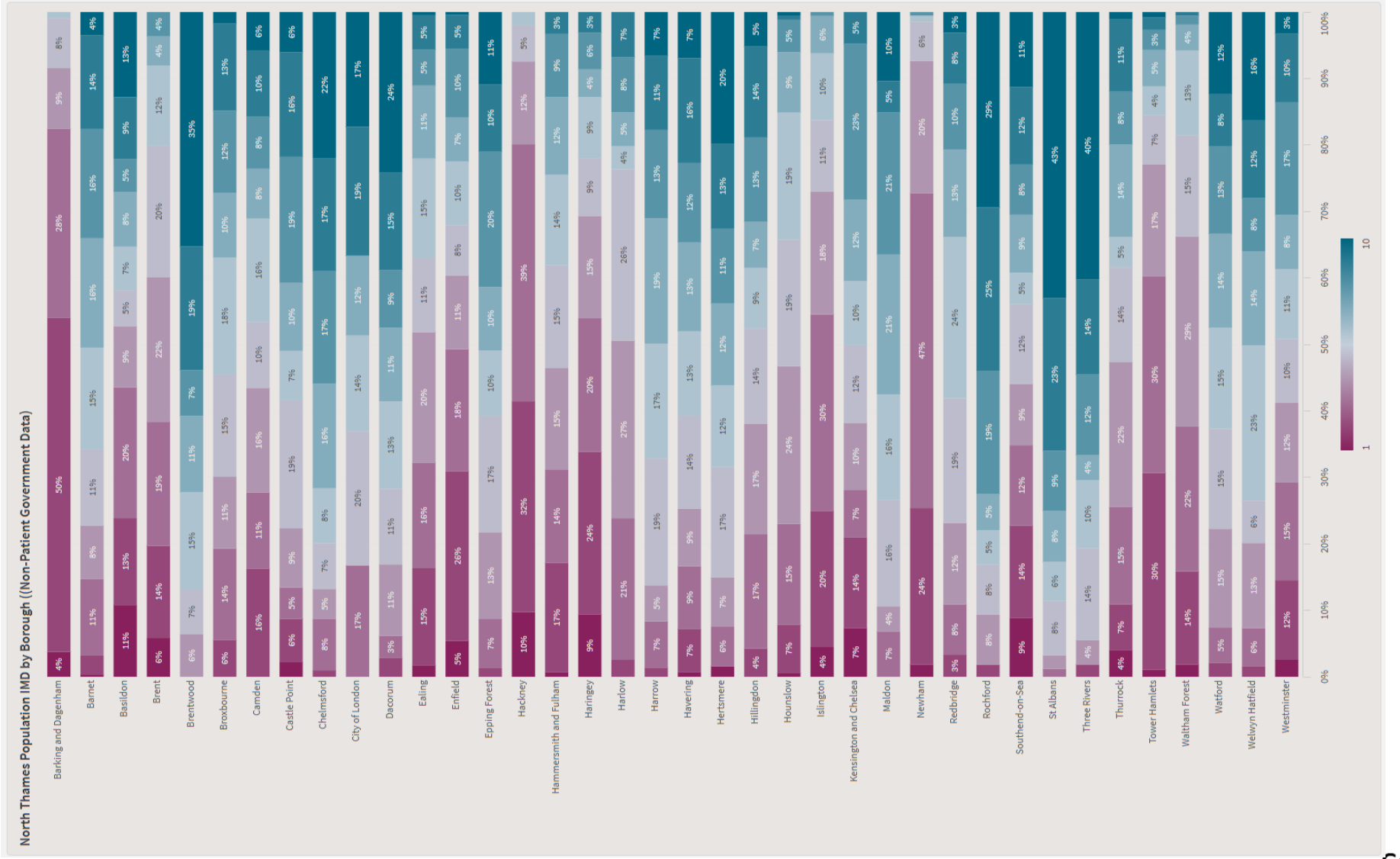
North Thames: IMD Data



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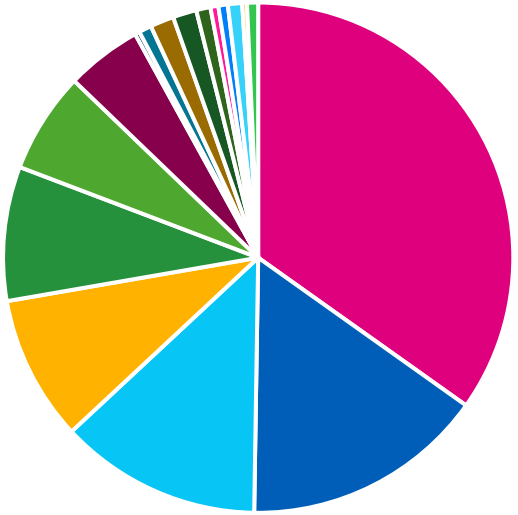
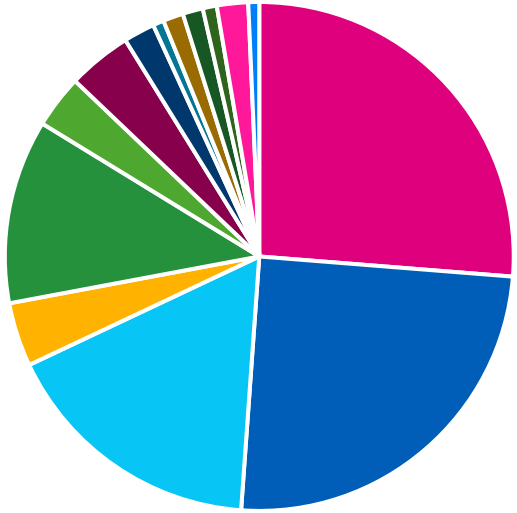
North Thames Recruiting Site Example

Ethnicity and Recruitment



Ethnicity at Booking

- Indian
- White British
- White any other background
- Pakistani
- Asian any other background
- Black African
- Any other ethnic background
- Mixed White and Black African
- Mixed White and Asian
- Mixed any other background
- Bangladeshi
- Black Caribbean
- Black any other background
- Chinese
- White Irish
- Not stated
- Mixed White and Black Caribbean



- Indian
- White British
- White any other background
- Pakistani
- Asian any other background
- Black African
- Any other ethnic background
- Mixed White and Asian
- Mixed any other background
- Bangladeshi
- Black any other background
- White Irish
- Not stated
- Mixed White and Black Caribbean

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Site Screening & Recruitment Data

With this data we will:

- Illustrate our efforts to recruit equitably
- Identify communities to focus engagement
- Evidence any need for additional resource to support equitable recruitment

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The Mosaic Community Trust

Mother and Baby's Health and Inherited Factors

A Community-Led Workshop at Mosaic Community Trust

Tina Prendeville – Lead Midwife North Thames GMSA

Pooja Dasani – Lead Genetic Counsellor North Thames GMSA

Yvonne Muwalo – Generation Study Regional Results Coordinator North Thames GMSA

Dominic Studart – Generation Study Regional Results Coordinator North Thames GMSA

Equity of Access: Community Engagement

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Thank you

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We are taking a short break

We will be back at 16:00

16:00 – Highly specialised testing: Now and the future

An overview of NHS highly specialised amyloid and autoinflammatory services

- Dr Dorota Rowczenio, Head of the National Amyloidosis Centre Molecular Genetic Service

Tailoring treatment response prediction in adult ALL through the development of minimal residual diagnostics

- Dr Bela Wrench, Clinical Lead of the National Adult ALL Minimal Residual Laboratory

Metagenomics for the diagnosis of infection

- Dr Julianne Brown, Principal Clinical Scientist at GOSH – Microbiology | Virology

world class expertise local care

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NHS Foundation Trust

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NHSE HSS National Amyloidosis and Autoinflammatory Services

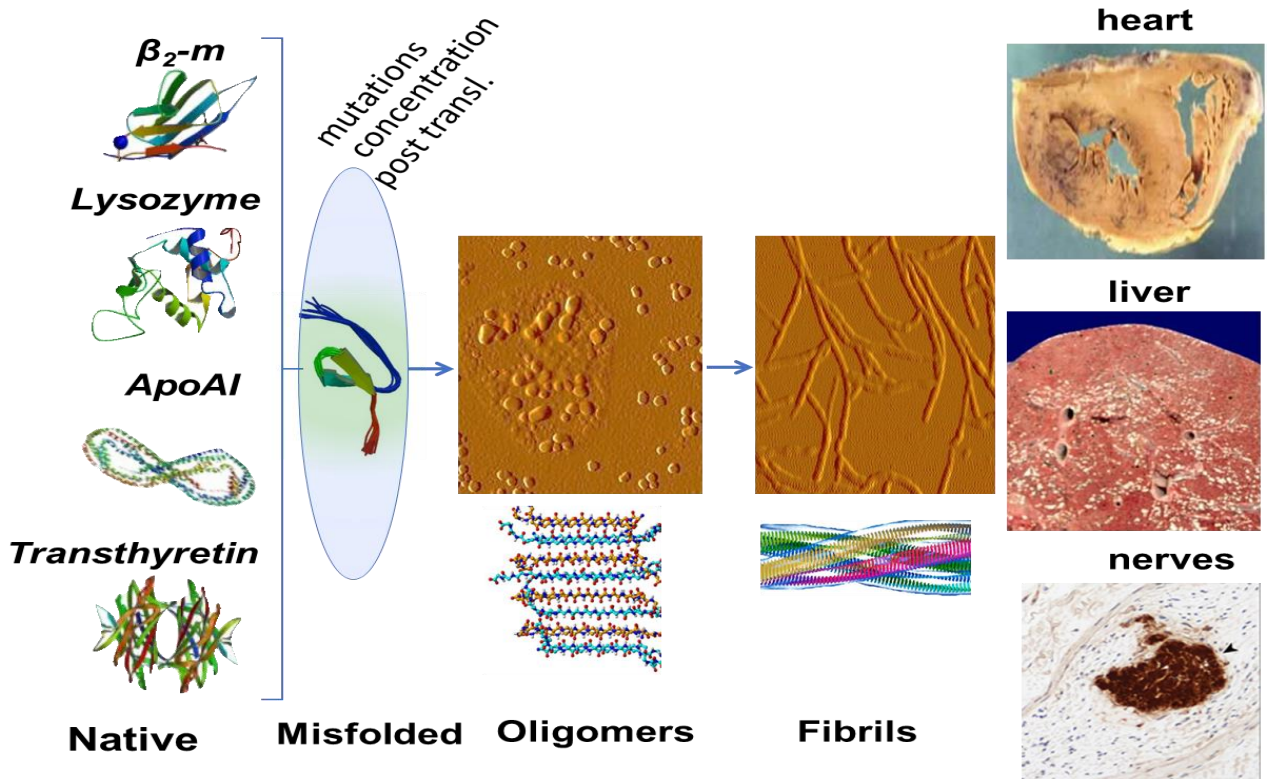
Dorota Rowczenio PhD FRCPath
Consultant Clinical Scientist & Head of Genomic Service
National Amyloidosis Centre

Amyloid

The term “amyloid” was introduced in 1854 by the German pathologist **Rudolf Virchow**

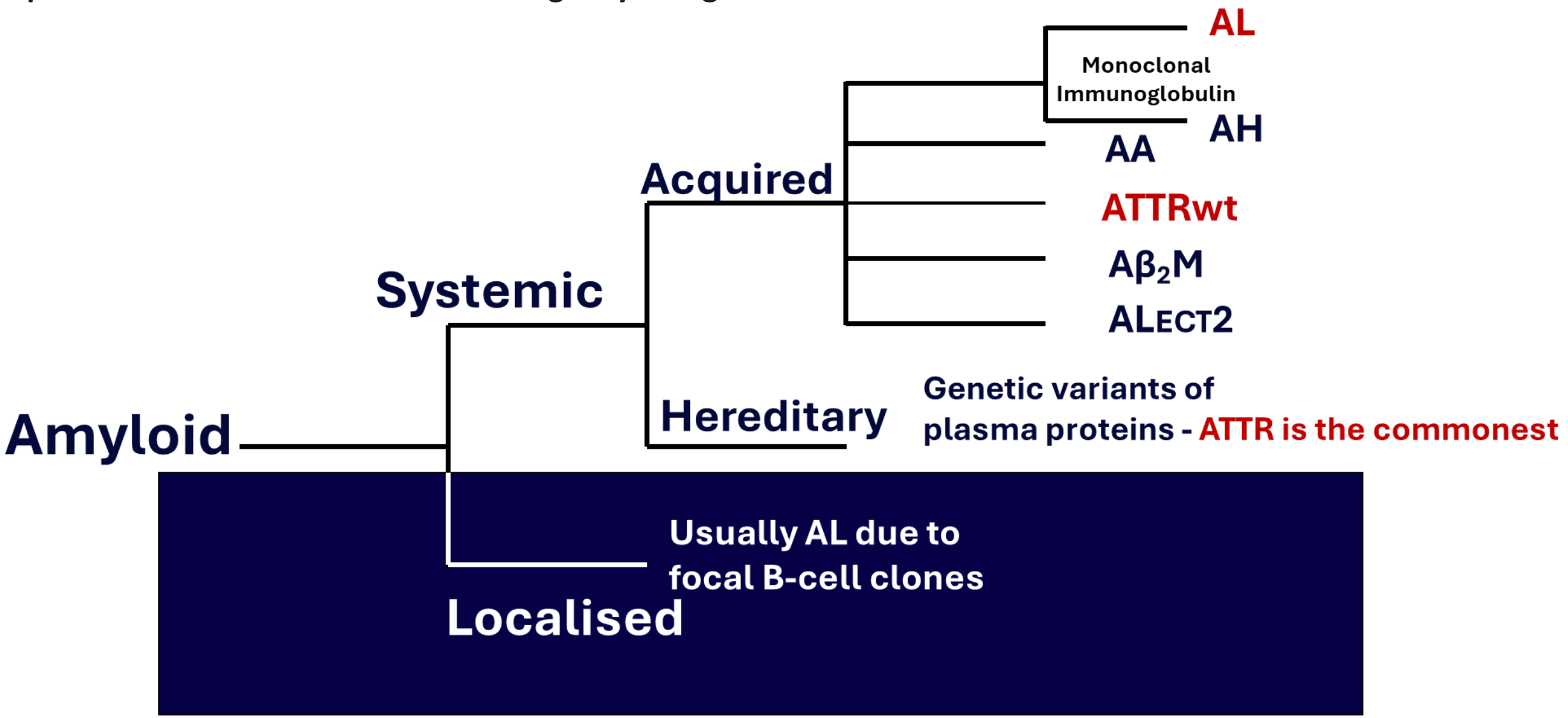
Amyloidosis – a disease of misfolded proteins

- Amyloid fibrils have high degree of molecular order, unusual stability, resistant to degradation and are made of β –sheet rich aggregates
- Mutation can make the protein less stable and more susceptible to misfold and potentially form amyloid
- Accumulation of amyloid fibrils disrupt the structure and function of affected organs



