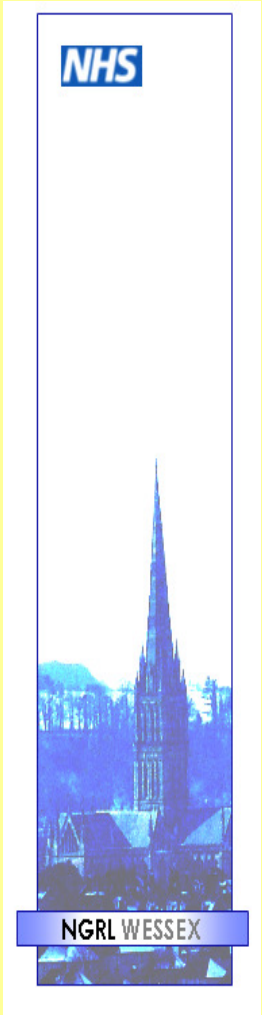
Implementation of array comparative genomic hybridisation into NHS genetics services

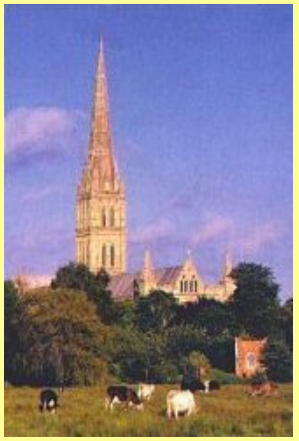
Royal College of Pathologists, Wednesday 8th July 2009

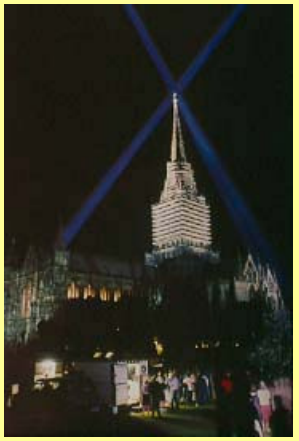


Laboratory perspective(s)

John CK Barber [1,2,3]

[1] National Genetics Reference Laboratory (Wessex)
and [2] Wessex Regional Genetics Laboratory
Salisbury NHS Foundation Trust, Salisbury
[3] Human Genetics Division
University of Southampton, Southampton





2003 White Paper "Our inheritance, our future: realising the potential of genetics in the NHS"

Investment in Regional Centres and the creation of National Genetics Reference Laboratories (NGRLs) which facilitated:

- **High throughput molecular laboratories**
- **Regional and devolved networks (e.g. SCOBEC)**
- **The capacity to meet new reporting time targets**

…and, in cytogenetics:

- **Increased use of automation**
- **MLPA for sub-telomere and microdeletion testing**
- **QF-PCR for rapid prenatal diagnosis**
- **Array CGH for the detection of constitutional abnormalities**

2006 Public Health Genetics (PHG) Foundation
"Evaluation of array-CGH for chromosomal abnormalities in clinical practice"

Recommendations:
1. As the cost of array CGH decreases, consideration should be given to…increasing the proportion of patients…(having array CGH) to minimise missed diagnoses."
2. Means (for) the revenue costs of array CGH…to be met".

PHG	**£117 per karyotype**	**£52 per FISH**	**£892 per array**
WRGL			**£355 per array (including follow up)**

PHG would be welcome to revisit their model with updated figures

National Genetics Reference Laboratory (Wessex):

Phase 1

- Customised an Agilent oligo array for constitutional use
- Pragmatic compromise between:
  a. 135 targeted microdel/dup syndromes
  b. "Backbone" coverage of all other gene and intergenic regions.
- 4x44K format with no need for a dye swap reduces cnsumables costs to ~ £150 per patient
- 24 laboratories in the UK and overseas

www.ngrl.org.uk/Wessex/arraycgh

Dr Shuwen Huang

Phase 2

The International Standard Cytogenomic Array (ISCA) Consortium – 37 laboratories to date

https://isca.genetics.emory.edu/iscaBrowser/)

BAC users - International BlueGnome user group

Edinburgh – collaboration with Birmingham and BlueGnome

Manchester – Affy 6

Birmingham – collaboration with Nijmegen, Paris and other labs

Cambridge – Affy 6

Salisbury – 24 labs registered to use NGRL(W) 4x44K design ISCA collaboration

Oxford – collaboration with Groningen on 2x105K design ISCA collaboration

Guy's St Thomas Serco (GSTS) NGRL(W) 4x44K patient:patient

Contributions to international Databases e.g. DECIPHER and ECARUCA

The International Standard Cytogenomic Array (ISCA) consortium:

