

BEYOND THE BLOODSPOT

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Testing and Screening beyond Newborn Screening: How do advances in prenatal testing impact screening of newborns?

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CONFLICT OF INTEREST



- The Department of Molecular and Human Genetics at Baylor College of Medicine (BCM) offers extensive genetic laboratory testing, and BCM derives revenue from this activity.

A VISION FOR REPRODUCTION IN THE 21ST CENTURY





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The first step to a healthy pregnancy

Babies with genetic disease are often born to healthy parents.
The Counsyl Test gives you insight to a healthy future.

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Shortened Life Expectancy

59 of the diseases fall into this category, including:

- Cystic fibrosis
- Hurler syndrome
- Spinal muscular atrophy

Intellectual Disability

45 of the diseases fall into this category, including:

- Fragile X syndrome
- Smith-Lemli-Opitz syndrome
- Costeff optic atrophy syndrome

Limited or No Treatment

78 of the diseases fall into this category, including:

- Tay-Sachs disease
- Ataxia-telangiectasia
- Beta thalassemia

Early Intervention

59 of the diseases fall into this category, including:

- Wilson Disease
- MCADD
- Galactosemia

OMIM #	NAME	DISEASE TYPE	Gene Symbol	Counsyl-93	Kingsmore	InheriGene-165 gene
124000	MITOCHONDRIAL COMPLEX III DEFICIENCY	metabolic	BCS1L	yes	yes	yes
141900	HEMOGLOBIN--BETA LOCUS; HBB	hematologic	HBB	yes	yes	yes
201450	ACYL-CoA DEHYDROGENASE, MEDIUM-CHAIN, DEFICIENCY OF	metabolic	ACADM	yes	yes	yes
204500	CEROID LIPOFUSCINOSIS, NEURONAL, 2; CLN2	neurological	TPP1	yes	yes	yes
208400	ASPARTYLGLUCOSAMINURIA	metabolic	AGA	yes	yes	yes
208900	ATAXIA-TELANGEICTASIA; AT	immunodeficiency	ATM	yes	yes	yes
210900	BLOOM SYNDROME; BLM	immunodeficiency	BLM	yes	yes	yes
212065	CONGENITAL DISORDER OF GLYCOSYLATION, Ia; CDG1A	metabolic	PMM2	yes	yes	yes
215100	RHIZOMELIC CHONDRODYSPLASIA PUNCTATA, 1; RCDP1	developmental	PEX7	yes	yes	yes
218000	AGENESIS OF THE CORPUS CALLOSUM WITH PERIPHERAL NEUROPATHY; ACCPN	neurological	SLC12A6	yes	yes	yes
219700	CYSTIC FIBROSIS; CF	respiratory	CFTR	yes	yes	yes
219750	CYSTINOSIS, ADULT NONNEPHROPATHIC	metabolic	CTNS	yes	yes	yes
219800	CYSTINOSIS, NEPHROPATHIC; CTNS	metabolic	CTNS	yes	yes	yes
219900	CYSTINOSIS, LATE-ONSET JUVENILE OR ADOLESCENT NEPHROPATHIC	metabolic	CTNS	yes	yes	yes
220111	LEIGH SYNDROME, FRENCH-CANADIAN ; LSFC	metabolic	LRPPRC	yes	yes	yes
222600	DIASTROPHIC DYSPLASIA	developmental	SLC26A2	yes	yes	yes
223900	NEUROPATHY, HEREDITARY SENSORY AND AUTONOMIC, III; HSN3	neurological	IKBKAP	yes	yes	yes
226650	EPIDERMOLYSIS BULLOSA, JUNCTIONAL, NON-HERLITZ	cutaneous	LAMA3	yes	yes	yes
226650	EPIDERMOLYSIS BULLOSA, JUNCTIONAL, NON-HERLITZ	cutaneous	LAMB3	yes	yes	yes

What is happening in noninvasive prenatal diagnosis?