Amyloidosis is remarkably diverse

42 proteins have been identified as being amyloidogenic in humans



Organ tropism

The Pathology of Amyloidosis in Classification: A Review

Maria M. Picken

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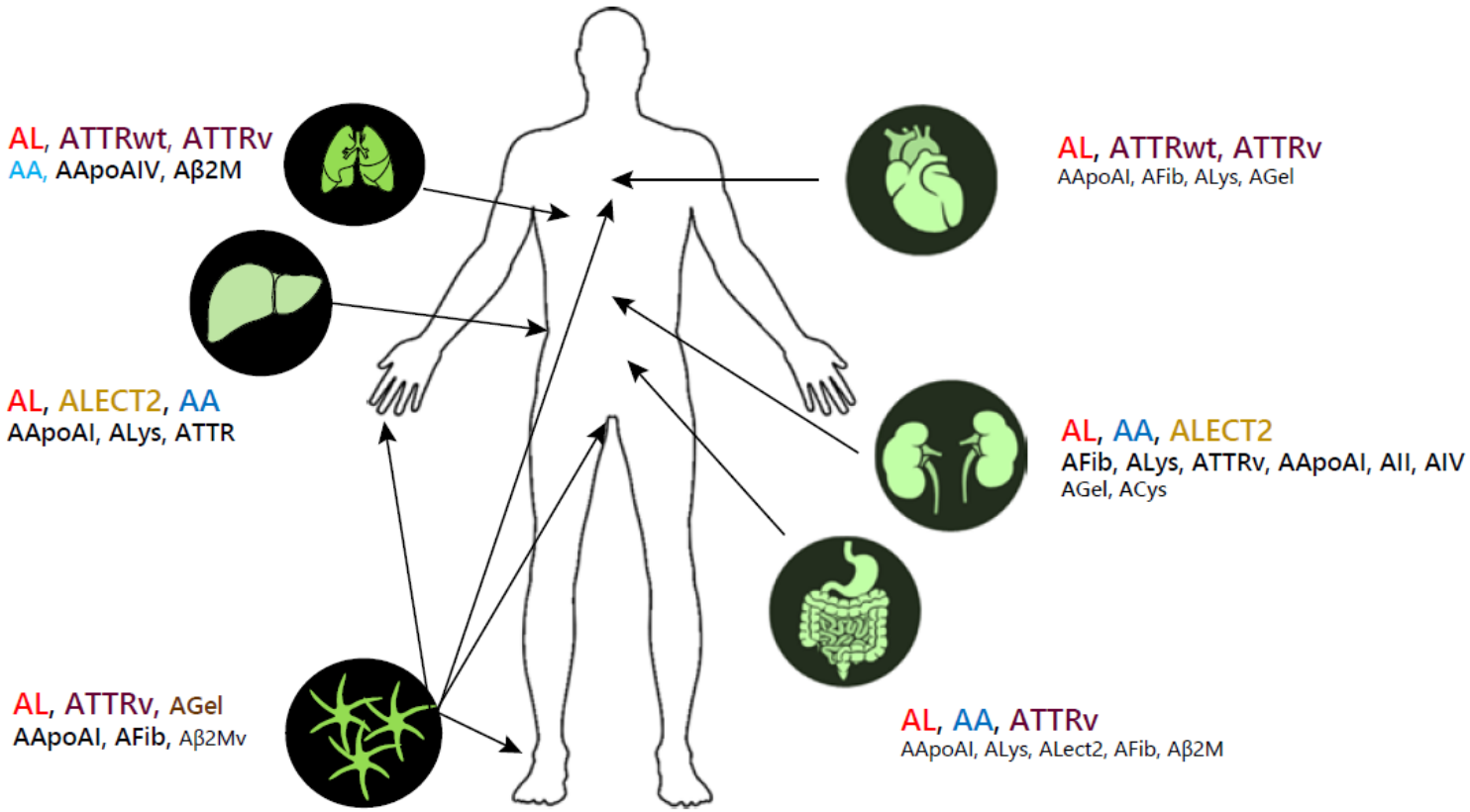
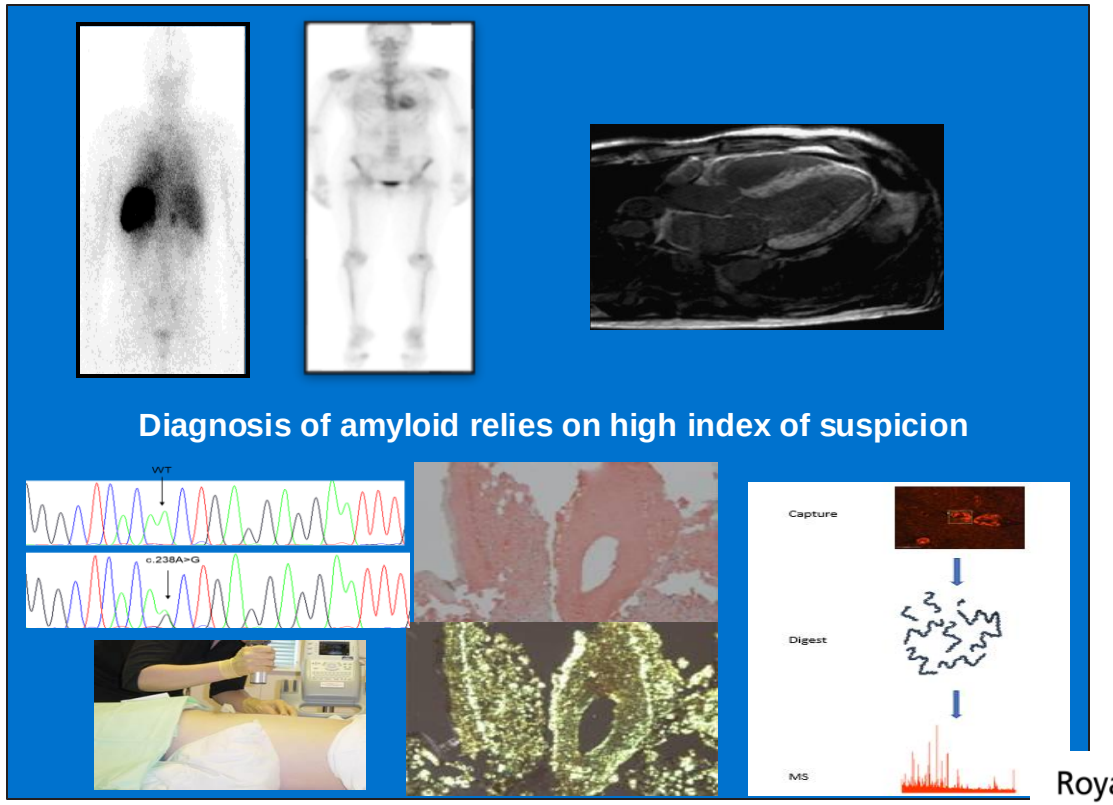


Amyloidosis is a systemic disease - Amyloid deposition may occur in almost any organ

Determining amyloid fibril type - why is it necessary?

- Untreated systemic amyloidosis is usually progressive and fatal
- Patient with suspected amyloidosis should undergo a series of investigations to identify amyloid deposits and look for associated organ involvement and dysfunction
- Current management depends upon identifying the fibril protein and reducing its abundance



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Investigating amyloid at NAC, UK

NAC Multidisciplinary team

- **Diagnostic laboratory (histology/proteomics/genetics**)
- Clinicians (cardiologists/nephrologists/ haematologists/rheumatologists)
- Nursing staff
- Echocardiographers
- Radiographers
- Genetic Counsellor
- Wolfson Drug Discovery Unit (WDDU) conducting amyloid research

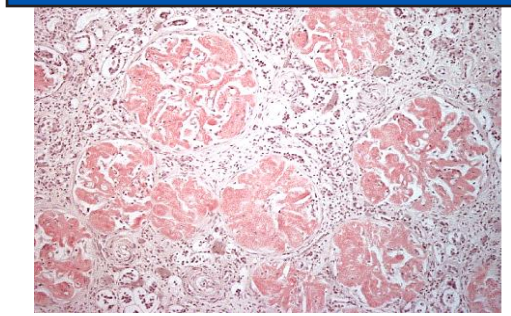
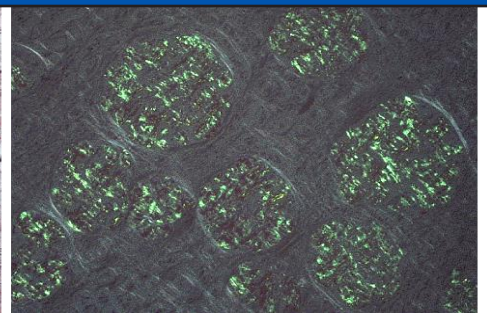
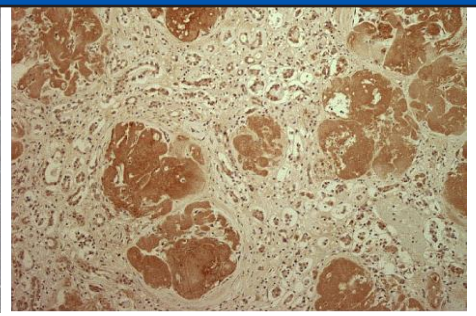
Amyloidosis Diagnostic Evaluation at NAC
Clinical consultation
6 minute walk test
Biomarkers of underlying clonal/inflammatory disease (FLC/IF etc; SAA) – track treatment response
Genetic testing
Histology for detection of amyloid deposits
Immunohistochemistry and proteomics for amyloid typing
Biomarkers of amyloidotic organ dysfunction (staging & monitoring of AL/ATTR amyloidosis)
ECG, echocardiogram
Multiparametric cardiac MRI
SAP scintigraphy
DPD scintigraphy
Liver elastography
Bioimpedence measurement
MDT management plan

Confirm presence and typing of amyloid fibrils

Congo red and immunohistochemistry - preferred methods in clinical practice, but with variable sensitivity and specificity!

- **Congo red dye -** identifies presence of amyloid
- **Immu** dies to identify the amylo

Immunohistochemistry in amyloidosis is not reliable - up to 30% false negatives

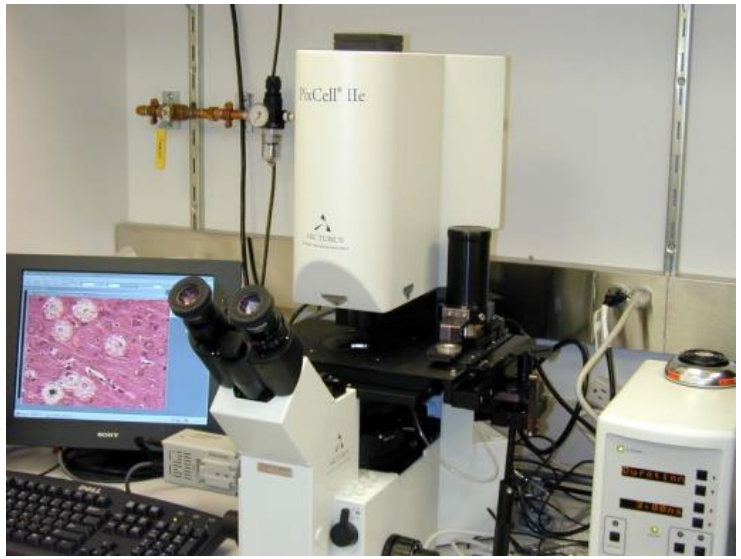




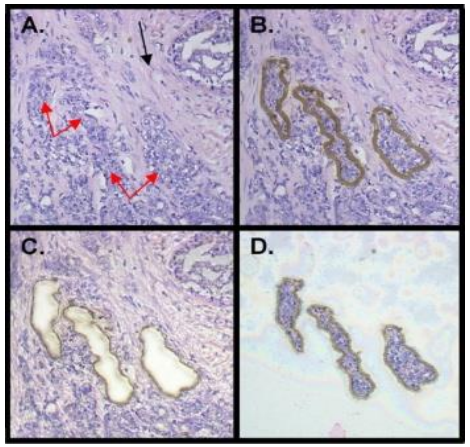
Laser microdissection and tandem mass spectrometry (LDMS)

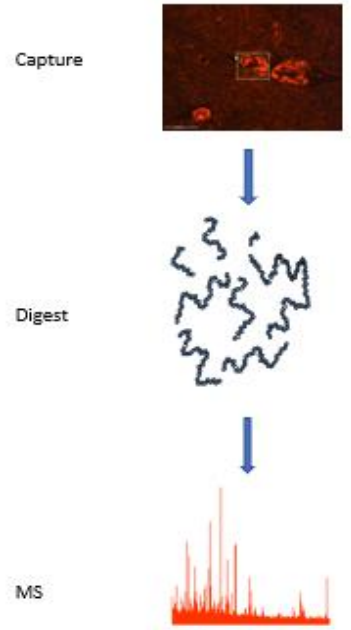
- ❑ New ‘Gold Standard’ for typing of amyloid pioneered by Mayo Clinic
- ❑ Cut out tiny fragments of amyloid from biopsies with laser dissection microscope
- ❑ Determines precise molecular size of protein, which reveals the identity of amyloid protein

Protein identification by MS (proteomics)

Lavatelli et al, Mol Cell Proteom 2008
Vrana et al, Blood 2009







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NHS Foundation Trust

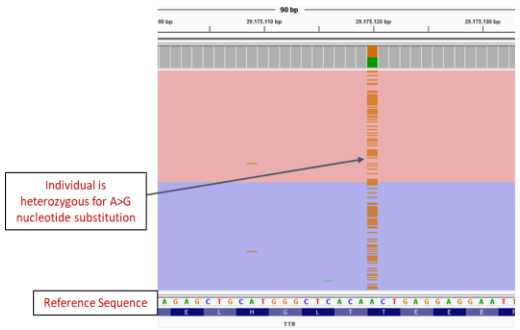
Probability Legend: over 95% / 80% to 94% / 50% to 79% / 20% to 49% / 0% to 19% — dentified proteins (189)	UNIPROT Identifier	Molecular Weight	Control	Patient 1, S1	Patient 1, S2	Patient 2, S1	Patient 2, S2	Patient 3, S1	Patient 3, S2	Patient 4, S1
olipoprotein A-I OS=Homo sapi...	APOA1_HU...	31 kDa		103	96	67	80	32	37	18
tronectin OS=Homo sapiens GN...	VTNC_HUM...	54 kDa		67	56	59	83	31	28	27
rum albumin OS=Homo sapiens...	ALBU_HUM...	69 kDa		23	19	56	85	28	65	
olipoprotein E OS=Homo sapie...	APOE_HUM...	36 kDa		17	15	50	61	19	10	40
moglobin subunit beta OS=Ho...	HBB_HUMAN	16 kDa						73	53	
rum amyloid P-component OS=...	SAMP_HUM...	25 kDa		27	33	21	32	35	24	7
moglobin subunit alpha OS=Ho...	HBA_HUMAN	15 kDa						46	35	
usterin OS=Homo sapiens GN=C...	CLUS_HUM...	52 kDa		12	11	16	29	25	20	
tin, alpha cardiac muscle 1 OS=...	ACTC_HUM...	42 kDa				5		17	33	6
llagen alpha-2(I) chain OS=Ho...	CO1A2_HU...	129 kDa		4		20	18	10	12	6
olipoprotein A-IV OS=Homo sa...	APOA4_HU...	45 kDa		17	19	23	29			
llagen alpha-1(I) chain OS=Ho...	CO1A1_HU...	139 kDa		3		20	18	7	7	3
ctotransferrin OS=Homo sapie...	TRFL_HUMAN	78 kDa					15		46	
llagen alpha-3(VI) chain OS=Ho...	CO6A3_HU...	344 kDa							29	
yosin-11 OS=Homo sapiens GN...	MYH11_HU...	227 kDa							21	

Genetic Analysis at the NAC

Next-generation sequencing (NGS)

Allows agnostic approach – sequencing many genes in patients presenting with non-specific phenotypes

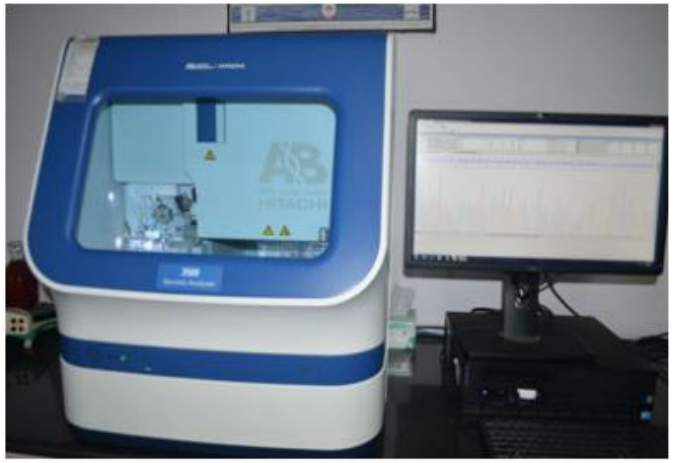
Illumina NextSeq 2000

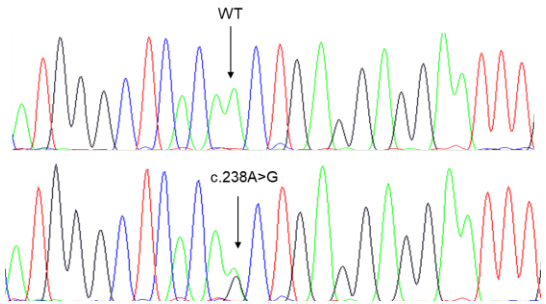


Illumina MiSeq

Sanger Sequencing

Analysis of a single gene that closely fits with the patient's clinical features





NAC Lab is commissioned by NHSE as a national test provider for hereditary amyloidosis and hereditary systemic autoinflammatory diseases

Two Targeted NGS panels

Autoinflammatory disorders: 24 genes panel- TD clinical indication is R413

AUTOINFLAMMATORY GENE PANEL			
Disease genes	Gene name	Gene symbol	Chromosomal location
Hereditary autoinflammatory disease genes	Adenosine deaminase 2	ADA2	22q11.1
	Caspase recruitment domain family member 14	CARD14	17q25.3
	Interleukin 1 receptor antagonist	IL1RN	2q14.1
	Interleukin 36 receptor antagonist	IL36RN	2q14.1
	Lipin 2	LPIN2	18q11.31
	MEFV, pyrin innate immunity regulator	MEFV	16q13.3
	Mevalonate kinase	MVK	16q13.3
	NLR family CARD domain containing 4	NLRC4	2q22.3
	NLR family pyrin domain containing 12	NLRP12	19q13.42
	NLR family pyrin domain containing 3	NLRP3	1q44
	Nucleotide binding oligomerization domain containing 2	NOD2	16q12.1
	OTU deubiquitinase with linear linkage specificity	OTULIN[New]	5p15.2
	Phospholipase C gamma 2	PLCG2	16q24.1
	Proteasome 205 subunit beta 8	PSMBB	6p21.32
	Proteasome 205 subunit beta 4	PSMB4	1q21.3
	Proteasome 205 subunit beta 9	PSMB9	6p21.32
	Proline-serine-threonine phosphatase interacting protein 1	PSTPIP1	15q24.3
	RANBP2-type and C3HC4-type zinc finger containing 1	RBCK1[New]	20p13
	SH3 domain binding protein 2	SH3BP2	4p16.3
	Solute carrier family 29 member 3	SLC29A3[New]	10q22.1
	TNF alpha induced protein 3	TNFAIP3	6p23.3
	TNF receptor superfamily member 1A	TNFRSF1A	12q13.31
	Transmembrane protein 173	TMEM173	5q31.2
	Ubiquitin like modifier activating enzyme 1	UBA1[New]	Xp11.3