UK questionnaire:

1. Is the list of targeted loci comprehensive? Broadly yes.

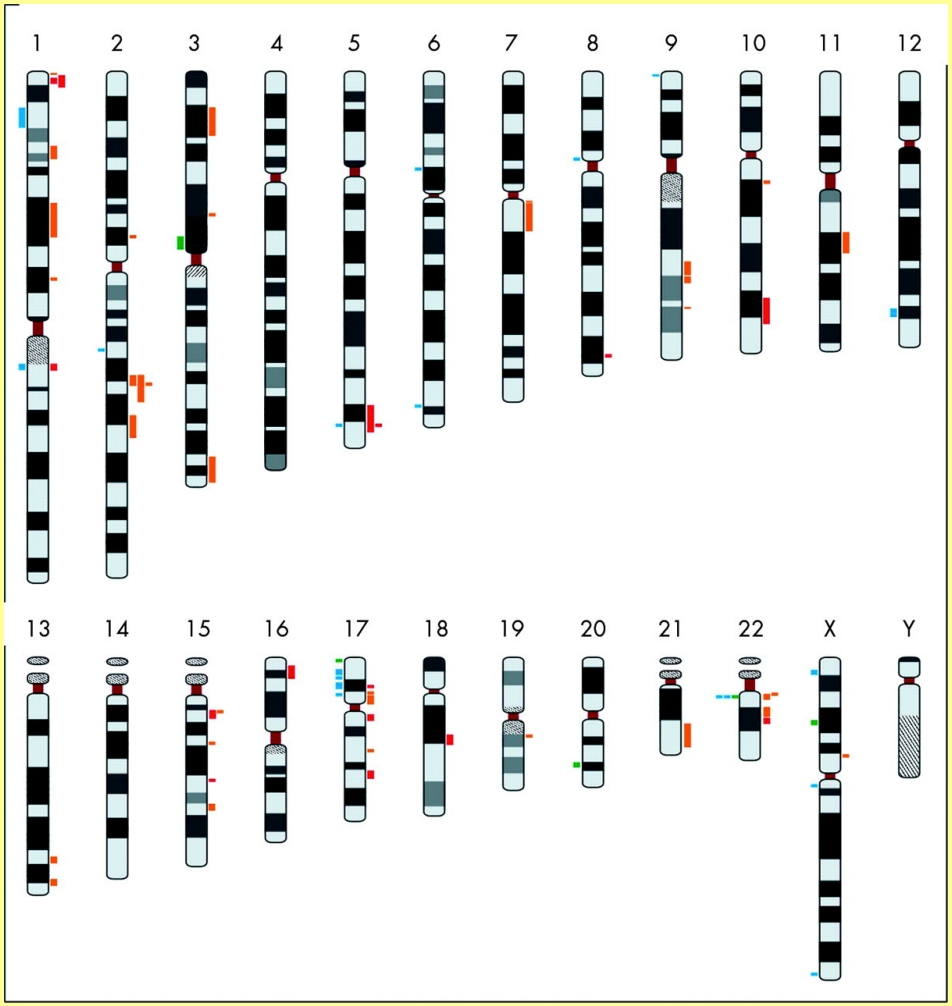
2. If currently using BAC arrays, are you considering a transfer to higher resolution array CGH? 10/12 Yes.

3. If switching, to oligo or SNP arrays?

- 6/10 switching to oligos
- 1/10 switching to Affymetrix SNP6
- 3/10 undecided

We already have an emerging consensus towards higher resolution platforms for array CGH

Array CGH as a front line test instead of karyotyping:



Syndromic mental retardation (Shaw-Smith et al, J Med Genet 2004;41:241-8; deVries et al, Am J Hum Genet 2005;77:606-16)

Syndromic Craniosynostosis Krepischi-Santos et al, Cytogenet Genome Res 2006;115:254-61

Syndromic autism (Jacquemont et al, J Med Genet 2006; 43:843-9;Sebat et al 2007;316:445-9)

Isolated heart defects (Erdogan et al, J Med Genet 2008;45:704-709)

Isolated neuropsychiatric conditions inc autism and schizophrenia (Weiss et al, 2008)

Heterogeneity - clinically significant abnormalities across the whole genome (see Menten et al, J Med Genet, 2006;43:625-633)

Array CGH as a front line test instead of karyotyping:

"New" and "established" syndromes microdeletion/duplication syndromes detected using customised 4x44K array CGH:

Microdeletion/ duplication	Reference	Frequency in 2419 samples*	Frequency in 2419 samples*	Population frequency (est)
22q11.2	DiGeorge/Velocardiofacial	16 (0.66%)	1 in 151	1 in 4,000
16p11.2	Weiss et al (2008)	14 (0.58%)	1 in 173	1 in 4,571
16p13.11	Hannes et al (2008)	12 (0.50%)	1 in 202	1 in 5,333
15q11.2	Prader-Willi/Angelman	11 (0.45%)	1 in 220	1 in 5,818
7q11.23	Williams	8 (0.33%)	1 in 302	1 in 8,000
17q12	Mefford et al (2007)	7 (0.29%)	1 in 346	1 in 9,142
1q21.1	Mefford et al (2008)	6 (0.25%)	1 in 403	1 in 10,667
15q13.3	Sharp et al (2008)	6 (0.25%)	1 in 403	1 in 10,667
3q29	Willatt et al (2005)	4 (0.17%)	1 in 605	1 in 16,000
17q21.31	Koolen et al (2006)	4 (0.17%)	1 in 605	1 in 16,000
17p11.2	Smith Magenis/Potocki-Lupski	3 (0.12%)	1 in 806	1 in 21,333
17p12	Charcot-Marie-Tooth	2 (0.08%)	1 in 1210	1 in 32,000
8p23.1	Barber et al (2008)	1 (0.04%)	1 in 2,419	1 in 64,000
Total		94 (3.9%)	1 in 26	1 in 681
Total new		54 (2.2%)	1 in 45	1 in 1,185
Cystic fibrosis				1 in 2,000

*(Rudd et al. Hum Mol Genet .2009; 0: ddp233v1-ddp233)

Array CGH as a front line test instead of karyotyping:

CNVs "the equivalent of molecular mis-sense mutations" and might be handled using a schematic 5 class reporting system based on that of Plon et al, 2008:

Class	Name	Evidence	Follow-up	Code
5	Known significance	1. Established syndrome. 2. Size between 1 and 10 Mb. 3. High gene density. 4. Dosage sensitive/candidate gene(s) relevant to the phenotype.	Parents for possible transmission and recurrence risk.	Copy number change -CNC
4	Likely significance	1. De novo imbalance. 2. Size between 200 kb and 1 Mb. 3. High gene density. 4. Dosage sensitive/candidate gene(s) relevant to the phenotype.	Parents to determine whether de novo or transmitted.	Likely copy number change - LCNC
3	Uncertain Significance	1.One or both parents unavailable. 2.Size between 100 kb and 0.5 Mb. 3. Average/low gene density. 4. No dosage sensitive/candidate gene(s).	Parents and other family members	Uncertain copy number variation UCNV
2	Unlikely significance	1. Size between 50 kb and 250 kb. 2. Region of low gene density or gene desert. 3. No dosage sensitive/candidate gene(s).	Parents and other family members.	Novel CNV NCNV
1	No clinical significance	Known copy number variable region from in e.g. Database of Genomic Variants (DOGV)/Redon CNV/regions in normal controls (e.g. de Smith et al, 2008).	No parental follow-up necessary and no report issued.	CNV

Plon SE et al "Sequence variant classification and reporting: recommendations for improving the interpretation of cancer susceptibility genetic test results." Hum Mutat 2008;29:1282-91

How to get prospective arrays funded?

No savings in personnel

Need to find cost of arrays and consumables.

