Post- & pre-natal applications of array-cgh: notes for discussion

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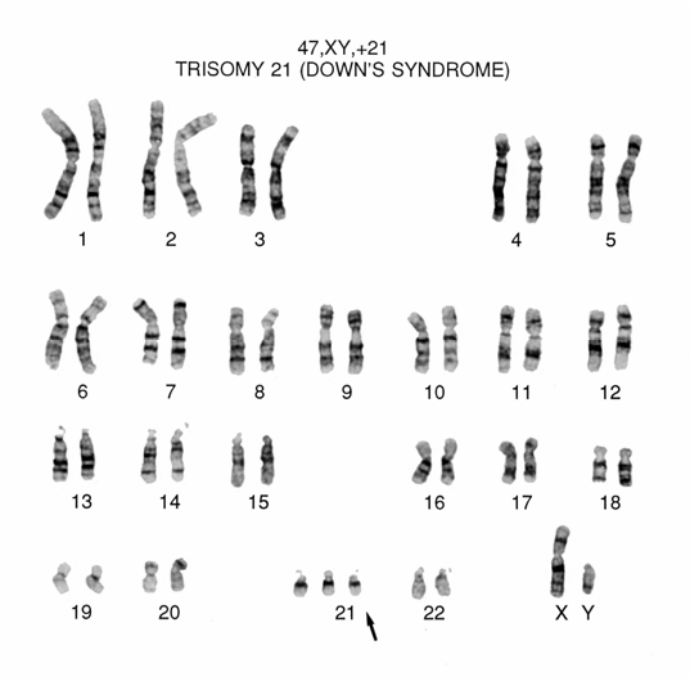
Points for discussion:

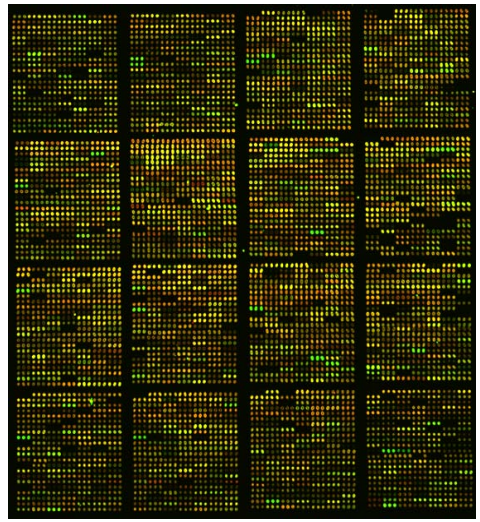
- **Constitutional postnatal aCGH & DD/MR/CA cohort**
- **Potential impact of aCGH on NHS Service Delivery Models***
- **Risks associated with too slow an implementation of aCGH as a first lie test**

POST-NATAL APPLICATIONS OF ARRAY-CGH

WHAT IS THE POTENTIAL FOR ARRAY-CGH?



KARYOTYPE ~ 5 Mb



ARRAY-CGH ≤50 Kb*

Resolution* increases from the chromosome band to the DNA base pair

*** Resolution = density of probes used**

DD/MR/CA preliminary normal v abnormal results

in ~900 reported retrospective cases*

Category		%
Abnormal		26
Normal		74
Total		100

* 4x44k customised oligo array

DD/MR/CA - % abnormalities detected*

Category		No		% abnormals
Confirmed *de novo*		27		22.1%
Segregating abnormalities**		10		8.2%
CNV*		37		30.3%
Abnormal in progress		48		39.3%
Sub-total abnormals		122		100%