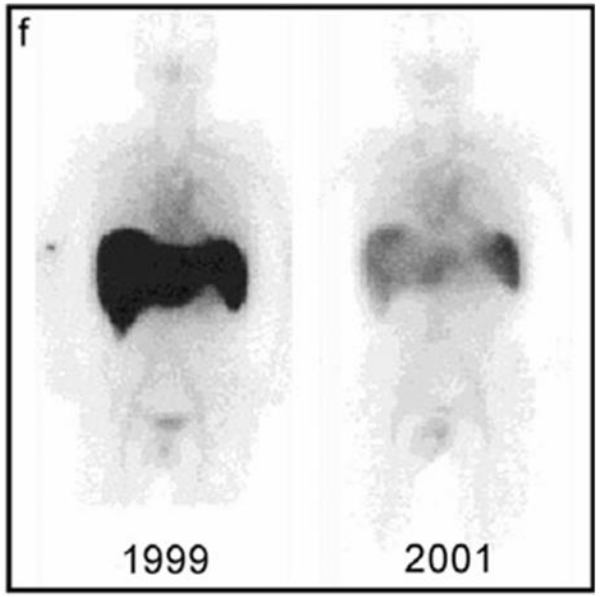
Hereditary Amyloidosis: 22 genes panel – TD clinical indication is R204

AMYLOID GENE PANEL			
Disease genes	Gene name	Gene symbol	Chromosomal location
Hereditary amyloidosis genes	Amyloid P component, serum	APCS. Synonym SAP	1q23.2
	Apolipoprotein E	APOE	19q13.32
	Apolipoprotein A4	APOA4	11q23.3
	Apolipoprotein A1	APOA1	11q23.3
	Apolipoprotein A2	APOA2	1q23.3
	Apolipoprotein C2	APOC2	19q13.32
	Apolipoprotein C3	APOC3	11q23.3
	Serum amyloid A1	SAA1	11q15.1
	Serum amyloid A2	SAA2	11q15.1
	Serum amyloid A4	SAA4	11q15.1
	C-reactive protein	CRP	1q23.2
	Lysozyme	LYZ	12q15
	Gelsolin	GSN	9q33.2
	Fibrinogen alpha chain	FGA	4q31.3
	Beta-2-macroglobulin	B2M	15q21.1
	Transthyretin	TTR	18q12.1
	Cystatin C	CST3	20q11.21
	Leukocyte cell derived chemotaxin 2	LECT2	5q31.1
	Myeloid differentiation primary response 88	MYD88	3q22.2
	Transforming growth factor beta induced	TGFB1, synonym BIGH3	5q31.1
	Oncostatin M Receptor	OSMR[New]	5p13.1
	Galectin 7	LGALS7[New]	19913.2

Serum Amyloid P component (SAP) Scintigraphy

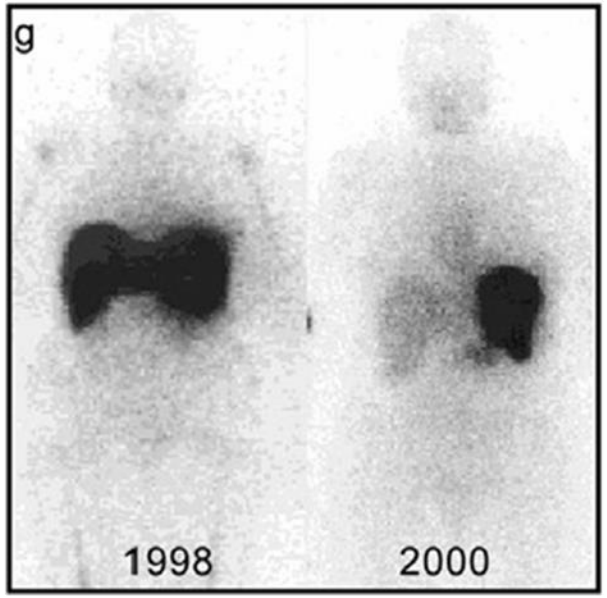
- Detects amyloid deposits in many organs (except heart, skin, nerves)
- Serial scans useful in monitoring disease progress as they show changes in amyloid load – good for monitoring the effects of treatment

AA amyloidosis[1]



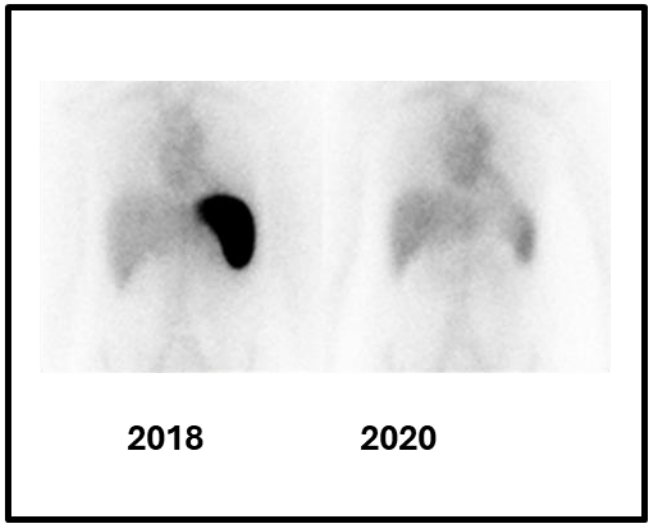
SAA suppression

AL amyloidosis[2]



Complete hematologic response

ATTR amyloidosis[3]



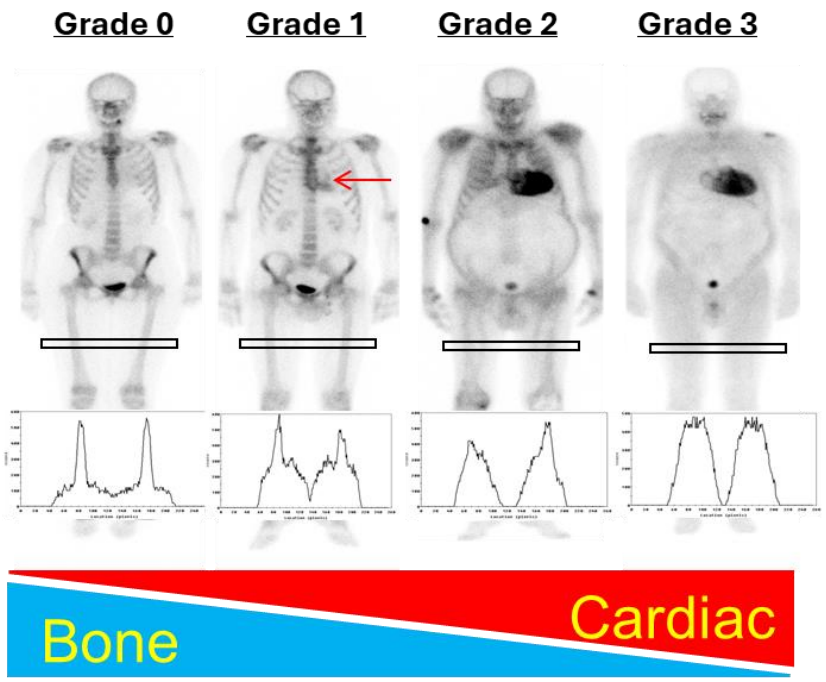
TTR knockdown with patisiran

[1]Gillmore JD *et al*, Lancet 2001;358:24-29
[2]Lachmann HJ *et al*, BJH 2003;122:78-84
[3]Patel R *et al,* Amyloid 2021;28:269-270

Diagnosis & tracking of cardiac amyloidosis

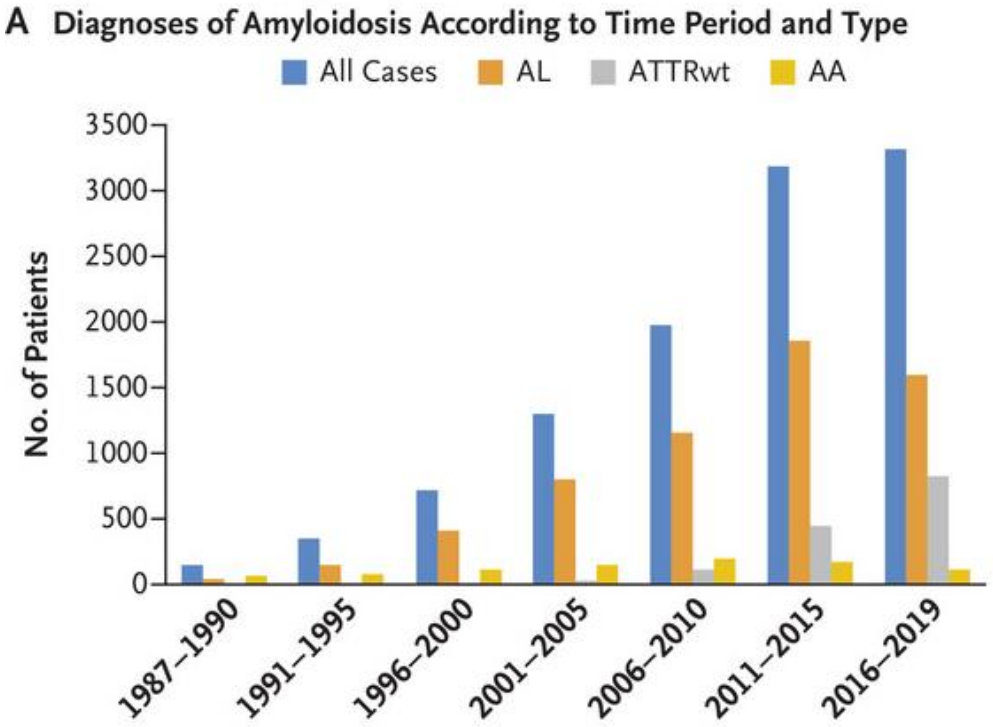
- Highly accurate for the non-invasive, in particular for diagnosis of transthyretin (ATTR) cardiac amyloidosis

^{99m}Tc-DPD scintigraphy

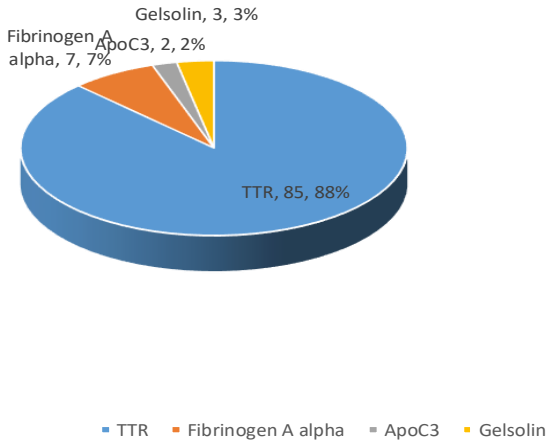


Cardiac MRI

Diagnosis of Amyloidosis over 3 Decades & Amyloidosis Types



Hereditary Amyloidosis account for 12%



- Transthyretin (*TTR*)
- Fibrinogen alpha chain (*FGA*)
- Lysozyme (*LYZ*)
- Apolipoprotein AI (*APOA1*)
- Apolipoprotein AII (*APOA2)*
- Apolipoprotein CII and CIII (*APOAC2/C3*)
- Gelsolin (*GSN*)
- Beta-2-microglobulin (B2M)
- Cystatin C

Systemic light chain (AL) amyloidosis was the most common diagnosis, but wild-type transthyretin amyloidosis (ATTRwt) is increasingly being recognised

S Ravichandran et al. N Engl J Med 2020;382:1567-1568.

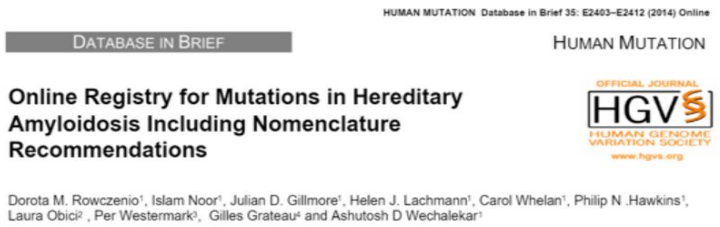
Royal Free London NHS
NHS Foundation Trust

Transthyretin (ATTR) amyloidosis is rapidly progressive, multisystemic fatal disease in which amyloid is derived from either mutant or wild-type transthyretin

Hereditary ATTR (hATTR) amyloidosis

- >130 amyloidogenic variants reported in the literature and on online registry

www.amyloidosismutations.com


HUMAN MUTATION Database in Brief 35: E2403–E2412 (2014) Online

DATABASE IN BRIEF

HUMAN MUTATION

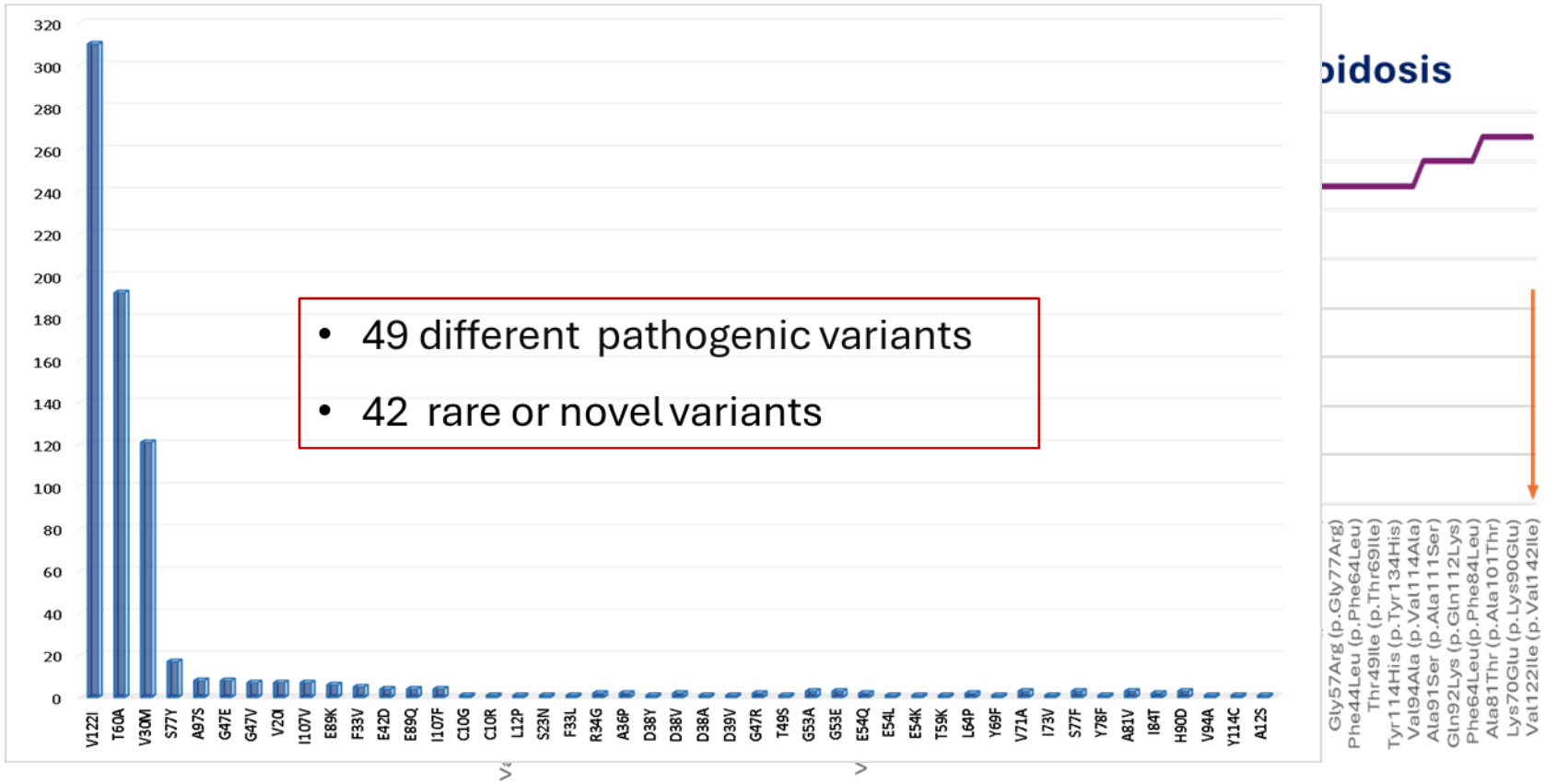
Online Registry for Mutations in Hereditary Amyloidosis Including Nomenclature Recommendations