- **A revolution.**
- **NIPT versus NIPD –testing v diagnosis**
- **Down syndrome and other trisomies**
- **Using cell-free DNA – current**
- **Using fetal cells – future**
- **Sequencing the genome of all fetuses in the first trimester using NIPD**

BACKGROUND

- For almost all disorders currently detected by NBS, the risk could be anticipated prior to conception.
- Exceptions include hypothyroidism (multifactorial), any de novo mutations such as DiGeorge syndrome deletions or new mutation Duchenne dystrophy, and congenital infection.

SPECTRUM FOR NBS

- Amino acid PKU – 95+%
- Galactosemia carbohydrate – 95+%
- Organic acid, fatty acid oxidation – 95+%
- Endocrine hypothyroid - low, congenital adrenal hyperplasia - high
- Hearing/deafness – 70-80%
- Hemoglobin – 95+%
- Cystic fibrosis – 95+%

Reproductive risks

```
graph TD; A[Reproductive risks] -- "Carrier test plus" --> B[Inherited mutations]; A -- "NIPD" --> C[De novo mutations]; B --> D["Autosomal recessive<br/>Autosomal dominant<br/>X-linked<br/>Deletions/<br/> duplicationsCNVs"]; C --> E["Point (small)<br/>mutations<br/>CNVs"];
```