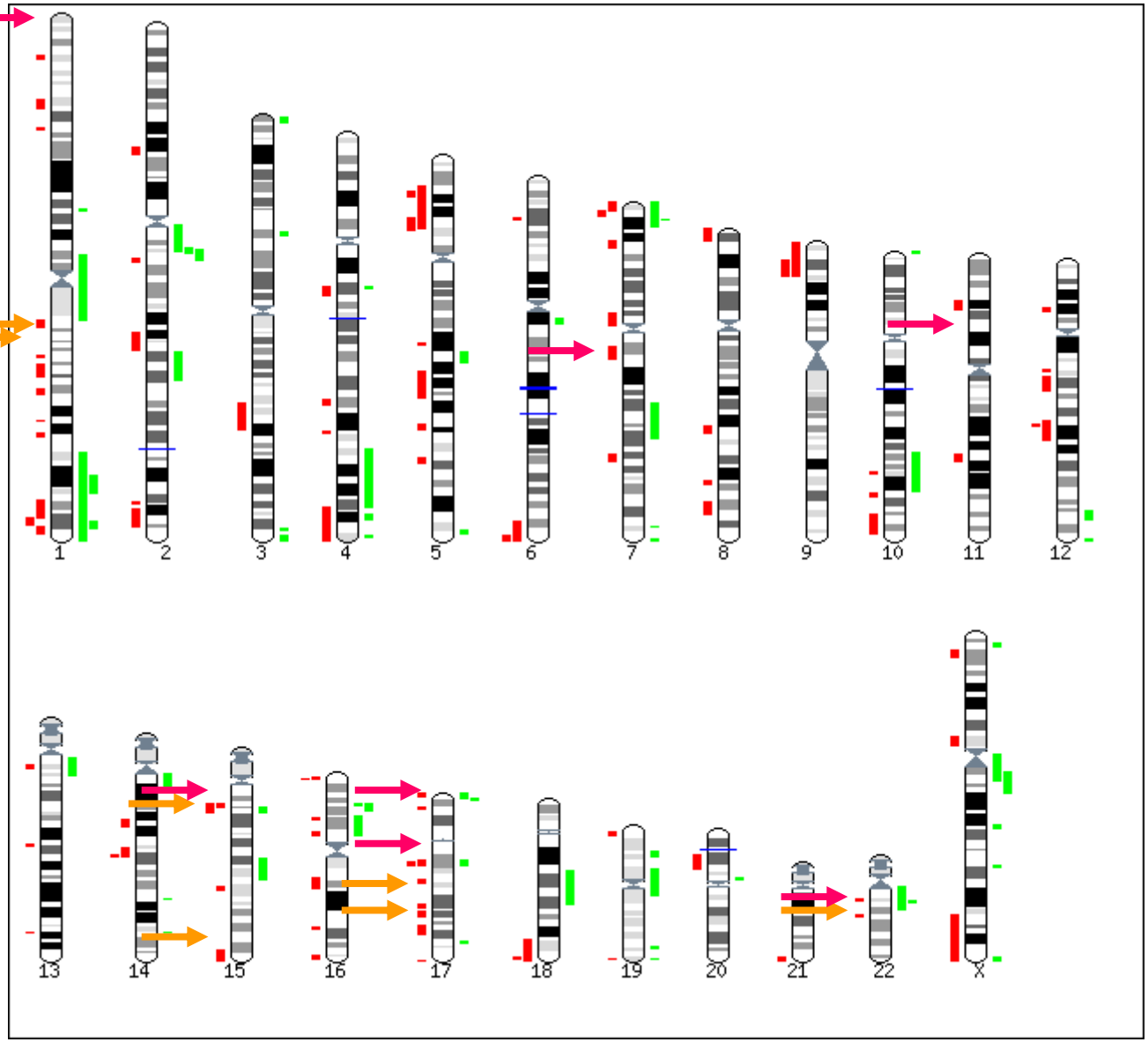
** Same abnormality found in parent with similar phenotype or penetrance of abnormality known to be variable e.g. del(1)(q21.1)

* Same abnormality found in apparently phenotypically normal parent

*12 month audit 2008; all retrospective cases

Resolution of aCGH (DD/MR/CA)

- 44k oligo aCGH gives ≥20% diagnostic enrichment of “pathogenic imbalances” over conventional karyotyping
- Will increasing this resolution provide significant improvements in diagnoses?
- NHS implementation could/should provide flexibility for platform variation