OFFICIAL JOURNAL HGVS HUMAN GENOME VARIATION SOCIETY www.hgvs.org

Dorota M. Rowczenio[1], Islam Noor[1], Julian D. Gillmore[1], Helen J. Lachmann[1], Carol Whelan[1], Philip N .Hawkins[1], Laura Obici[2] , Per Westermark[3], Gilles Grateau[4] and Ashutosh D Wechalekar[1]

- Majority are a single base substitution
- Variable age at onset, but typically > 50 years
- Except the p.(Val50Met) in endemic areas family history is rare
- TTR mutations are typically associated with a particular phenotype, however, the same variant may result in different phenotypes even within the same family
- Diagnosis is challenging due to the heterogeneity of clinical presentation, incomplete penetrance and de novo mutations
- ATTRv is rapidly progressing and causes severe organ damage - early diagnosis is important

TTR mutations identified at NAC

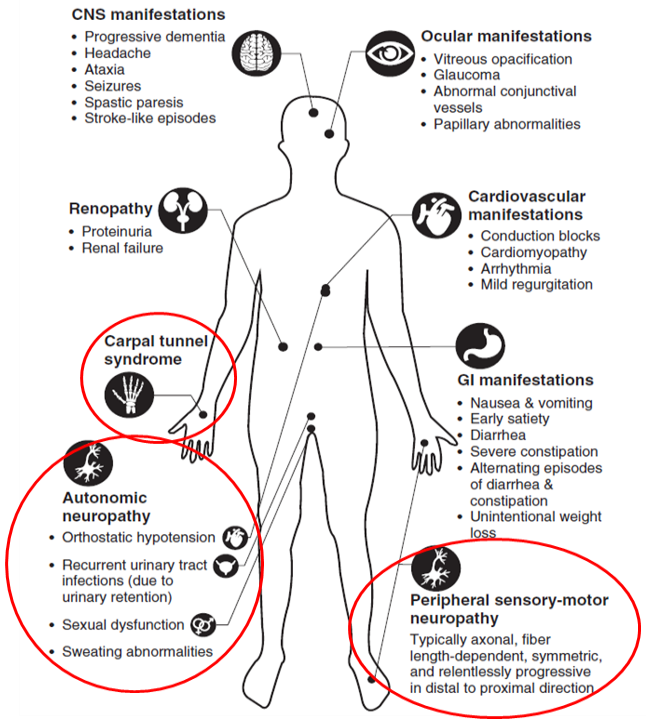


Rowczenio et al Hum Mutat. 2019

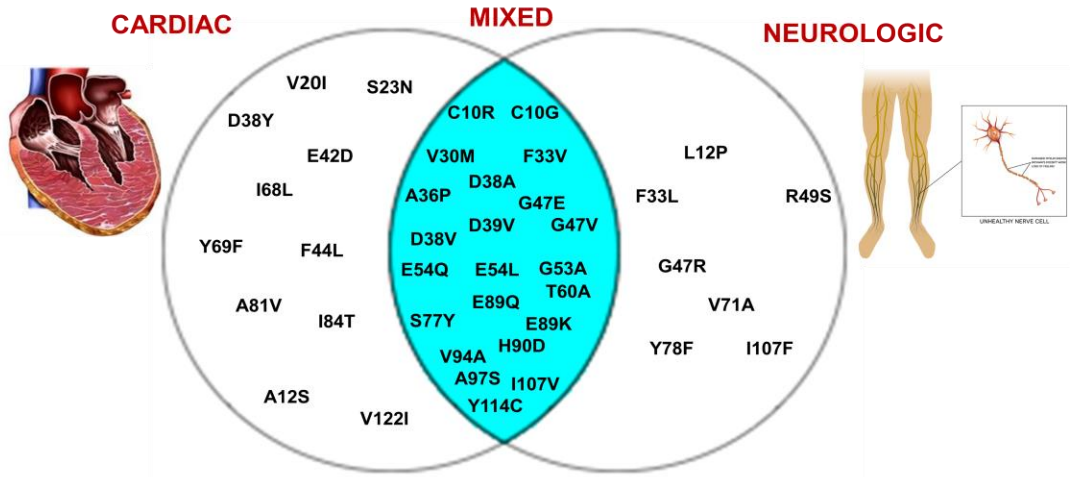
- The biggest biobank of samples from patients with hereditary ATTR amyloidosis worldwide
- In the UK, the predominant *TTR* gene variants are: V142I, T80A and V50M

Phenotypic spectrum of *TTR* mutations

- Globally, cardiomyopathy is most frequent presentation
- Clinical presentation: usually heart failure resulting in shortness of breath



TTR mutations display different tissue tropism



Other associated phenotypes

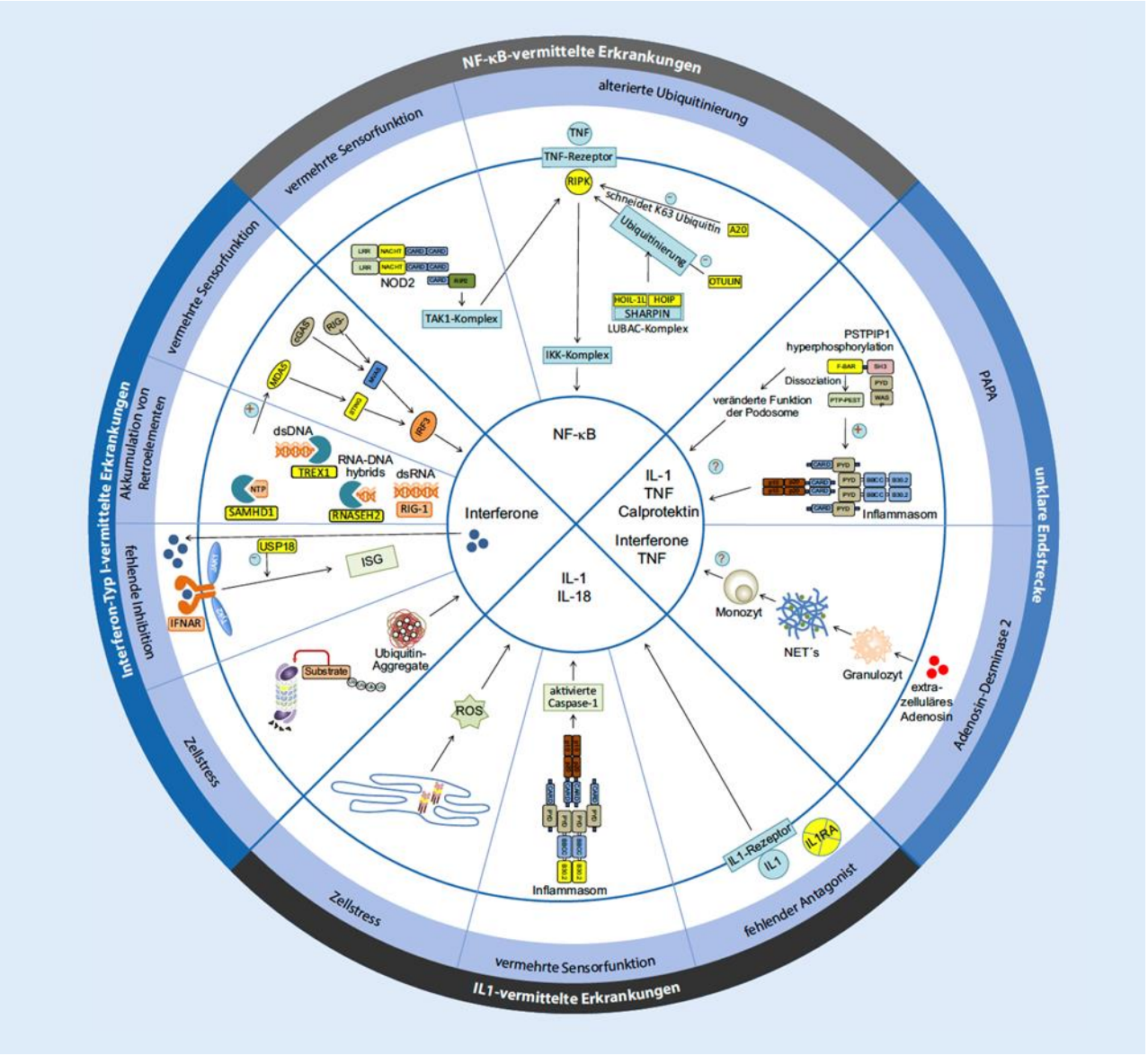
Vitreous amyloid with: R34G; A36P; F33V; I84S

Leptomeningeal amyloid with: S52P ; L12P

- Carpal tunnel syndrome
- Pins and needles, pain and/or numbness in the feet and hands
- GI – diarrhoea / constipation
- Weight loss
- Erectile dysfunction
- Low blood pressure
- Progressive
- Bedbound – severe sensory and motor
- Loss of muscle and weakness

Monogenic Systemic Autoinflammatory Diseases (SAIDs)

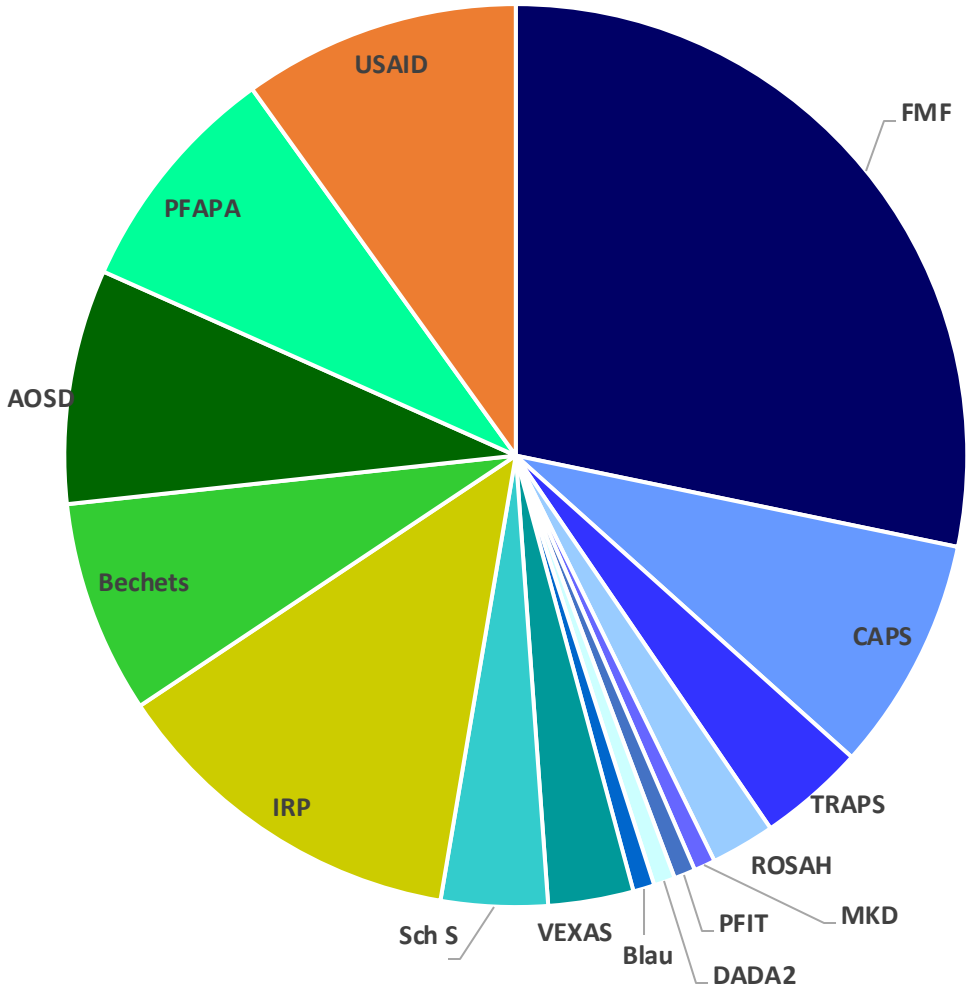
- **Caused by both germline and somatic pathogenic mutations in >50 genes**
- The genetics of SAIDs is complex and heterogeneous, including dominant, recessive, X-linked, germline and somatic variants
- Pathogenic variants in SAIDs can act as gain-of-function (GoF) or loss-of-function (LoF) depending on the mutation's effect on the protein function, but ultimately result in the activation of various immune and inflammatory pathways



Approximately 35 new referrals a month to our HS Autoinflammatory clinic

- 43% - diagnosis of SAID
- 57% - no evidence of SAID diagnosis

DIAGNOSIS	#	%
Not SAID	175	57%
FMF	37	12%
CAPS	11	4%
TRAPS	5	2%
ROSAH	3	1%
MKD	1	
PFIT	1	
DADA2	1	
Blau	1	
VEXAS	4	1%
Sch S	5	2%
IRP	17	6%
Bechets	10	3%
AOSD	11	4%
PFAPA	11	4%
USAID	13	4%



Recognising the patient with Systemic Autoinflammatory Diseases (SAIDs)

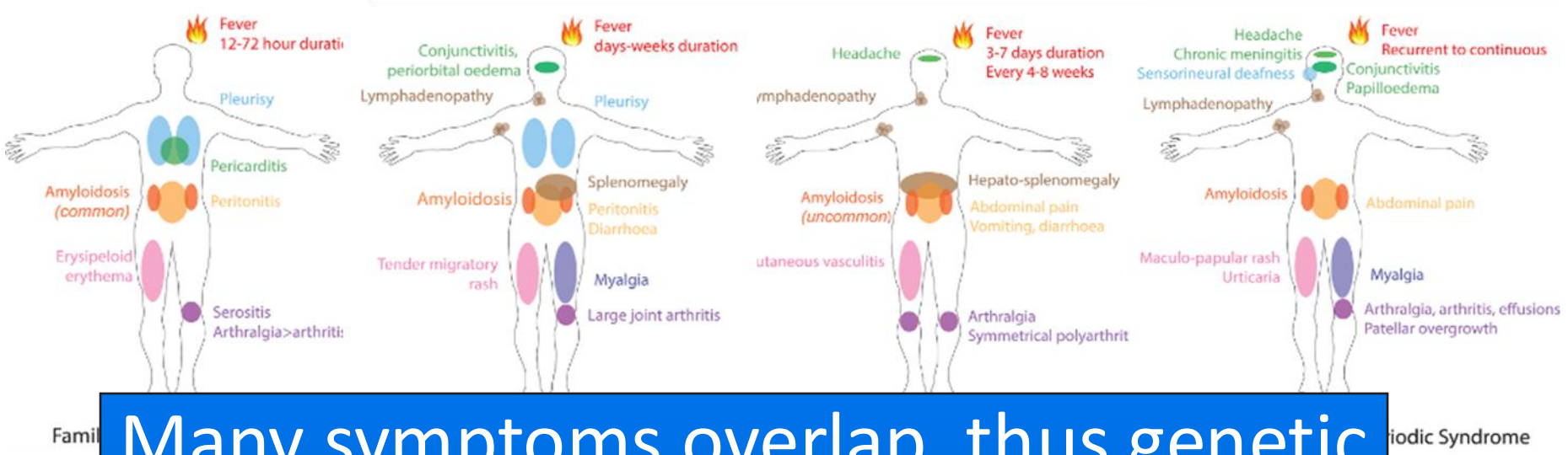
Caused by mutations in genes involved in the innate immune response

- Recurrent or continuous symptoms
  - Fever, rash, serositis, joint pain or arthritis

Accompanied by an ↑↑ elevated acute phase response

- Family history
- Onset in infancy ↔ young adulthood
- No other explanation – patients underwent extensive investigations for exclusion of: infection, immunodeficiency, connective tissue disease, malignancy etc
- AA amyloidosis is the most frequent, potentially fatal, long-term complication of SAIDs

4 Most Common Monogenic SAIDs



Famil iodic Syndrome

Many symptoms overlap, thus genetic testing is crucial for accurate diagnosis

lymphadenopathy.

FCAS	NLRP3 AD	First year of life	12 h–2 days	Urticarial rash induced by cold, arthralgia, conjunctivitis.
MWS	NLRP3 AD	Childhood	2–3 days, if present	Urticarial rash, sensorineural deafness.
NOMID	NLRP3 AD (sporadic)	Neonatal	Variable, if present	Rash, neurologic symptoms, skeletal abnormalities.
TRAPS	TNFRSF1A AD	First year of life	1–3 weeks	Arthromyalgia, fasciitis, rash, conjunctivitis and periorbital edema, splenomegaly.