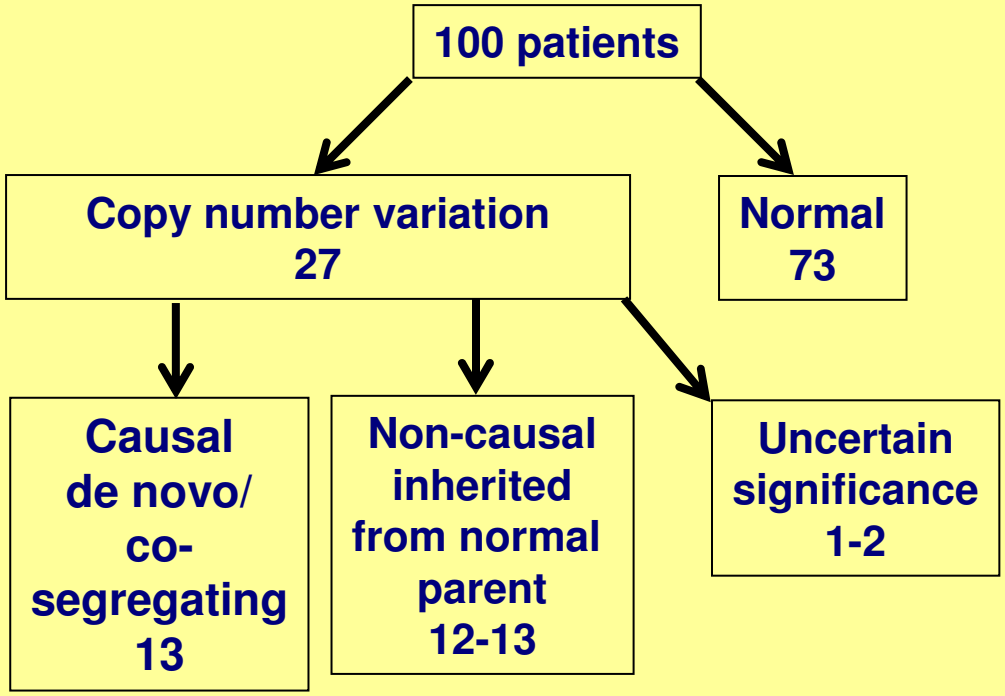
Convince local commissioners of clinical utility and the need to fund the difference between karyotyping and array CGH.

Re-configure services.

UK Genetics Testing Network (UK GTN) www.ukgtn.nhs.uk

Array CGH for selected DD/MR/CA referrals only

Simplified workflow for adjunct:



Costs of:
1. Karyotype
2. FISH/MLPA
3. Array CGH
4. Follow up:

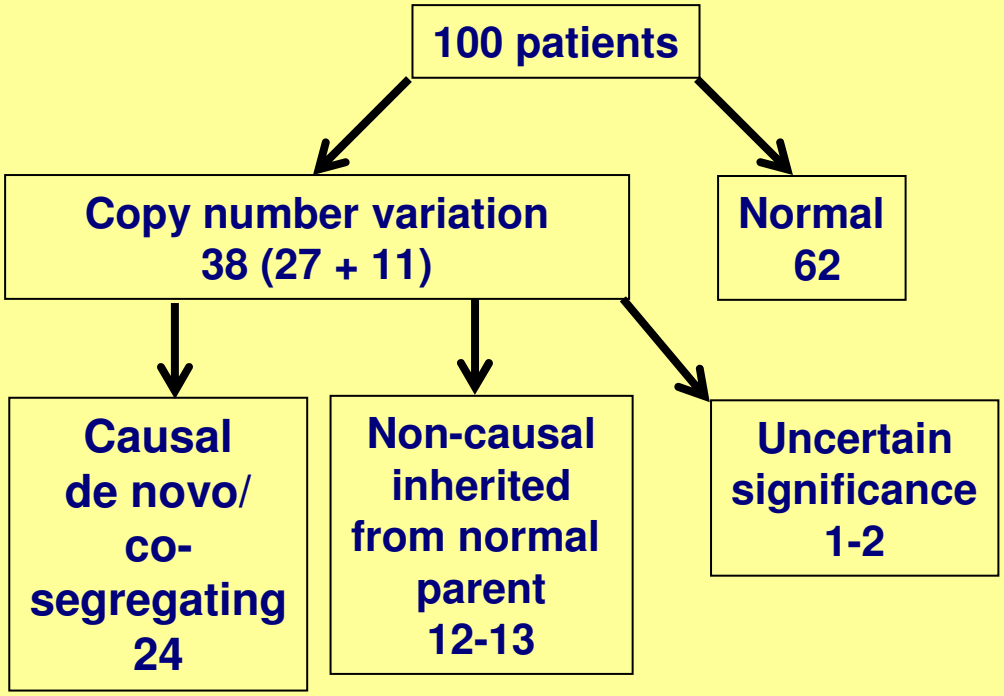
~£700

~13% of cases de novo or co-segregating copy number changes (CNCs)
~13% will have benign copy number variations (CNVs)

UK Genetics Testing Network (UK GTN) www.ukgtn.nhs.uk

Array CGH as front line test for DD/MR/CA referrals

Simplified workflow for replacement:



Costs of array CGH and follow up:

~£350

~24% of cases de novo or co-segregating copy number changes (CNCs)
~13% will have benign copy number variations (CNVs)
~11% of DD/MR/CA referrals have chromosome abnormalities which the arrays will detect

Cause of more than 1 in 5 DD/MR/CA referrals (>20%)
Benign copy number variations present in another 1 in 8 (13%).