28th Jan 2009

161 patients registered with DECIPHER

deletions

amplifications

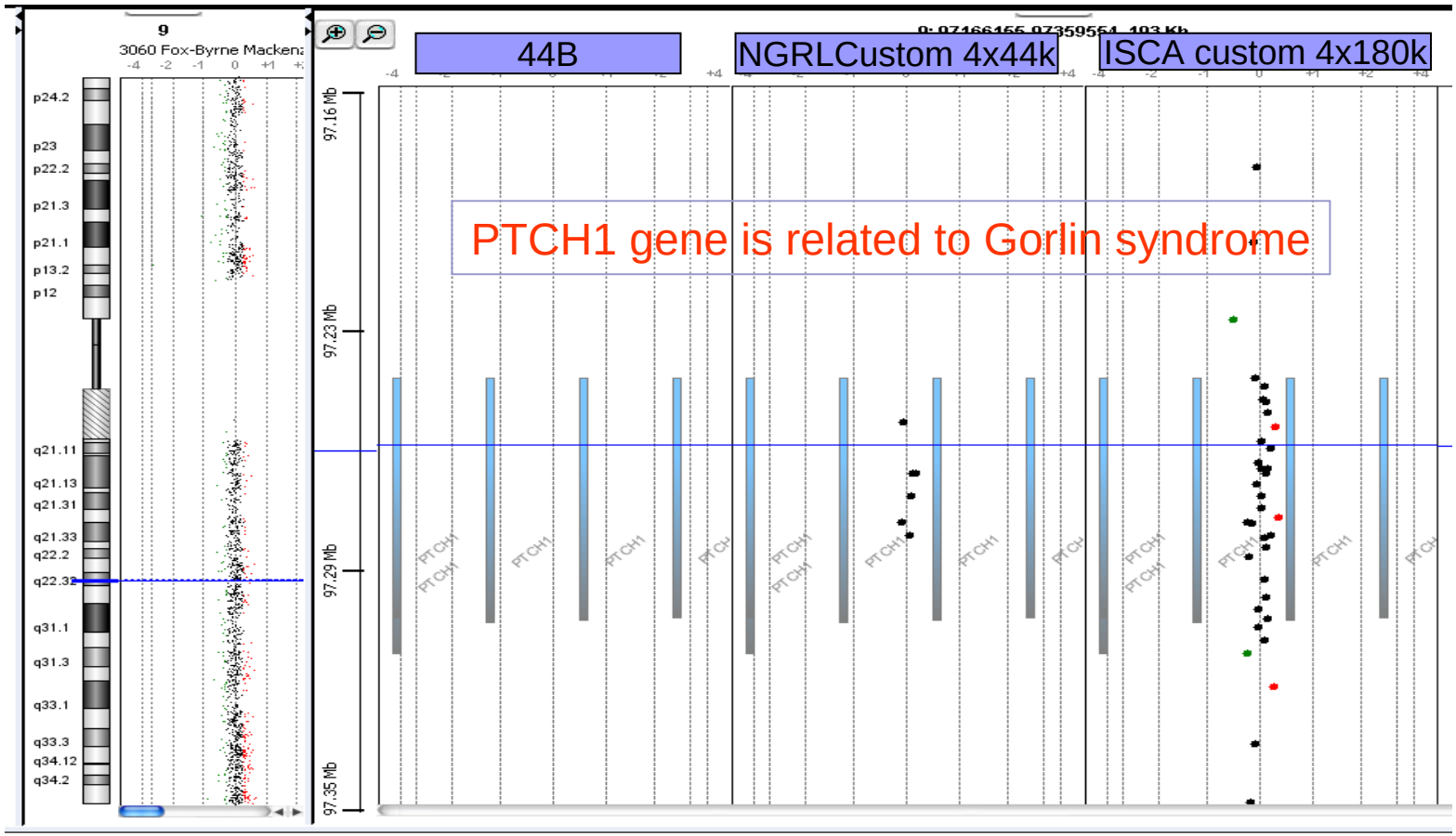
Translocation breakpoint

Common microdeletion syndromes

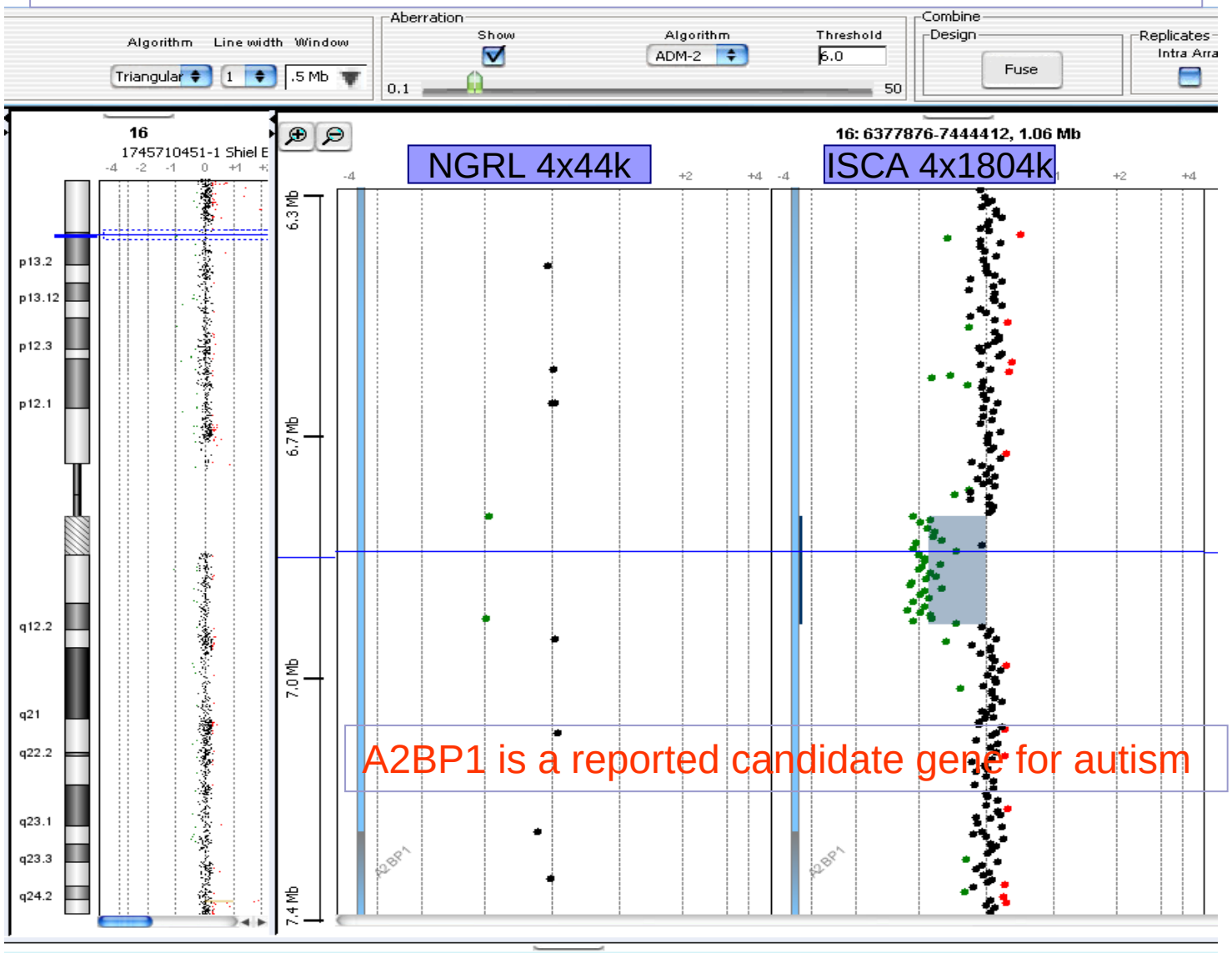
Recurring array-cgh copy number changes

Array design – why is it important?

Example 1: some regions are not covered by catalogue array.