REVIEW

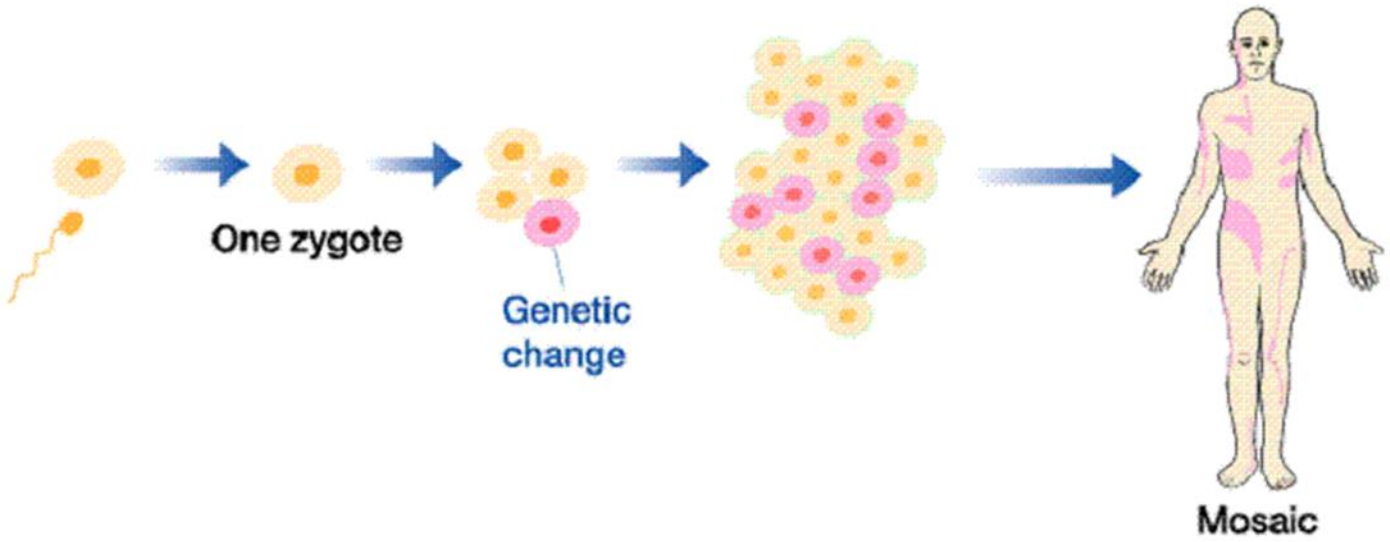
Monogenic autoinflammatory disorders: beyond the periodic fever

Fiona Moghaddas [1,2,3]

Royal Free London NHS
NHS Foundation Trust

Mosaic SAIDs

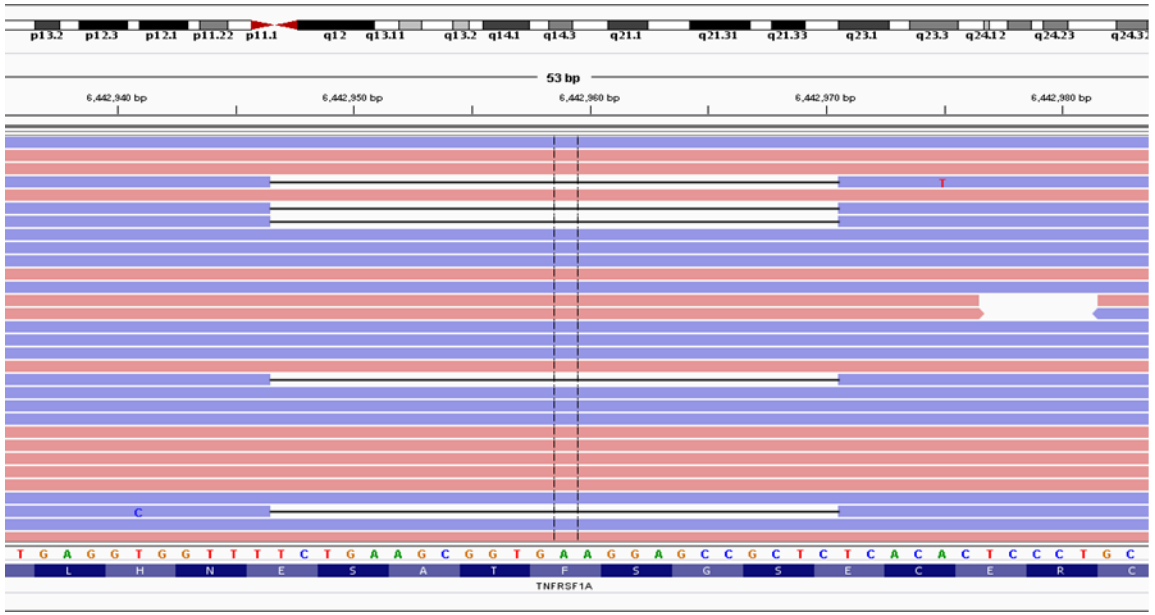
- Somatic mutations have been identified in several genes and mostly affect myeloid cells
- In CAPS up to 20% of patients carry a somatic mutation in *NLRP3* gene, particularly those with the most severe form NOMID/CINCA phenotype
- The ratio of somatic mosaicisms varies, but it can be 3% in peripheral blood samples, thus requires deep sequencing NGS screening methods

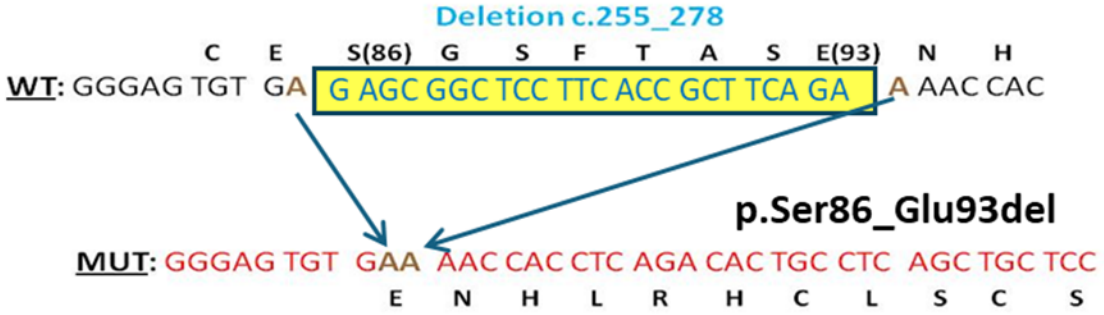


Association of Tumor Necrosis Factor Receptor–Associated Periodic Syndrome With Gonosomal Mosaicism of a Novel 24-Nucleotide *TNFRSF1A* Deletion

Dorota M. Rowczenio,[1] Hadija Trojer,[1] Ebun Omoyinmi,[1] Juan I. Aróstegui,[2] Grigor Arakelov,[3] Anna Mensa-Vilaro,[2] Anna Baginska,[1] Caroline Silva Pilorz,[1] Guosu Wang,[1] Thirusha Lane,[1] Paul Brogan,[1] Philip N. Hawkins,[1] and Helen J. Lachmann[1]

- 41-year-old British man with classical TRAPS phenotype, no FH, elevated SAA & CRP
- Deletion of 8 amino acids p.Ser86_Glu93del affecting 5% of alleles





Racing to the South and North Pole – with TRAPS!

Just as I was about to set off on one of the biggest, toughest and most gruelling expeditions in my life... the news came.

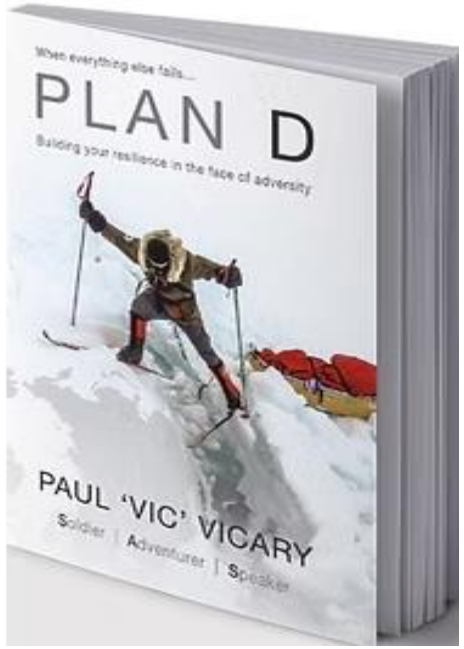
"You've got an extremely rare genetic disorder." the Dr told me.

Before this moment, I'd almost gotten used to the pain. For five years I had to have tests, examinations and invasive investigations, all whilst serving in the military. But at the point where I felt most hopeless like I'd gone crazy, like it was all in my head... I finally got my diagnosis.

"You've got TRAPS" the Dr told me.

Tumor Necrosis Factor Receptor Associated Periodic Syndrome (TRAPS) is a rare genetic disease with episodes of recurrent fever; abdominal, chest, and muscle pain; red and swollen eyes; and a typical rash lasting for more than one week.

The sense of relief it brought me to finally have an answer was something I can't explain. But at the same time, the anxiety of not knowing what was going to happen in the future and the daily need to inject my medication left me feeling very torn. "How can I make this work when exploring the South Pole?!"

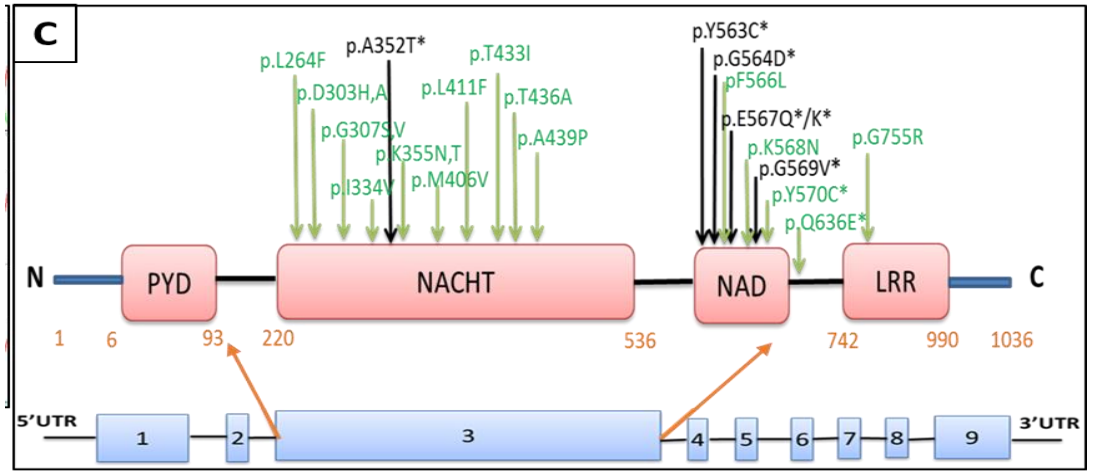


Late-Onset Cryopyrin-Associated Periodic Syndromes Caused by Somatic NLRP3 Mosaicism—UK Single Center Experience

Dorota M. Rowczenio[1†], Sónia Melo Gomes[2†], Juan I. Aróstegui[3], Anna Mensa-Vilaro[3], Ebun Omoyinmi[2], Hadija Trojer[1], Anna Baginska[1], Alberto Baroja-Mazo[4], Pablo Pelegrin[4], Sinisa Savic[5], Thirusha Lane[1], Rene Williams[1], Paul Brogan[2], Helen J. Lachmann[1] and Philip N. Hawkins[1]*

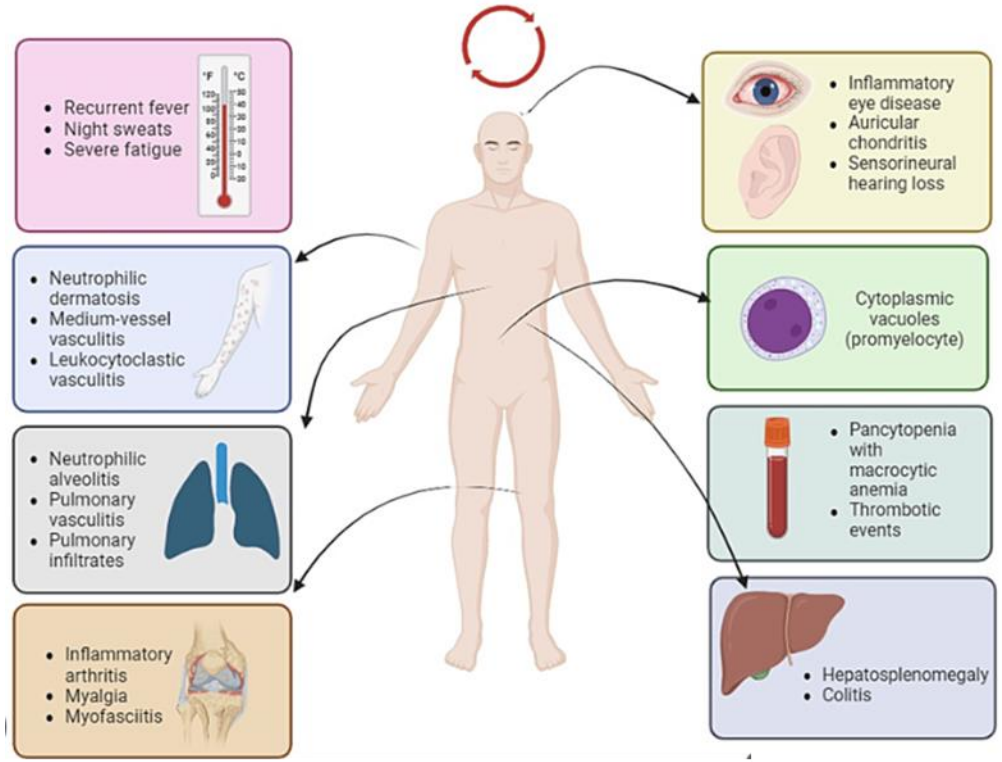
Clinical characteristics in 8 patients with the late onset of CAPS caused by somatic mosaicism in the *NLRP3* gene

Subject	Clinical symptoms	Duration of symptoms / Age at diagnosis (years)	Pre-treatment SAA/CRP (mg/L)	DNA substitution / protein variant	MAF Mean (%)	Coverage of mutation Mean (X)
1	UR, HF, BSD, conjunctivitis, headaches, papilloedema	20 / 70	415 / 82	c.1688A>G / p.Y563C	5.1	1994
2	UR, HF, BSD, arthralgia, headaches, nausea, diarrhoea and marked lyphodenopathy.	10 / 61	446/53	c.1688A>G / p.Y563C	3.2	11969
3	UR, HF, BSD, iritis, optic neuritis, nephrotic syndrome, AA amyloidosis	10 / 64	473 / 162	c.1688A>G / p.Y563C	11.1	1085
4	UR, HF, BSD, abdominal pain, fatigue, clubbing, nephrotic syndrome, AA amyloidosis	20 / 66	79 / 42	c.1054G>A / p.A352T	14.6	6738
5	UR, HF, BSD, lymphadenopathy, conjunctivitis, patient died of pancreatic cancer	8 / 79	397 / 108	c.1706G>T / p.G569V	21.1	2535
6	UR, HF, BSD, conjunctivitis, fatigue, arthralgia, headaches, finger clubbing	10 / 51	121 / 54	c.1699G>A / p.E567K	5.4	1293
7	UR, HF, BSD, arthralgia and myalgia, conjunctivitis and severe headaches.	20 / 51	276 / 291	c.1699 G>C / p.E567Q	15	4612
8	UR, HF, BSD, headaches, myalgia	15 / 65	SAA not done / CRP 146	c.1691G>A / p.G564D	5.0	2592



The landscape of acquired late onset SAIDs has been transformed by the discovery of VEXAS (vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic) syndrome in 2020

- Severe adult-onset autoinflammatory disorder caused by somatic loss of function mutations in the UBA1 gene located on the X chromosome, thus reported almost exclusively in older men
- VEXAS is severe, progressive disease with clinical features that bridge rheumatologic and hematologic conditions



N Engl J Med. 2020 Dec 31;383(27):2628-2638. doi: 10.1056/NEJMoa2026834. Epub 2020 Oct 27.