UK Genetics Testing Network (UK GTN) www.ukgtn.nhs.uk

1. Gene dossier for 4x44K array as an adjunct to karyotyping accepted by UK GTN gene dossier group – 2,000 arrays at £350 = £700,000.

2. Gene dossier for 4x180K as a replacement for karyotyping to be submitted to UK GTN - 12,000 at £150 = £1.8 million - 6 times as many for 2.5 times the cost

3. Laboratories should ensure array CGH included in SHA Operational Plans and PCT Local Development Plans for 2010/2011.

Phased replacement of karyotyping with array CGH as a front line test in "person sized" chunks of ~250 – 300 referrals:

Phase 1 - Scientist selected DD/MR/CA referrals (pink)

Phase 2 - "high risk" categories (blue)

Phase 3 - Severe dev delay/learning difficulties (yellow)

Phase 4 – Mild dev delay/learning difficulties (grey)

Member of staff moves to molecular cytogenetics with each phase.

Council Recommendation on an Action in the Field of Rare Diseases Adopted by the EU Council of Ministers

There are 30 million people affected by rare disorders throughout Europe

In the UK 3.5 million people will be affected by a rare disorder at some point in their life

75% of rare diseases affect children and 30% of rare disease patients die before the age of 5

There are over 6,000 rare diseases affecting 3.5 million people (1 in 17) in the UK. Collectively, rare conditions are not rare.

Strategically, improved methods of testing for the genetic basis of rare diseases should be an integral part of the UK response to this initiative.

RARE DISEASE | UK

The National Alliance for people with rare diseases & all who support them

Perspectives:

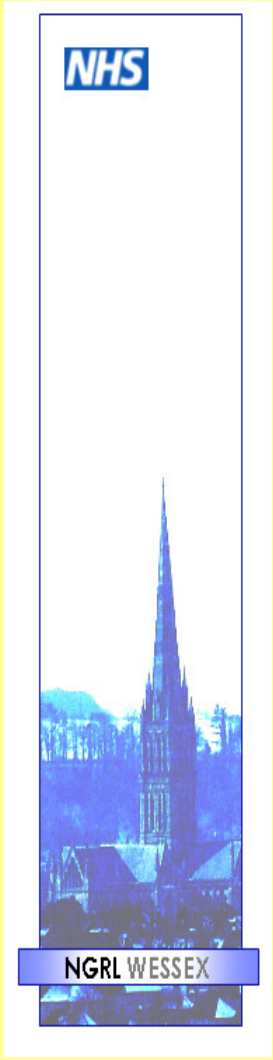
1. **Array CGH: literature and practice indicate that it is time to replace karyotyping with prospective array CGH testing.**
2. **UK GTN: Endorsement of array CGH as an adjunct to karyotyping is welcome but does not go far enough – where is the technological NICE?**
3. **Funding: as a minimum, laboratories need funding for the differential consumables costs of arrays.**
4. **Regulation: The ACC and CMGS should consider treating Voluntary Registration as the equivalent of Statutory Registration to allow a progressive shift from genetic scientists to genetic technologists.**
5. **Training: MSC is already defining new integrated cytogenetic and molecular genetic training schemes that will be available to all laboratories.**
6. **Service re-configuration: If Commissioners are unable to fund the introduction of array CGH, we need to decide how to re-model existing services.**
7. **Urgency: Inaction is not an option – class actions for negligence could follow the preventable birth of affected children.**
8. **European dimension: implementation of prospective array CGH testing could be part of the UK's response to the European Action in the Field of Rare Diseases.**

RARE DISEASE | UK

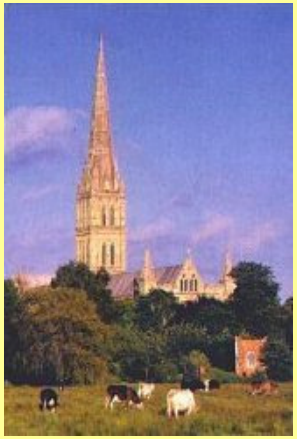
The National Alliance for people with rare diseases & all who support them

Implementation of array comparative genomic hybridisation into NHS genetics services

Royal College of Pathologists, Wednesday 8th July 2009



Thank you for your attention



Acknowledgement

UK Department of Health for funding the National Genetics Reference Laboratory (Wessex)