Higher resolution increases confidence of calls but increases CNV “noise”.



aCGH

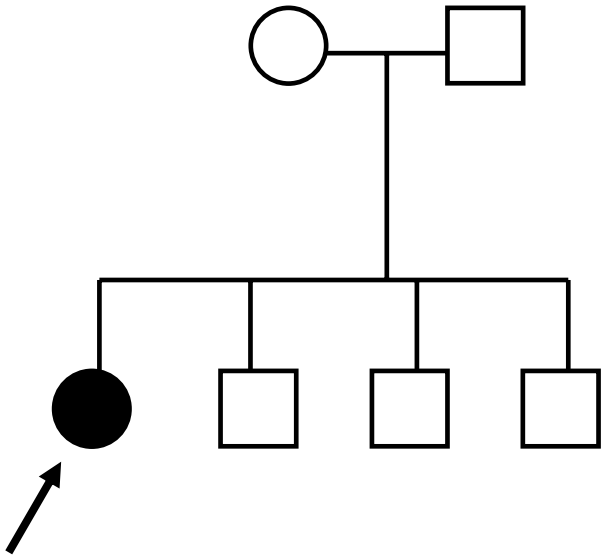
- **Has a proven diagnostic enhancement utility in a retrospective *post-natal* setting**
- **Will detect all chromosome imbalances currently diagnosed by karyotyping**
- **Will not detect balanced chromosome rearrangents**

De novo CCRs and translocations			
Array detected abnormalities (+abnormal phenotype)			
	CCR		
Study	**Normal**	**Deletions**	**Total**
DeGregori	2	16	18
Present	1	6	7
Total	3	24 (96%)	25
	ABSCR		
Study	**Normal**	**Deletions**	**Total**
DeGregori	16	11	27
Baptista	12	4	16
Gribble	4	6	10
Total	32	21 (39%)	53

Karyotyping v array-cgh in the DD/MR/CA cohort

- A thought…….