Somatic Mutations in *UBA1* and Severe Adult-Onset Autoinflammatory Disease

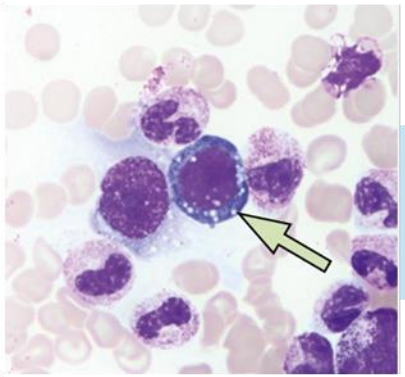
David B Beck [1], Marcela A Ferrada [1], Keith A Sikora [1], Amanda K Ombrello [1], Jason C Collins [1],

RED FLAGS

male sex
+ Age >50 years
+ Systemic inflammation
+ Multiorgan involvement

Clinical features

- Macrocytic anemia, Myelodysplastic syndrome, thrombocytopenia
- Skin lesions (e.g. neutrophilic dermatosis, vasculitis)
- Nasal and/or auricular chondritis
- Pulmonary involvement
- Deep vein thrombosis

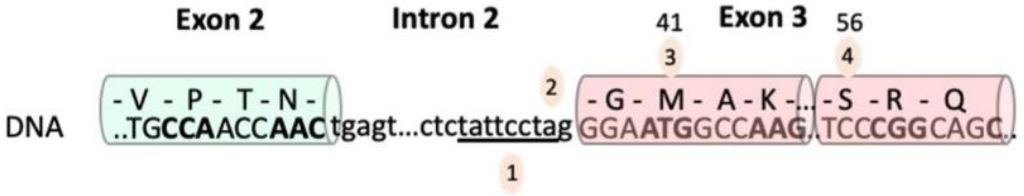


vacuoles in myeloid progenitor cells in bone marrow

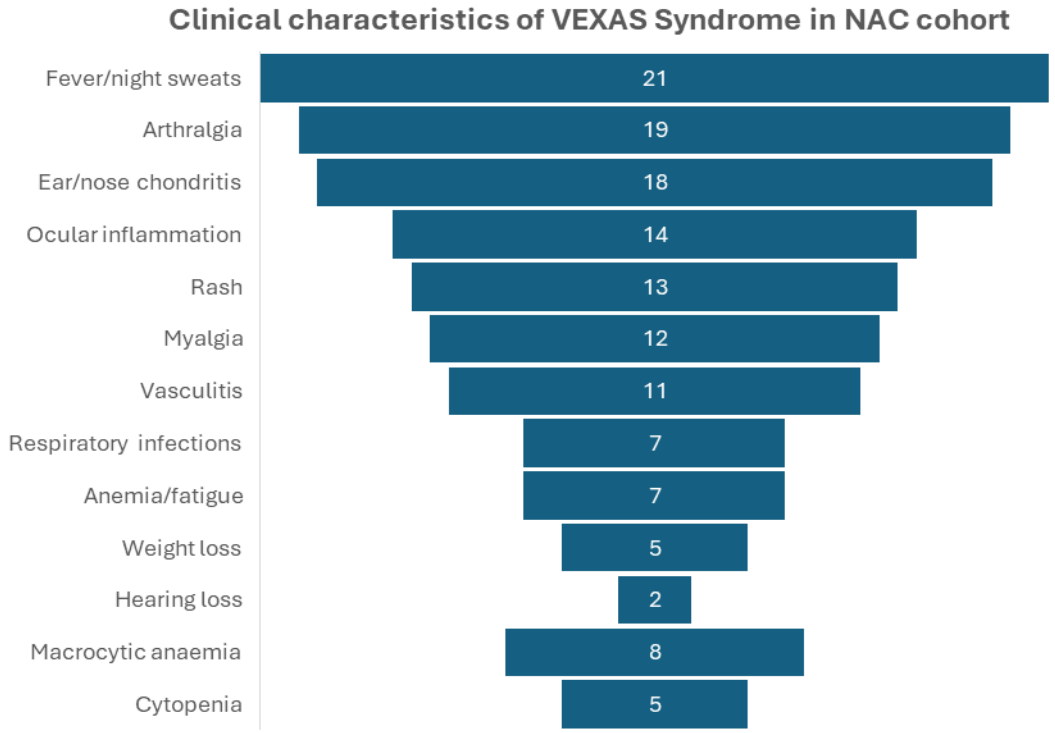
VEXAS syndrome among referrals for autoinflammatory disorders

At NAC we identified 35 patients with VEXAS syndrome

Clinical characteristics of VEXAS Syndrome in NAC cohort	
Demographics	**n=35**
Age of disease onset, years, median (range)	**66 (48–79)**
Male sex, n (%)	**34 (97)**
Clinical Diagnosis, n (%)	
Relapsing polychondritis	15
MDS	11 (35)
Sweet's syndrome	2 (6)
Clinical manifestations, n (%)	
Fever/night swets	21 (60)
Arthralgia	19 (54)
Ear/nose chondritis	18 (51)
Ocular inflammation	14 (40)
Rash	13 (37)
Myalgia	12 (34)
Vasculitis	11 (31)
Respiratory infections	7 (20)
Anemia/fatigue	7 (20)
Weight loss	5 (14)
Hearing loss	2 (6)
Haematological manifestations n (%)	
Macrocytic anaemia	8 (23)
Cytopenia	5 (14)



1 Deletion of the site splice : c.118-9_118-2del
2 Point mutation in splice site : c.118-1 et c.118-2
3 Mutation p.Met41
4 Mutation p.Ser56



New Developments:

- UK Amyloidosis Network of Excellence - 4 new expert regional centres; NAC remaining as central hub for diagnosis, specialist imaging & coordination

- Rosetrees major project grant for functional testing in SAIDs– awarded Jan 2025
    - Cytokine mini panels
    - Interferon related gene assay
    - Adenosine Deaminase 2 enzyme activity

- Grant for WES to identify genetic susceptibility and disease modulators in patients with ATTR amyloid cardiomyopathy - awarded Jan 2025

- Participation in several clinical trials in ATTR and AL amyloidosis and SAIDs

- Newborn Genomes Program

NHS NAC (Clinical) & UCL CfA (Research)

Centre has unique ‘bench to bedside’ research incorporating protein biophysics and biochemistry, proteomics, animal models of disease, and clinical research

Clinical Trials & Observational Studies NAC

Intelligent drugs Designed on molecular targets

Disease in the patient

Natural history of the disease (Signs symptoms evolution)

World’s Largest Amyloid BioResource NAC & CfA

New Animal Models CfA

Experimental Molecular and Biological models

State of the art diagnosis

‘State of the art’ dedicated Imaging Centre NAC

Protein Biochemistry CfA

Molecular diagnostics

Precision medicine

UK’s First Accredited Clinical Proteomics laboratory, NAC & CfA

Translational

Molecular Biology & NGS laboratory, NAC

Thank you!

Acknowledgments:

NAC laboratory

Doctors & Patients

http://www.ucl.ac.uk/amylidosis www.amyloidosis.org.uk

National Laboratory for Adult ALL MRD

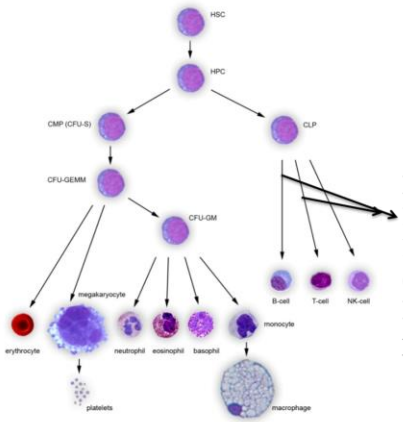
(the present and in the future)

Dr Bela Wrench

Clinical/*Academic Head of Service**

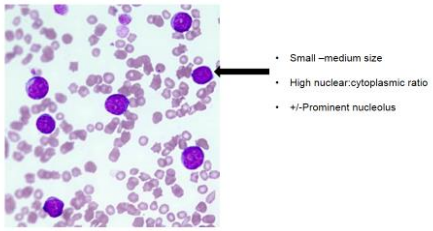
Reader/Consultant in Haemato-oncology

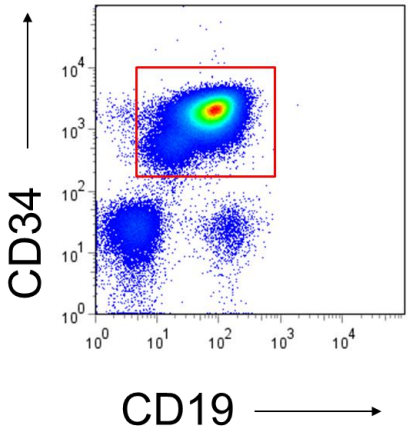
Duality of ALL cancers



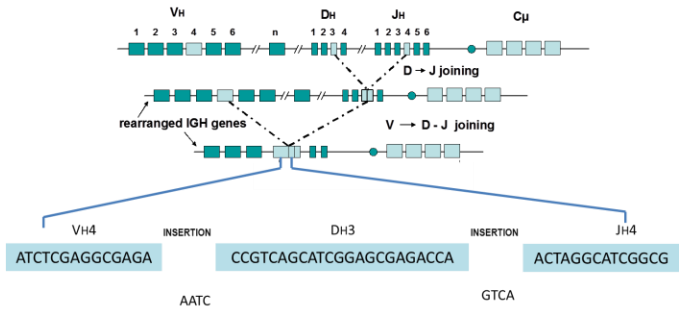
Pre B/T acute lymphoblastic leukaemia (originates from B/T cell precursor)

ALL cells in peripheral blood





Immunoglobulin gene locus



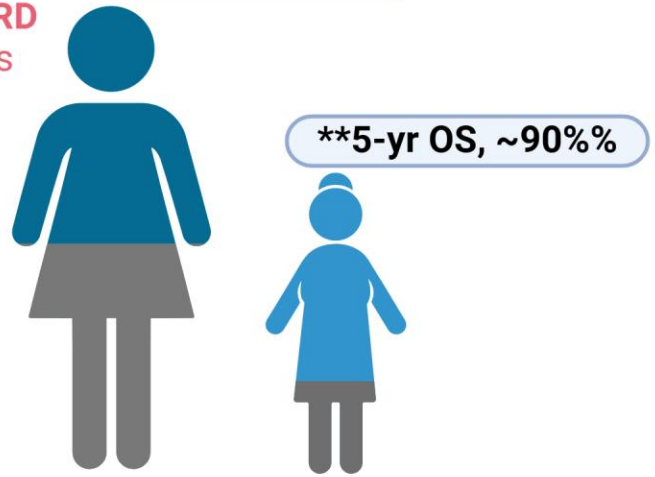
Diagnostic homogeneity

Age-associated diagnostic, treatment and response variables

Diagnostic
- Adverse genotypes
- **Non-evaluable MRD**
- Diagnostic failures

Response
- Relapse
- Resistance
- Refractoriness

Treatment
- Treatment intensity
- Toxicity



*Marks et al The Lancet Haematology, April 2022.

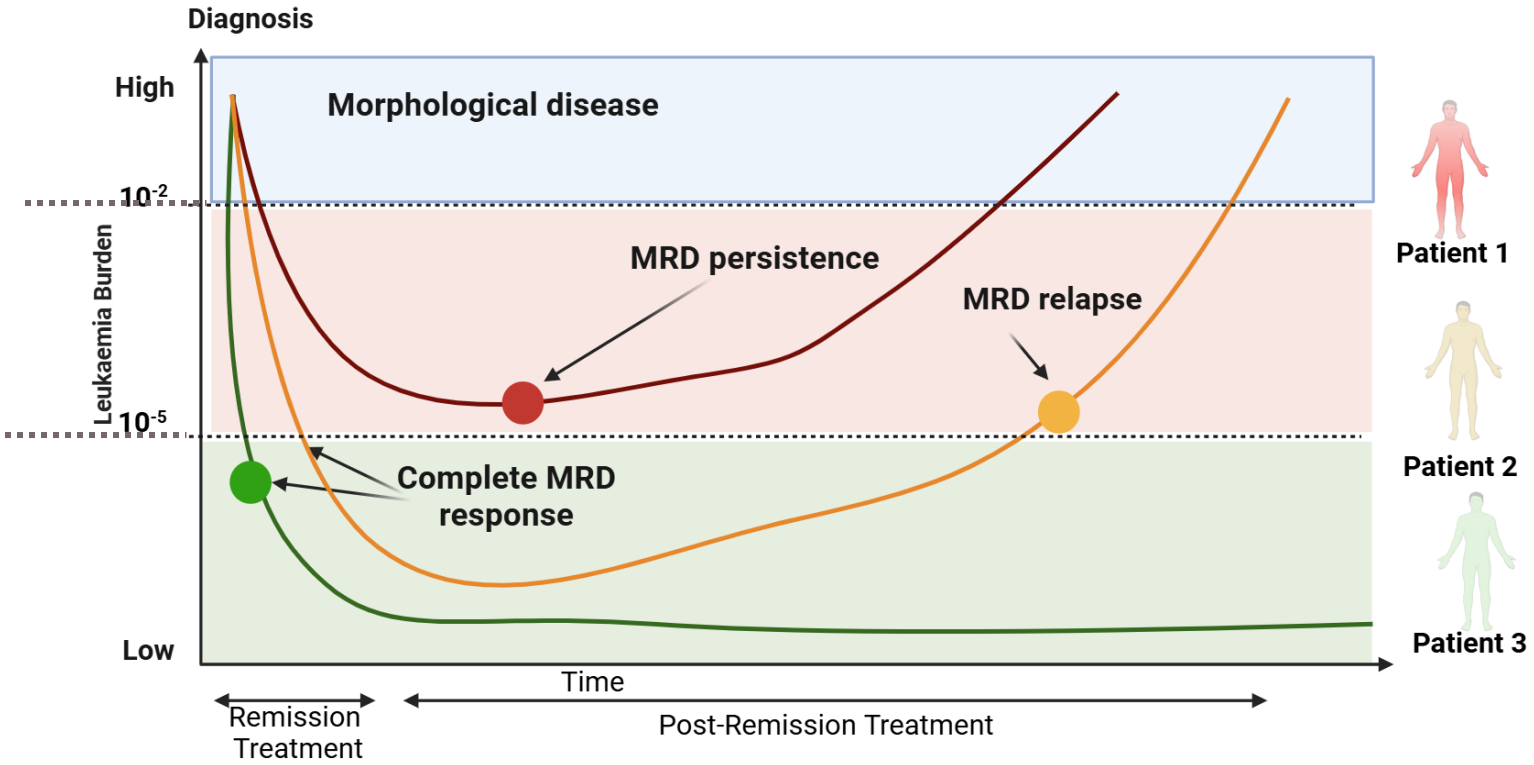
**Goulden et al, *Blood* (2017) 130 (Supplement 1): 141.

Clinical heterogeneity

Minimal (measurable) Residual Disease versus CR

Complete morphological remission

Current lower limit of MRD detection



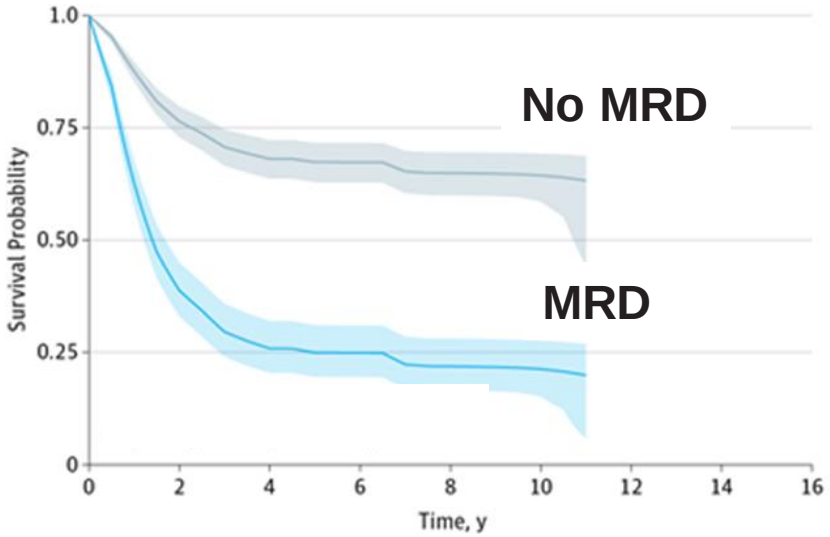
Minimal (Measurable) Residual Disease measurements during therapy provide personalised predictions of ALL outcomes

"Measurable disease detectable by sensitive techniques in patients achieving complete morphological remission (CR)"

Clinical Significance of MRD in adult ALL

EFS adult ALL according to MRD status (post-induction and consolidation):

16 studies with 2076 patients

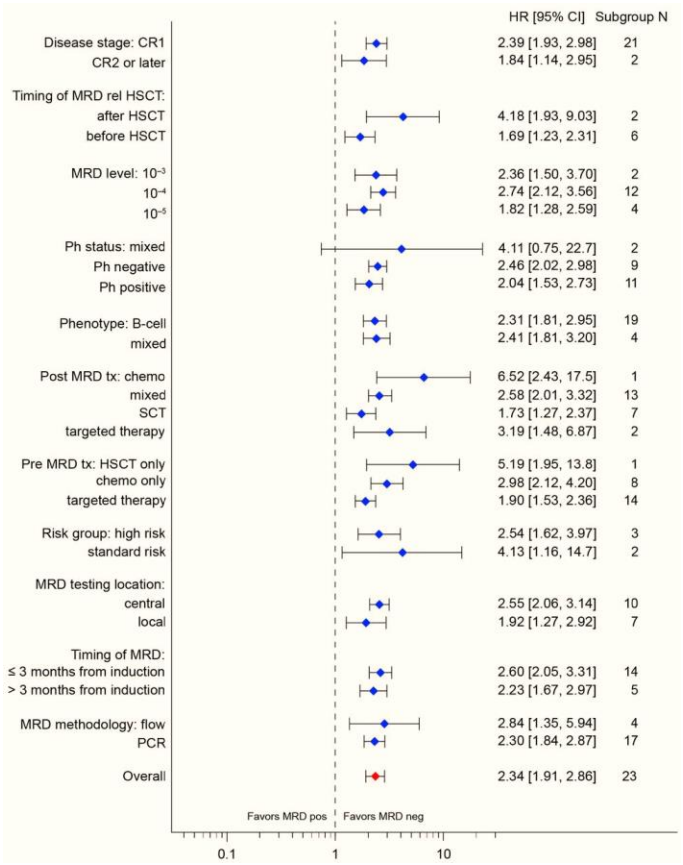


10-year EFS: 64% vs 21%.

EFS HR for MRD negativity 0.28; 95% BCI, (0.24-0.33)

Multiple subgroups

Favours MRD-pos **Favours MRD-neg**



RFS HR: Overall: 2.34;1.91–2.86]

N = 23 studies
N=3578
patients
B-ALL
PCR/Flow

Impact of MRD consistent: across therapies: (SCT vs chemo), methods and times of MRD assessment, cutoff levels, and disease subtypes

Berry et al JAMA Oncol. 2017;3(7):e170580.

Bassan et al 2019, Haematologica Oct;104(10):2028-2039.

National Laboratory for Adult ALL MRD Overview

Guiding Principle

"To deliver a high-quality service that is tailored to the unique needs of an adult ALL population"

History

- Concept conceived in the 1990s,research/academic testing provision Formally commisioned in 2021 (Barts Health). National diagnostic services to UK Adult ALL.
- *Centralised infrastructure*

Core activities

- MRD target screening. Rapid, quantitative, accurate MRD diagnostics, benchmarked standards
- Overarching quality assurance framework (consistency and accuracy),EUROMRD

Strategic delivery

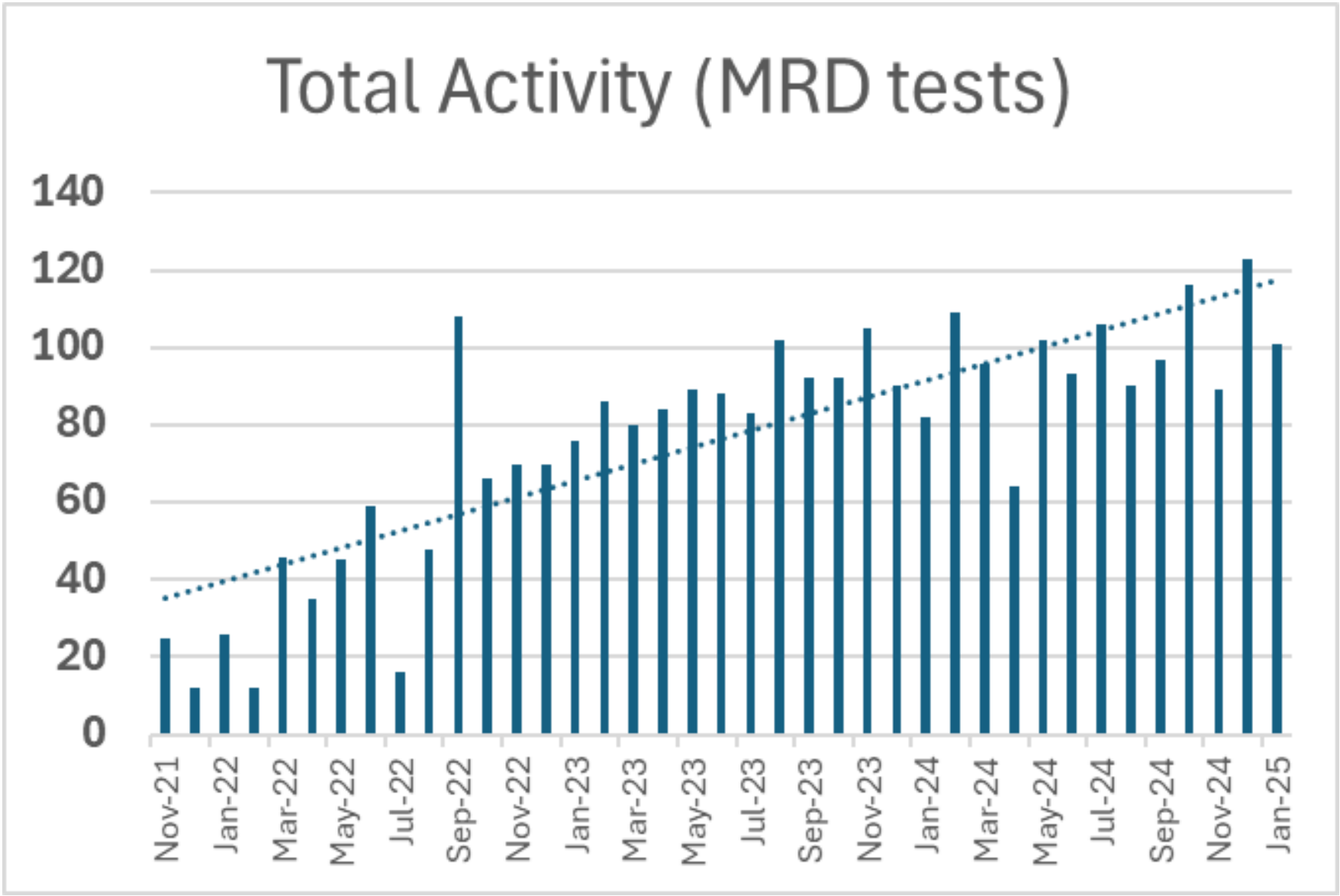
- Clinical trial delivery (UKALL 14,registry, EWAAL, ALL-RIC, *UKALL 15*)
- Translational research coordination/ Embed R and Development

MRD screening activity/annum

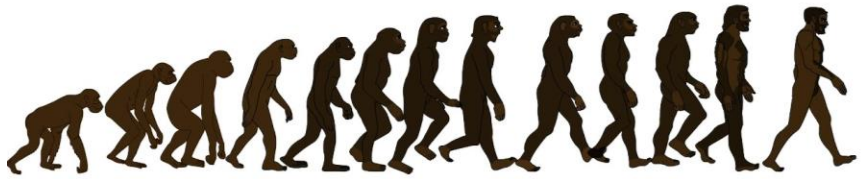
2022 232

2023 213

2024 262



Integration of MRD analysis in adult ALL



Correlation

Risk Stratification

Surrogate endpoint

MRD-indicated therapies

1993 -2006

2010 - 2018

2019

2025..

UKALL 12

UKALL14

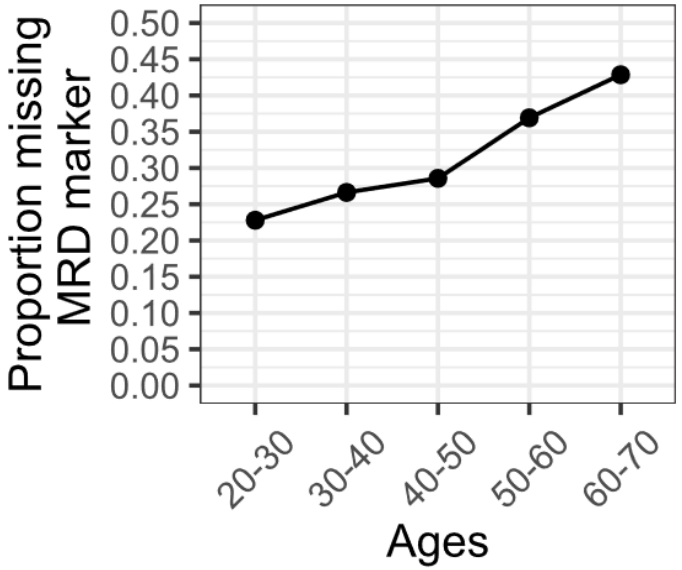
2013 - 2018

UKALL60+

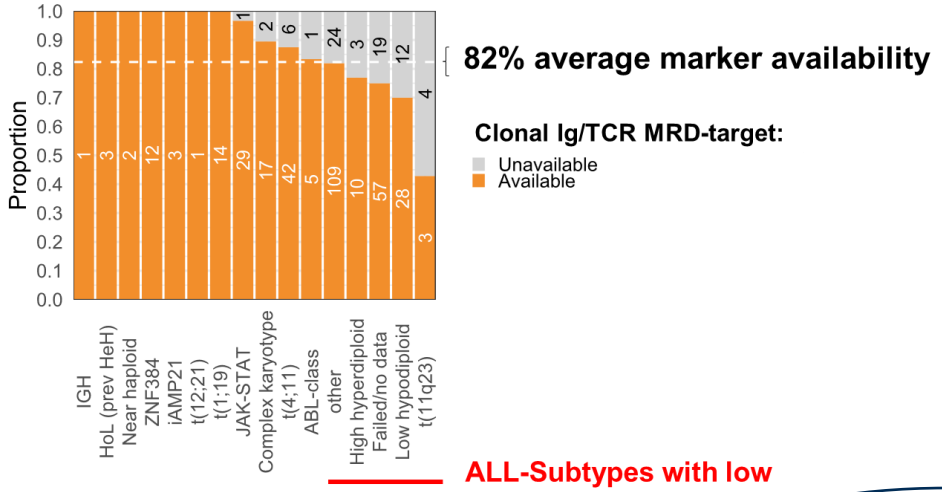
.....Increasing MRD clinical actionability

Current challenges in Adult ALL MRD

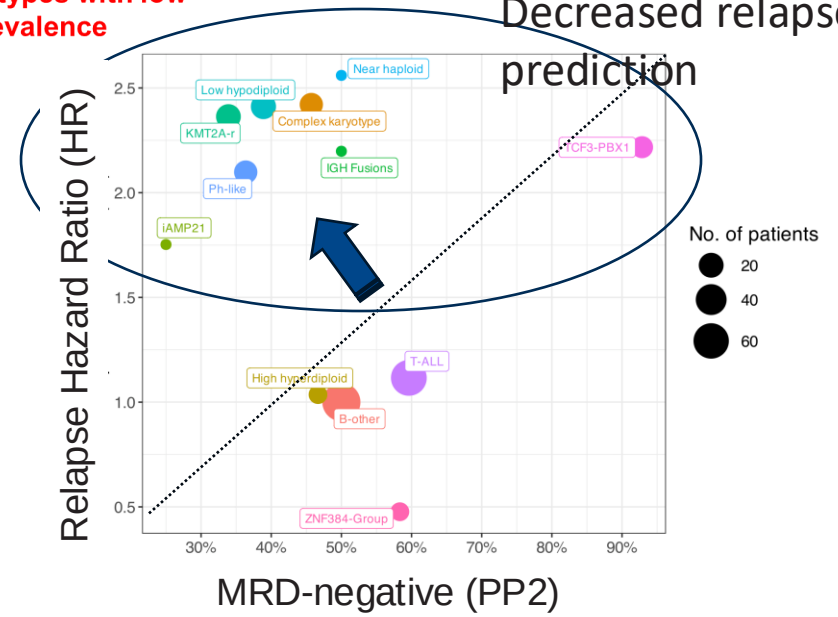
Impact of patient age



Impact of genetic subtype



Decreased relapse prediction



Variability in diagnostic utility...

1. Disease-specific experts
   Adult ALL Research Network (NCRI)
   Clinical Trial,Education, Scientific
2. Discovery Science Programmes
3. NHS cancer plan
4. Adult ALL MRD central lab

Review and Set Clinical Priorities

Leverage New Knowledge

Systems enablement

National delivery platform

National-scale improvements to patient care

Equitability

State-of-the-art ALL-MRD

personalisation

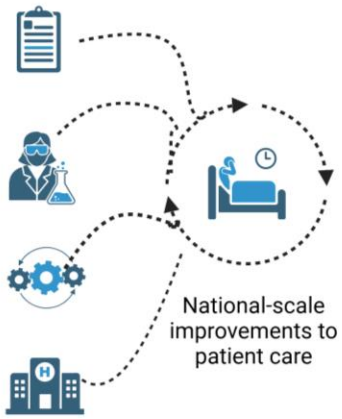
Advanced technologies

Research/NHS interface

Key Strategic Priorities

Transformation Plan

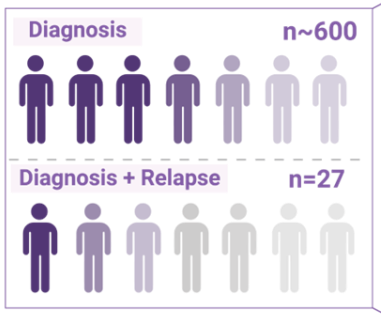
1. Review and Set Clinical Priorities
2. Leverage New Knowledge
3. Systems enablement
4. National delivery platform



Progress and development.....

1. UKALL14 Clinical Cohort
n=814

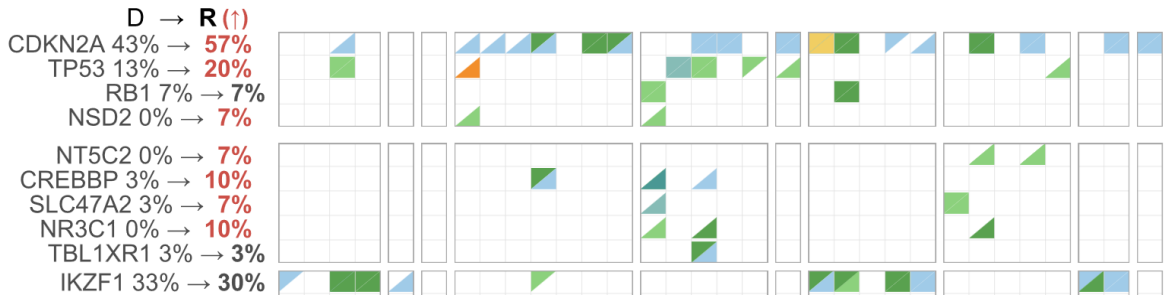
Genomics Profiling Cohort

2. 

3. **National (England) Genomic Strategy**

- April 2003 – the human genome was published
- 2012 – David Cameron announced the 100,000 Genomes Project
  - Genomics England was set up to deliver this flagship project
  - Sequence 100,000 whole genomes from NHS patients
- October 2018 – NHS (England) Genomic Medicine Service (GMS) launched
  - Ensure equitable access to genomic testing across the country
  - Embed advanced genomic technologies in mainstream care
  - Consolidation

Nominate next-generation MRD biomarkers



4. ## Coming soon...

- **NGS** Ig/TCR screening
- **Target expansion** (DNA/RNA fusion genes e.g. KMT2A fusions), long-read seq
- **High-depth** MRD techniques (<10^{-5})

Acknowledgments

Barts Health Adult ALL MRD team

Our values

Drive equity through innovation

Foster partnership working

Pioneer new ways to integrate research and clinical care

Lisa Brown
Dr Marianne Grantham (Head of Molecular Haematology Service)
Emile Thomas
Dr Shaun Bevan (Lead Clinical Scientist)
Helen Warwicker
Krisztina Alapi
Sharoniya Taylor

UCL Academic MRD laboratory

Adele Fielding
Soo Wah Lee
Krisztina Alapi

Thanks for listening and thanks for supporting the service!