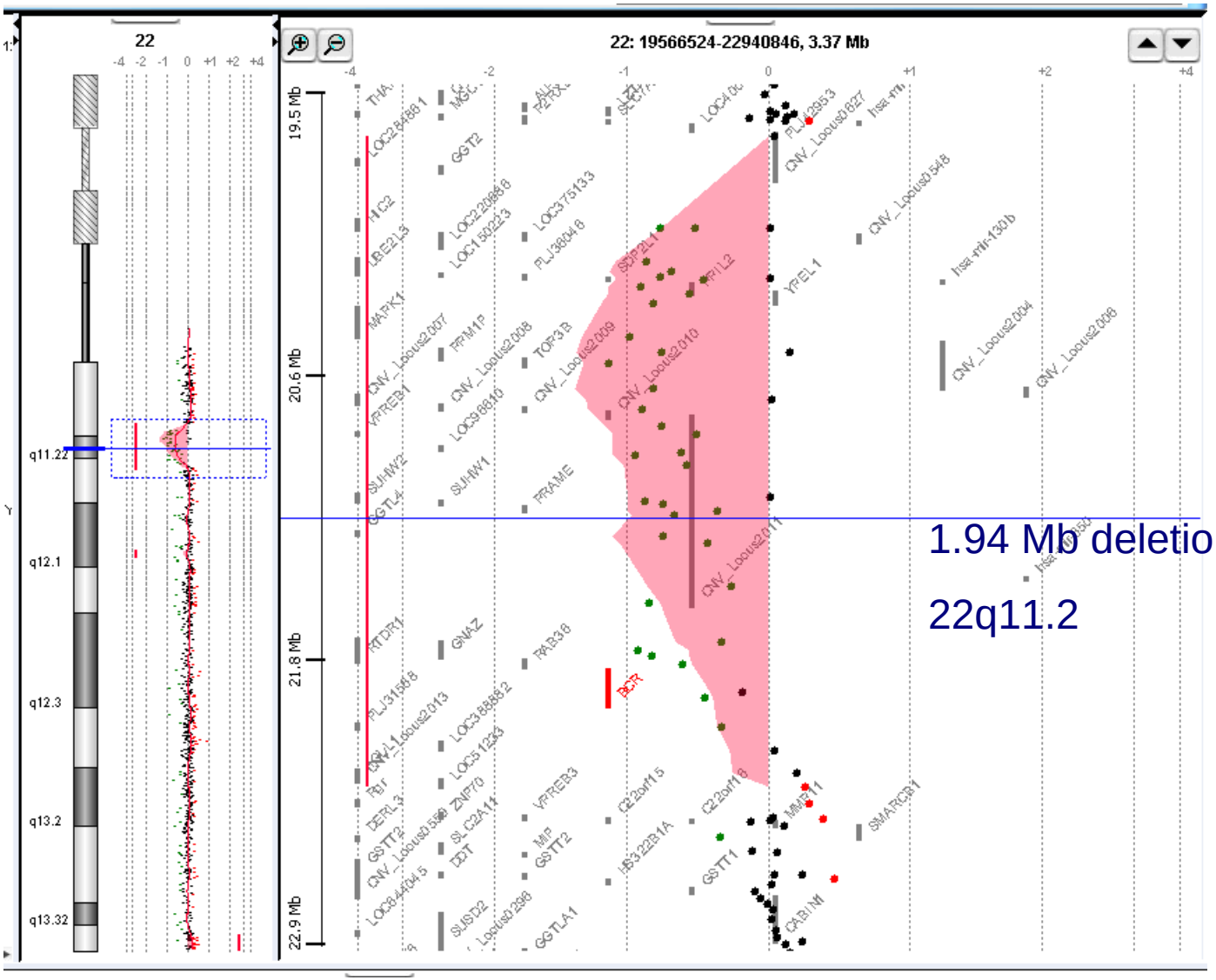
Pedigree

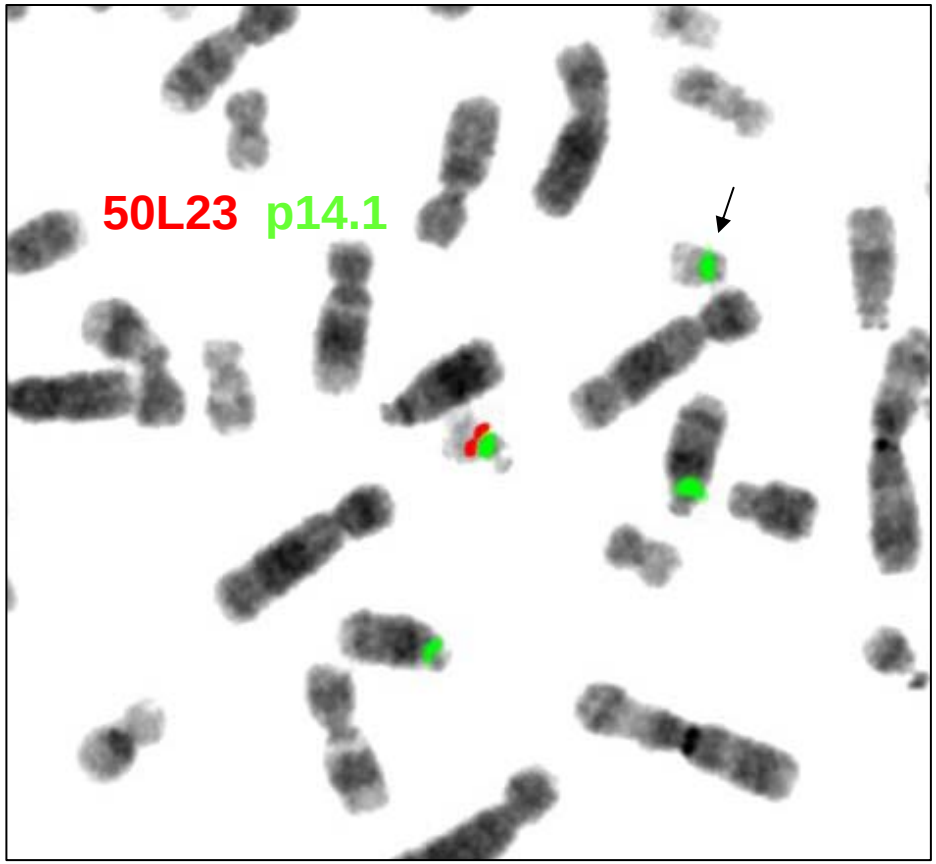


- **12 yr old female**
- **developmental delay**
- **dysmorphic features**

Karyotype January 2008: 46,XX (Q7) – no parental follow-up

Proband referred for array-cgh – July 2008

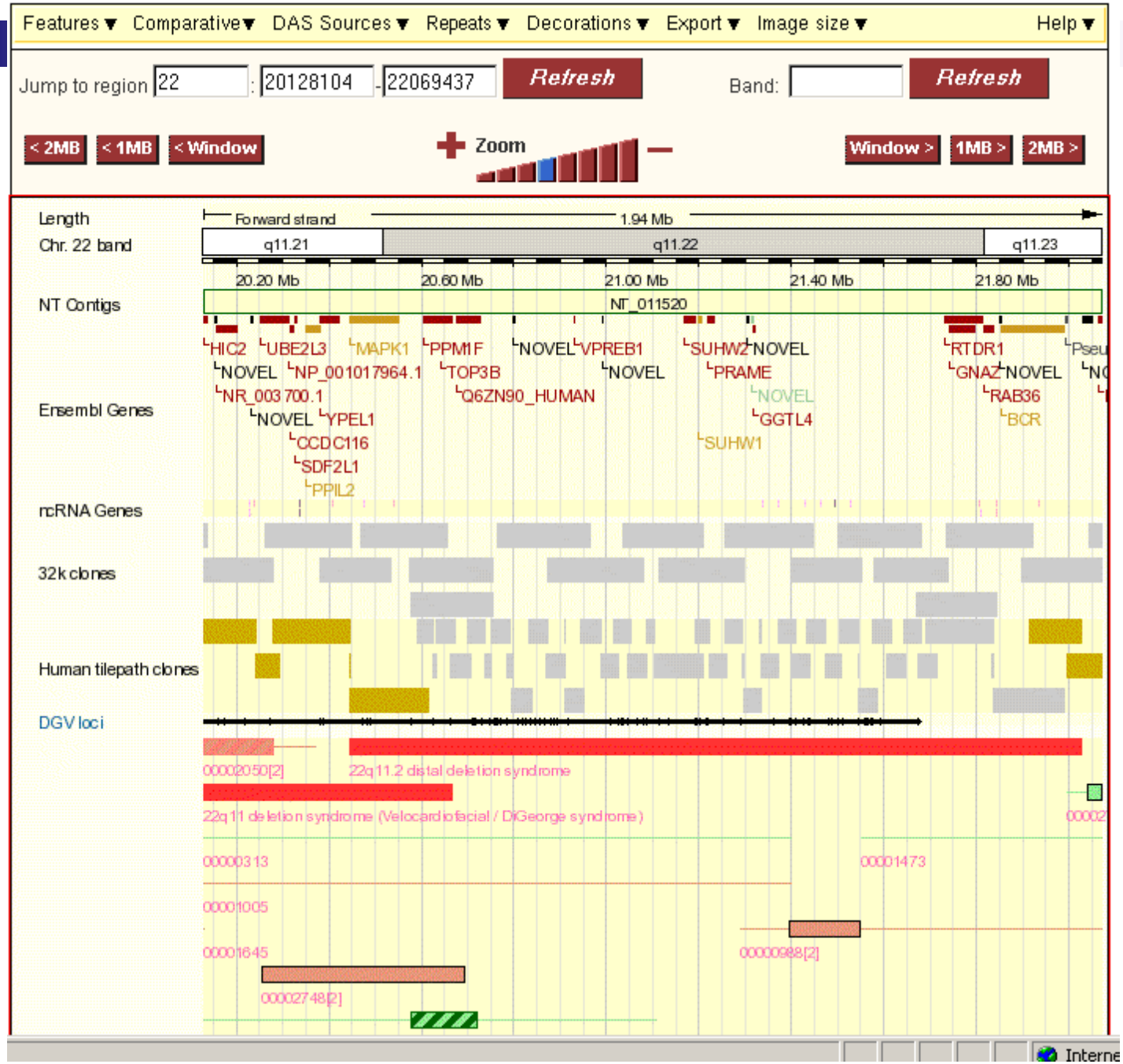




22q11.2 Distal Deletion: A Recurrent Genomic Disorder Distinct from DiGeorge Syndrome and Velocardiofacial Syndrome

Shay Ben-Shachar et al