North Thames
Genomic Medicine Service

Highly specialised testing: Now and the future

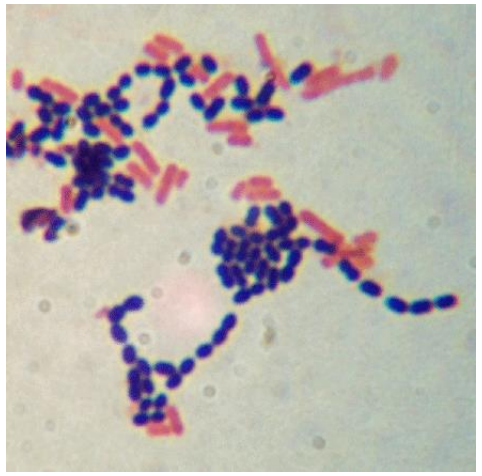
Metagenomics for the Diagnosis of Infection

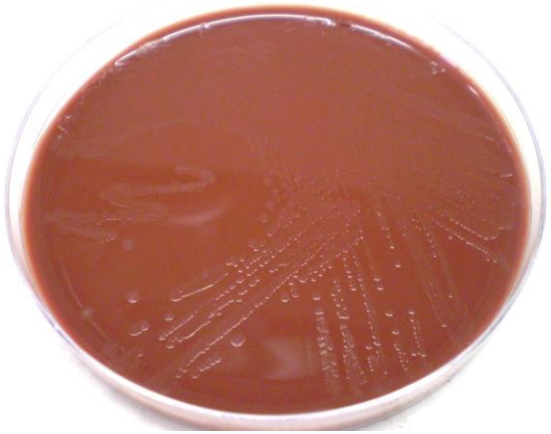
Dr. Julianne Brown (Principal Clinical Scientist | Microbiology & Virology)

Metagenomics for the Diagnosis of Infection

- How infections are diagnosed
- The problem with current methods
- Metagenomics to diagnose infection
- Some interesting cases
- Metagenomics for the future
- Take home messages

How infections are diagnosed – grow bacteria

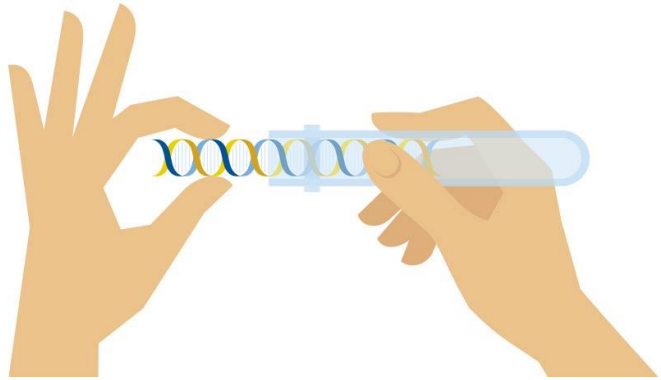




- Culture: Test patient samples to see if bacteria grow
- Detect and identify bacteria causing infection
- Diagnose and treat infection

- The problem:
  - Some bacteria don’t grow (unculturable)
  - Viruses don’t grow
  - Bacteria may not grow if patient is on antibiotics

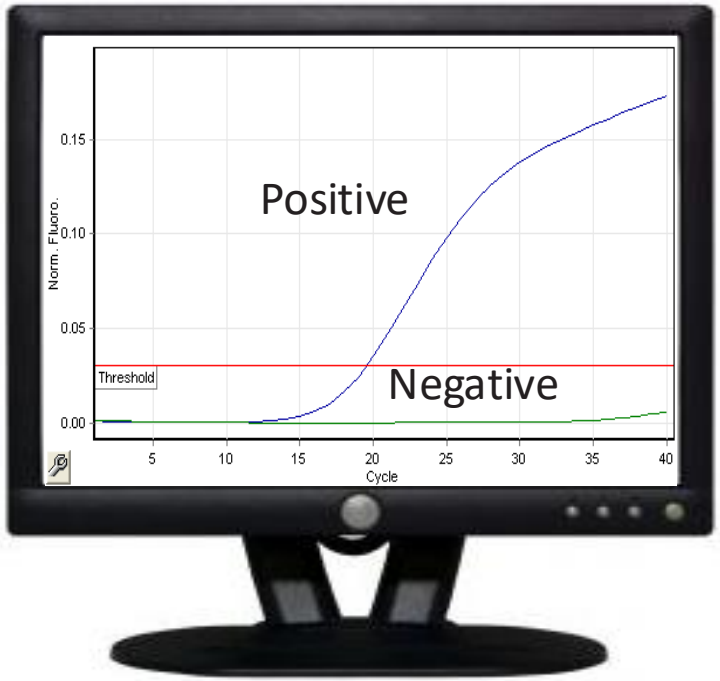
How infections are diagnosed – look for DNA



PCR: Look for the DNA of specific viruses or bacteria in patient samples

- Yes or no answer

- Pros:
  - Fast (few hours)
  - Inexpensive
  - Sensitive



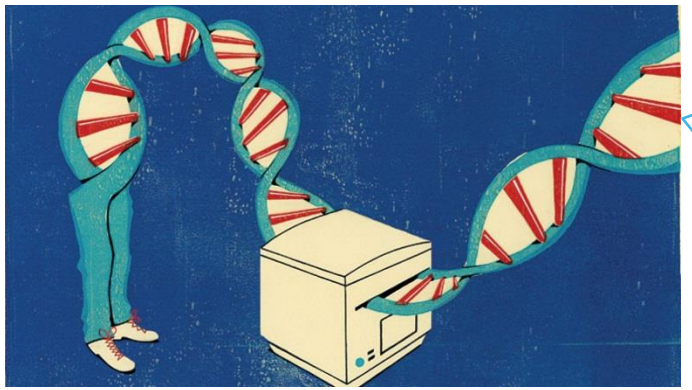
Need new tools to fill the diagnostic gap

The trouble with PCR

- One test for every infection
  - →Insufficient sample (prioritise likely culprits)
- Need to know what you're looking for
  - →If we don't look for it, we won't find it
  - →Can't detect new or unexpected pathogens
  - →In 63% of cases of encephalitis we don't know the cause

Metagenomics

Sequencing **all** of the DNA and RNA in a sample



brain biopsy or CSF

Human sequences

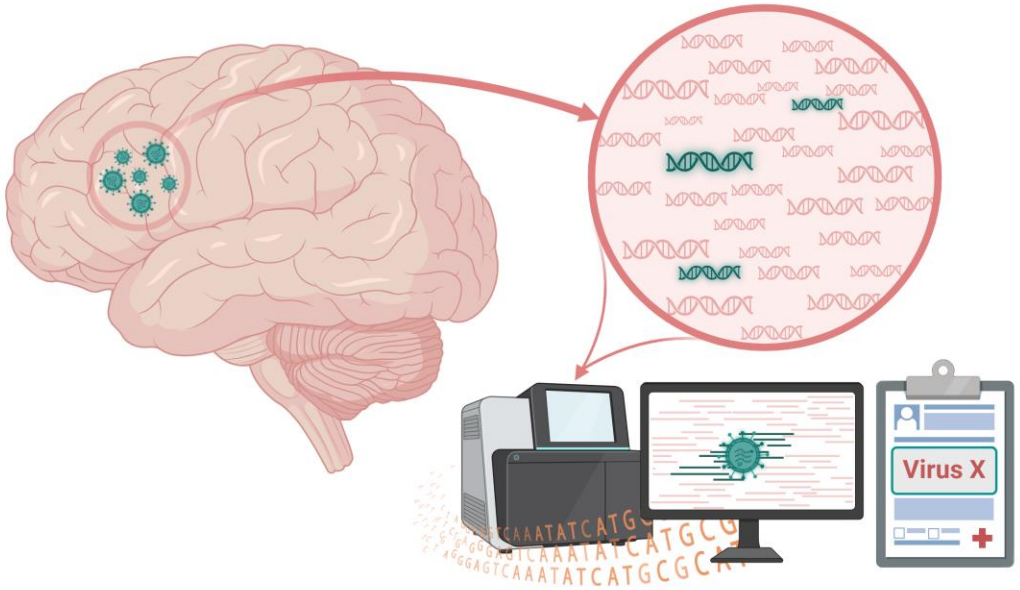
Viral or bacterial sequences (all non-human DNA and RNA)

Can detect any virus or bacteria in one go

Don’t need to know what we’re looking for

Can detect unusual or unexpected infections

Metagenomics – a clinical service at GOSH



- 10 years since we started
- Embedded in routine diagnostics for patients with high suspicion of infection but no diagnosis (GOSH and wider NHS)
  - Encephalitis
  - Hepatitis
  - Eye infections
  - Respiratory infections
- First and only UK lab to provide clinical metagenomics service and achieve UKAS accreditation to ISO:15189 standards
- Can detect what we're not looking for
- Provides an infection diagnosis for patients who couldn't get one (filling the diagnostic gap)

Interesting cases over the years

Case 1 (Outbreak)

- Explanted livers (and blood), Children <5 years old
- Outbreak of non-A-E acute hepatitis globally, many cases in Europe and UK
- Adenovirus F41 detected by PCR
- Is there anything else?

Adeno associated virus 2 (AAV2)

Case 2

- Brain biopsy, 16 year old M
- Primary HLH diagnosis, HSCT 1 year old
- Immunoglobulin replacement therapy for antibody deficiency
- Attended school, cognitively normal
- 15 years post-HSCT encephalitis

Avian paramyxovirus type 1 (Newcastle Disease)

Case 3

- Ocular fluid, 28 yr old F
- Chronic uveitis following trip to South America 6 years previously
- Treated with topical, oral and local steroids and immunomodulatory therapy
- Worsening inflammation and flare ups

Leptospira santarosai

Case 4

- Brain biopsy (FFPE), 70 year old F
- Previously fit and well
- Encephalitis
- Radiology: CAARI (Cerebral Amyloid Angiopathy–Related Inflammation)
- Treated with dexamethasone only
- Histopathology: didn't quite fit with CAARI

HSV-1

Metagenomics for the future

Turn-around-time

- 1-2 weeks
- Need hours or 1-2 days

Detecting low levels of pathogens

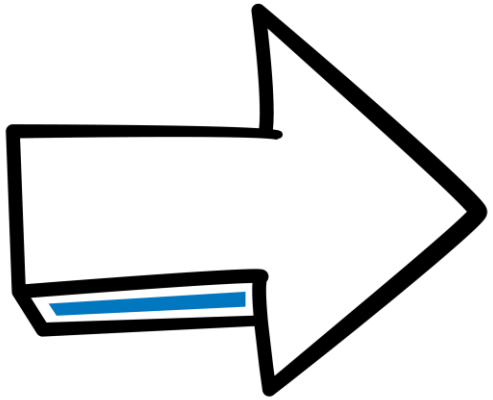
- For some sample types (e.g. tissue, respiratory) not as sensitive as PCR
- Used as last resort after all other testing done
- Need to rule out infection
- Replace current methods to use as first line test

Cost per sample

- £1300
- Need £100-200

Standardised controls and reagents

- Working with other UK and European teams



Wider adoption in healthcare laboratories

Metagenomics for diagnosis of infection

- Diagnosis of infection is critical for patient management
- Current methods grow bacteria or look for DNA of specific viruses/ bacteria – can't detect organisms that don't grow or that not specifically looking for
- Metagenomics is a new method that can detect any organism, even if unexpected
- New innovative method – GOSH are first in UK
- Improvements underway to make it faster, cheaper and more sensitive so can be used more widely and as first line test

Acknowledgements

UCL

- Dr. Sofia Morfopoulou
- Oscar Torres
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- Laura Atkinson
- Dee Davis
- Angelika Kopec
- Alex Lennon

NHS Guy's and St Thomas' NHS Foundation Trust

CIDR Centre for Clinical Infection & Diagnostics Research

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- Rahul Batra

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- Tommy Lever
- Rowena Couto
- Microbiology, Virology and Infection Control Department
- Neuro-ID MDT

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GOSH Charity Paediatric Research Grant (2017-2019)

NIHR Biomedical Research Centre at GOSH and UCL

North Thames
Genomic Medicine Service

A look forward

Dr Angela George – North Thames Genomic Service Medical Director

Genomics in the NHS

By 2035, NHSE predict that genomics will be part of 50% of healthcare journeys and may feature repeatedly across a patient's lifetime.

Testing of parents prior to conception to provide information on inherited conditions.

Delivery of fetal genomic testing, including non-invasive prenatal testing, to provide families and clinical teams with as much genomic information as possible.

The newborn blood spot screening test provides further genetic information to new parents, while research programmes like the Generation Study hope to diagnose treatable conditions earlier.

Early intervention and diagnosis of childhood onset conditions, including rare and complex disorders.

Throughout life genomic testing may be a vital part of a person's healthcare journey. Testing for rare diseases, providing vital information following a cancer diagnosis and, in a developing field, understanding how our genes may impact our reaction to medication.

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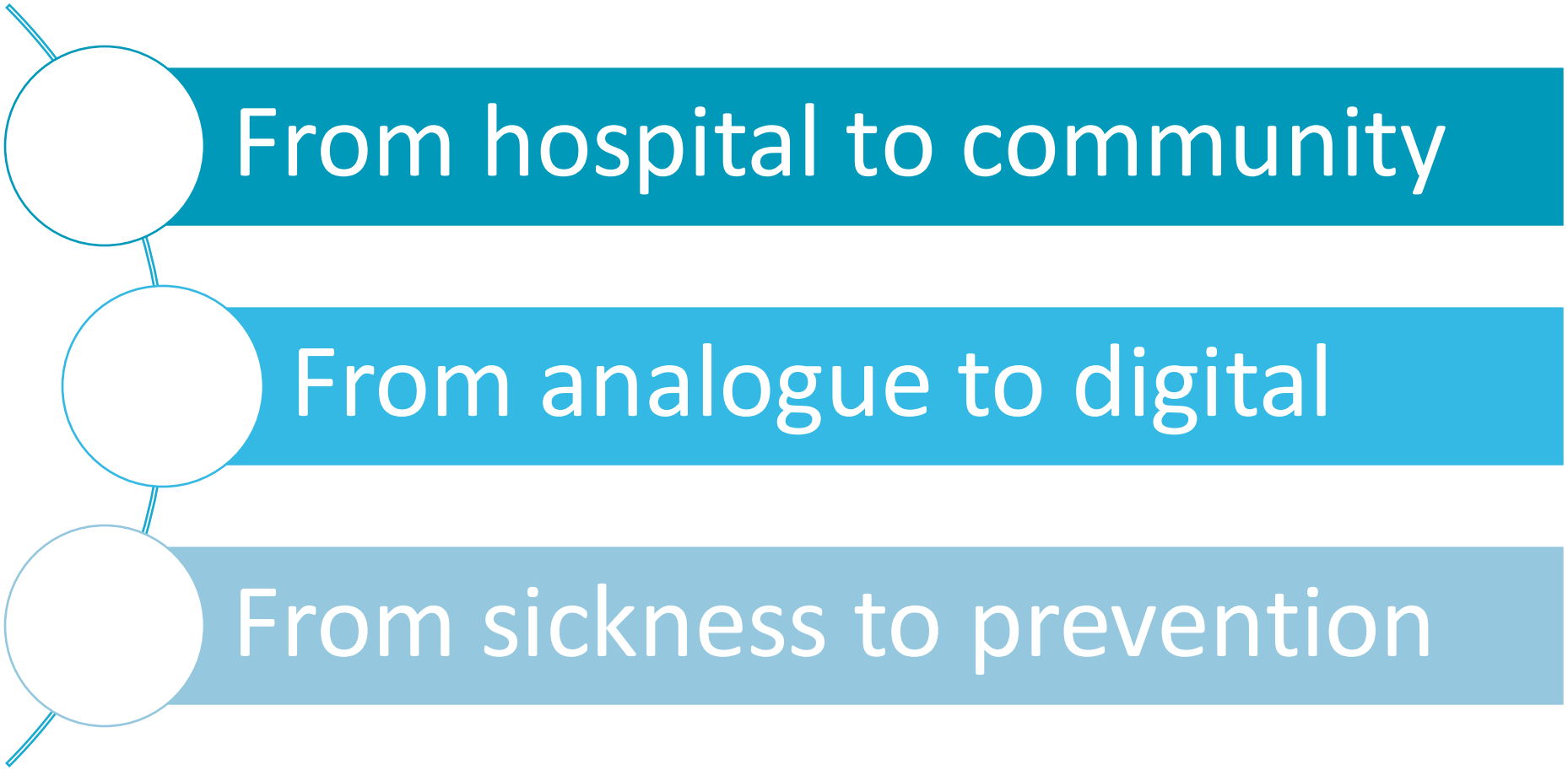
Genomics in the NHS



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From hospital to community

Working with community healthcare professionals to understand how we bring genomics to the community

Within the North Thames Genomic Medicine Service we are working with community healthcare professionals to centre their workforce into our plans:

- GP Leads – Dr Dania Shoeb, Faye Dannhauser and Dr Anwar Khan
- Health Visitor Lead – Kate Marsh
- Community Paediatric Lead – Dr Ahmed Ahmed

Working to provide tailored education and training, raising awareness and identifying gaps in knowledge. Help managing community questions and concerns about genomics.

Our Primary Care team have worked with Clinical Genetics teams to create an improved cancer referral form – to ensure correct referrals are being made.

Centring the patient voice

Our Patient, Public and Carer Panel

Our patient, public and carer panel is made up of representatives from across our region. They work with us across all areas, providing vital insights and co-producing key projects.

Recently they have joined groups focusing on:

- Developing our equity strategy
- Providing patient voice to our Generation Study oversight
- Investigating how we can integrate AI into the GMS
- Specific project work (i.e. Sudden Cardiac Death project)

Contact Fiona.calvert@gosh.nhs.uk to find out more

From analogue to digital

Using digital tools and automation to increase efficiency

Working with NHSE to continue to test the National Order project, moving the test directory and the requesting process into an efficient online tool.

Continuing to lead the way in integrating automated tools to drive forward testing efficiency

Pharmacogenomic data – the Progress RX tool

Pharmacogenomics uses genetic information to understand how a person will respond to a medication before it is prescribed. This is already being integrated into healthcare, NHSE are currently piloting the use of pharmacogenomic testing in stroke patients.

As part of this pilot, the team are testing the use of a “end-to-end diagnostic interpretation tool” that translates genomic results into practical prescribing advise, integrated into established clinical systems.

From sickness to prevention

The Generation Study – diagnosing rare diseases before symptoms appear

Cancer Vaccine Launch Pad

The Jewish BRCA project and retrospective testing

The Jewish BRCA project was established in 2023 and gives people in England with Jewish ancestry, a high-risk population, access to at home BRCA testing. The test has so far been requested by 20,000+ people.

We are now about to launch a retrospective BRCA testing pilot project March 2025

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Thank you for joining this year's showcase

Please scan the QR Code to complete your feedback