The American Journal of Human Genetics 82, 214–221, January 2008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NT_011520
Ensembl Genes
HIC2 UBE2L3 MAPK1 PPM1F NOVEL VPREB1 SUHW2 NOVEL RTDR1
NOVEL NP_001017964.1 TOP3B NOVEL PRAME GNAZ NOVEL
NR_003700.1 Q6ZN90_HUMAN NOVEL RAB36
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22q11 deletion syndrome (Velocardiofacial / DiGeorge syndrome)
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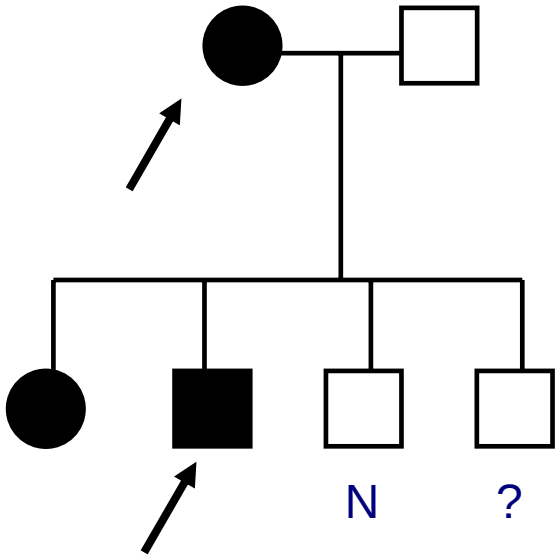
Pedigree

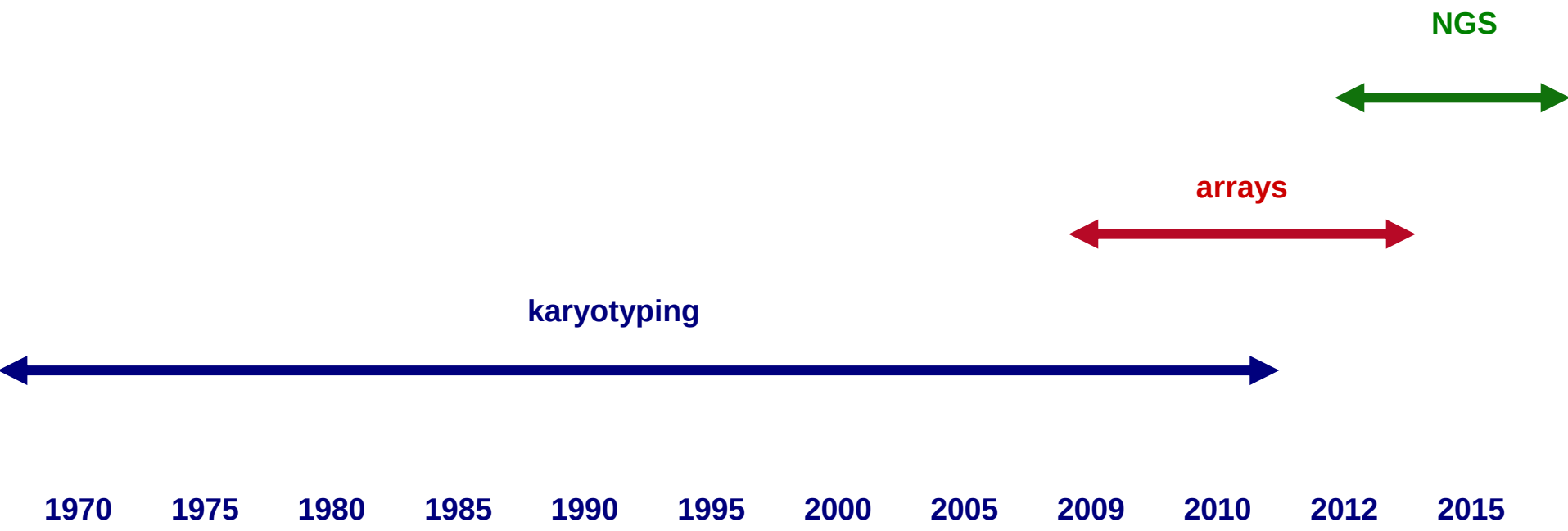


Karyotype January 2008: 46,XX (Q7)

Recurrence risk ~ 50%

- **44k oligo array-cgh currently detecting ≥20% enrichment of *de novo* abnormalities not detectable by conventional karyotyping**
- **Will soon be actionable if an array had not been performed and a second affected child is born?**
- **In Wessex, this amounts to ~200 prospective "missed" diagnoses per annum if we continue with karyotyping as the front line test.**

aCGH - implementation timeframe



Recommendation

- DD/MR/CA ascertainment groups must have array-cgh at minimum of 44k oligo as first line test
- Low resolution (? automated) karyotyping introduced for all other referral categories
- Retraining needed for bioinformatics and data analyses.
- U.K. NHS consortium approach to purchasing, platform and analytical stages of array-cgh

- Implementation need to take into account demand for retrospective array-CGH
- What is the right balance between array-CGH and karyotyping?
- Difficult choices will have to be made about current service configurations.

Pre-natal application of array-cgh

Screening and DS risk assessment

≥1:250 / ≥1:150

Amnio/CVS

(All ascertainment)

(No USS abnormalities)

Rapid test

(+ve & -ve)

Report & action

Rapid test

(+ve)

(-ve)

Karyotype

Report & action

(All ascertainment)

Karyotype

(+ve & -ve)

Report & action

Regions providing rapid testing as stand alone test

5,038,849

7,428,590

Requirements for routine prenatal array-cgh - 1

- Specifically designed array required
- Fast turn around times
- Fast throughput and bioinformatic tools
- Ability to distinguish between CNVs and pathogenic changes

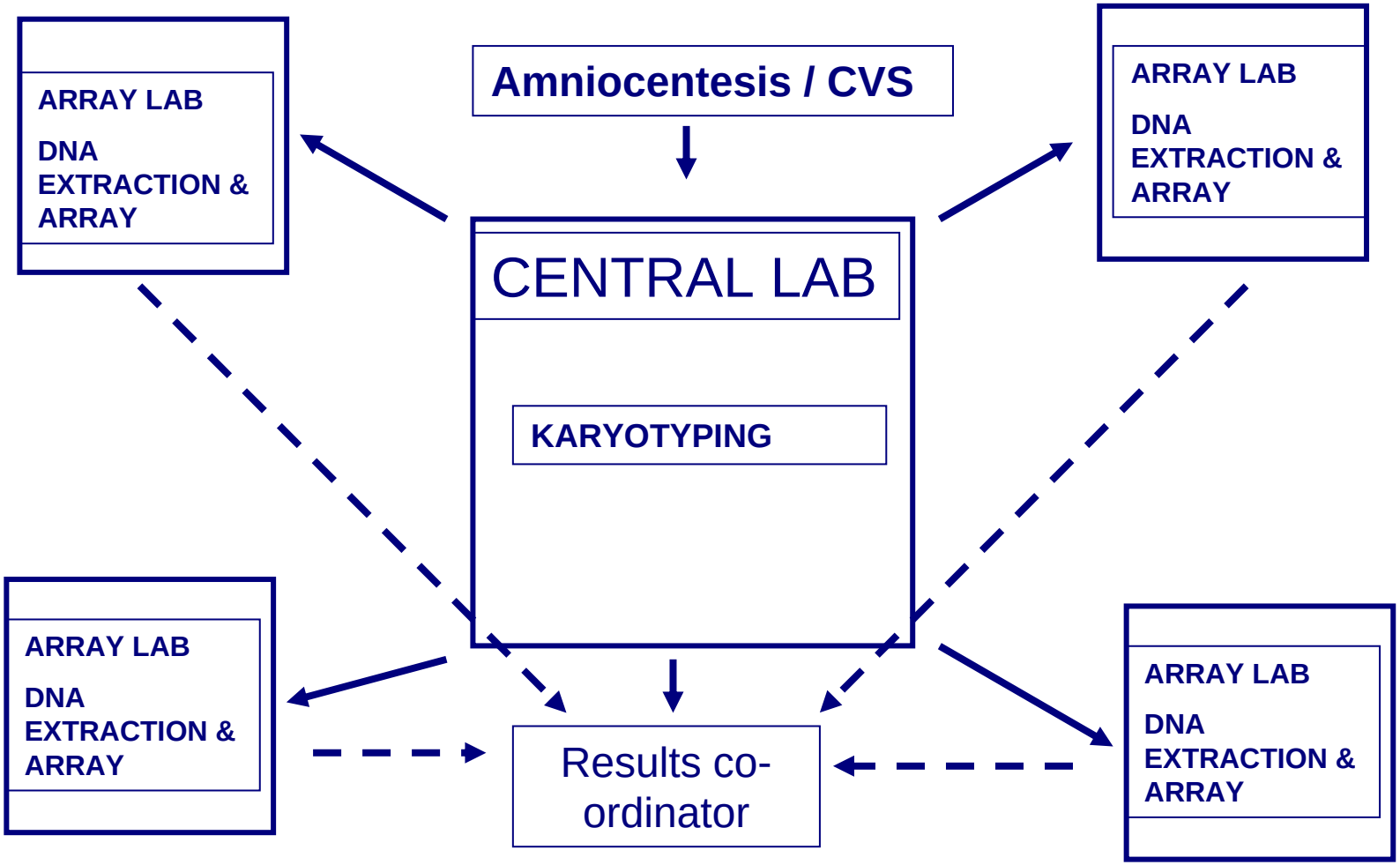
Requirements for routine prenatal array-cgh - 2

- Rapid trio (family studies) required in relatively high proportion of cases
- Interpretation for microdeletions with know variable penetrance (e.g. 22q11.2, 1q21.2)
- Standardised protocols and platforms so that data can be shared rapidly
- Laboratory follow up studies conducted as rapidly as the array itself

USA PROSPECTIVE ARRAY-CGH PRENATAL TRIAL

- 4 X 44K OLIGO "CUSTOMISED" ARRAY
- PERICENTRIC AND TELOMERIC DENSE COVERAGE
- NIMBLEGEN AND AFFY PLATFORMS BEING EVALUATED
- 4,000 PREGNANCIES
  - ~2,000 "ROUTINE" (MATERNAL AGE)
  - ~2,000 WITH AT LEAST 2 USS ABNORMALITIES

USA PROSPECTIVE ARRAY PRENATAL TRIAL



Screening and DS risk assessment

Amnio/CVS

(No USS abnormalities)

Rapid test

(+ve & -ve)

Report & action

(All ascertainments)

Rapid test

(+ve)

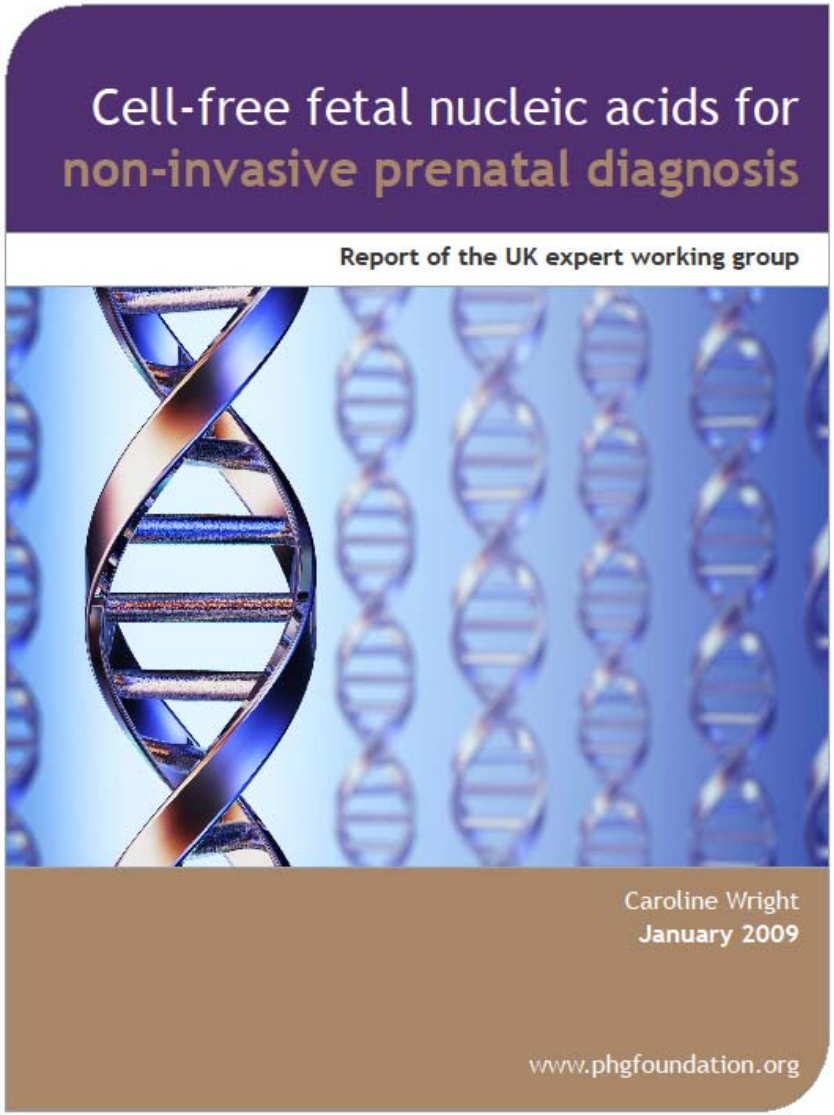
Report & action

(-ve)

Karyotype

Report & action

phg foundation
making science work for health



Reliable Accurate Prenatal non-Invasive Diagnosis

RAPID

rapid@ich.ucl.ac.uk www.rapid.nhs.uk

NIPD at 8 – 10 weeks gestation

(All ascertainments or population based)

(+ve)

Rapid test?

Report & action

- will account for ~80% of abnormalities
- rapid test confirmations centralised
- role for cytogenetics in rearrangements & abnormal scans
- fast turnaround and rationalisation
- array-cgh/shotgun sequencing

(-ve)

Abn USS

Karyotype

Report & action

Implementation of array-cgh into NHS genetics services: RCPath 8th July 2009

The End……

- Thank you for your attention