**Carrier
test plus**

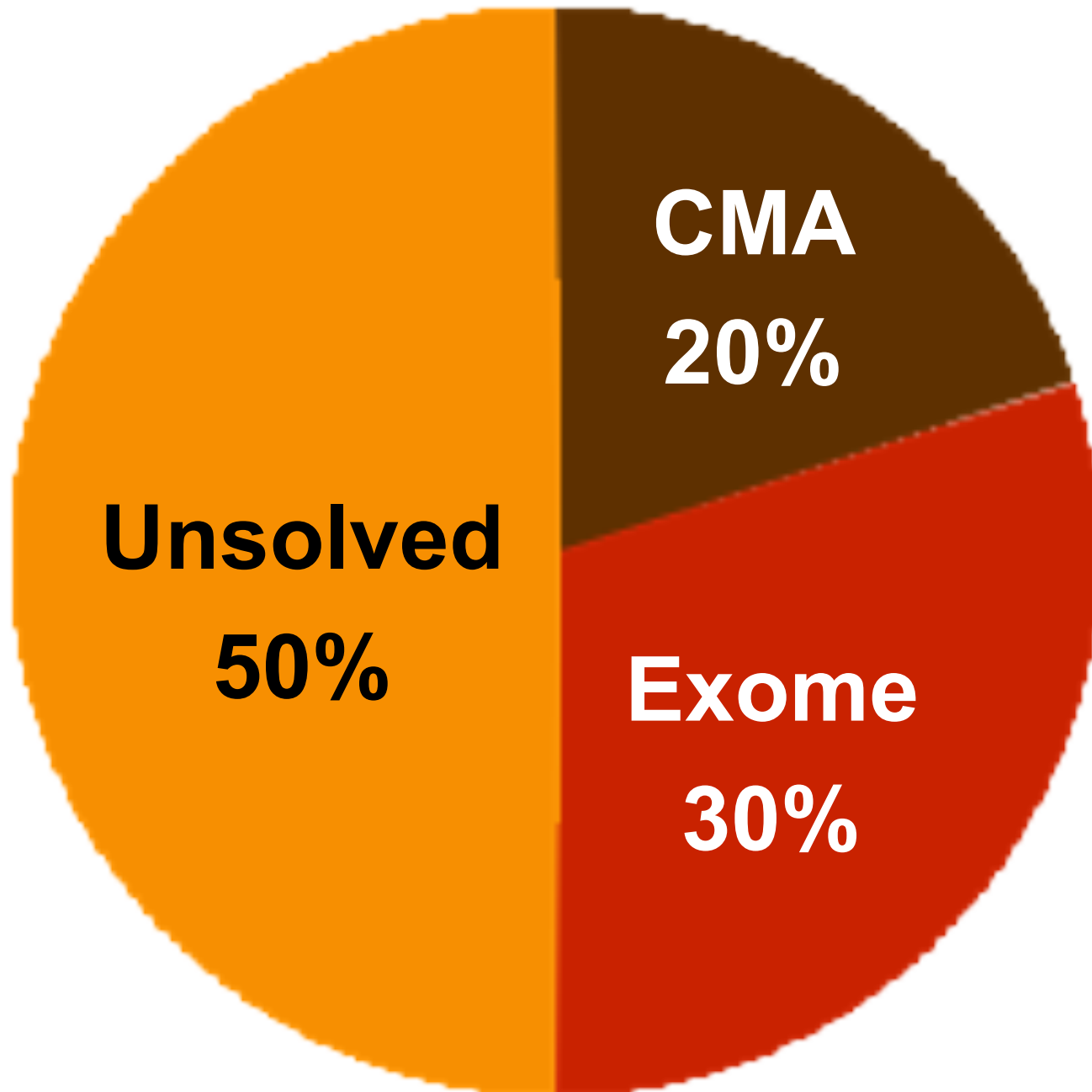
**Inherited
mutations**

Autosomal recessive
Autosomal dominant
X-linked
**Deletions/
duplicationsCNVs**

NIPD

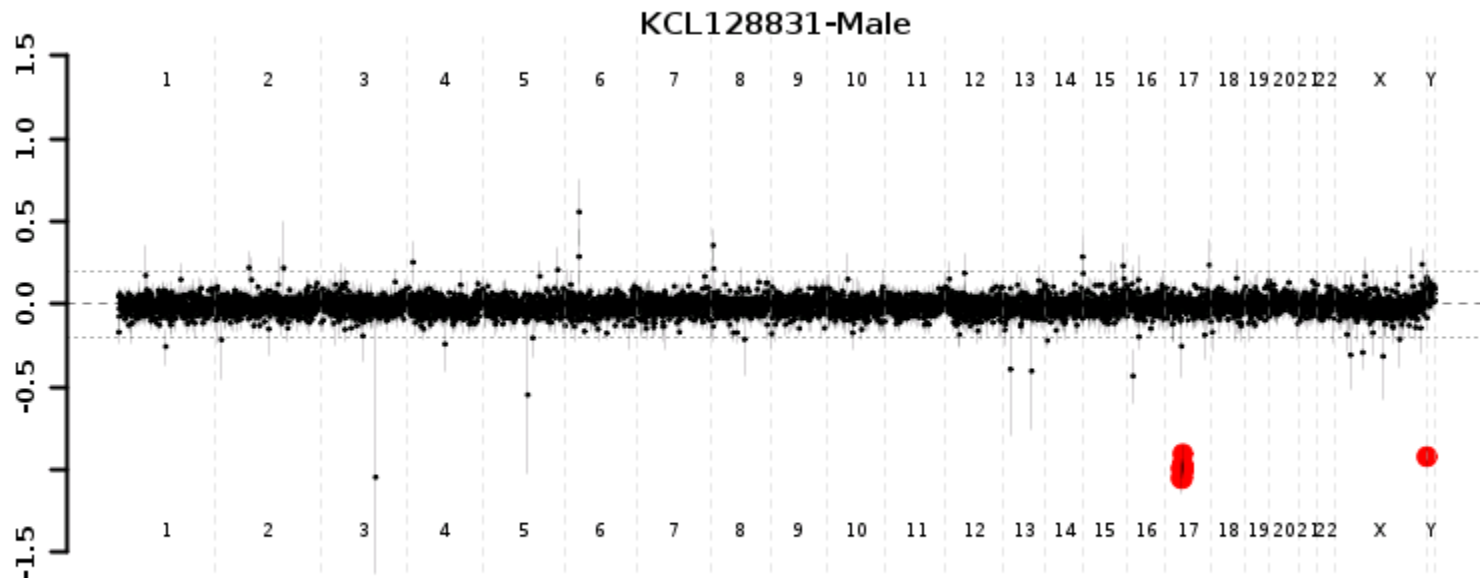
**De novo
mutations**

**Point (small)
mutations**
CNVs

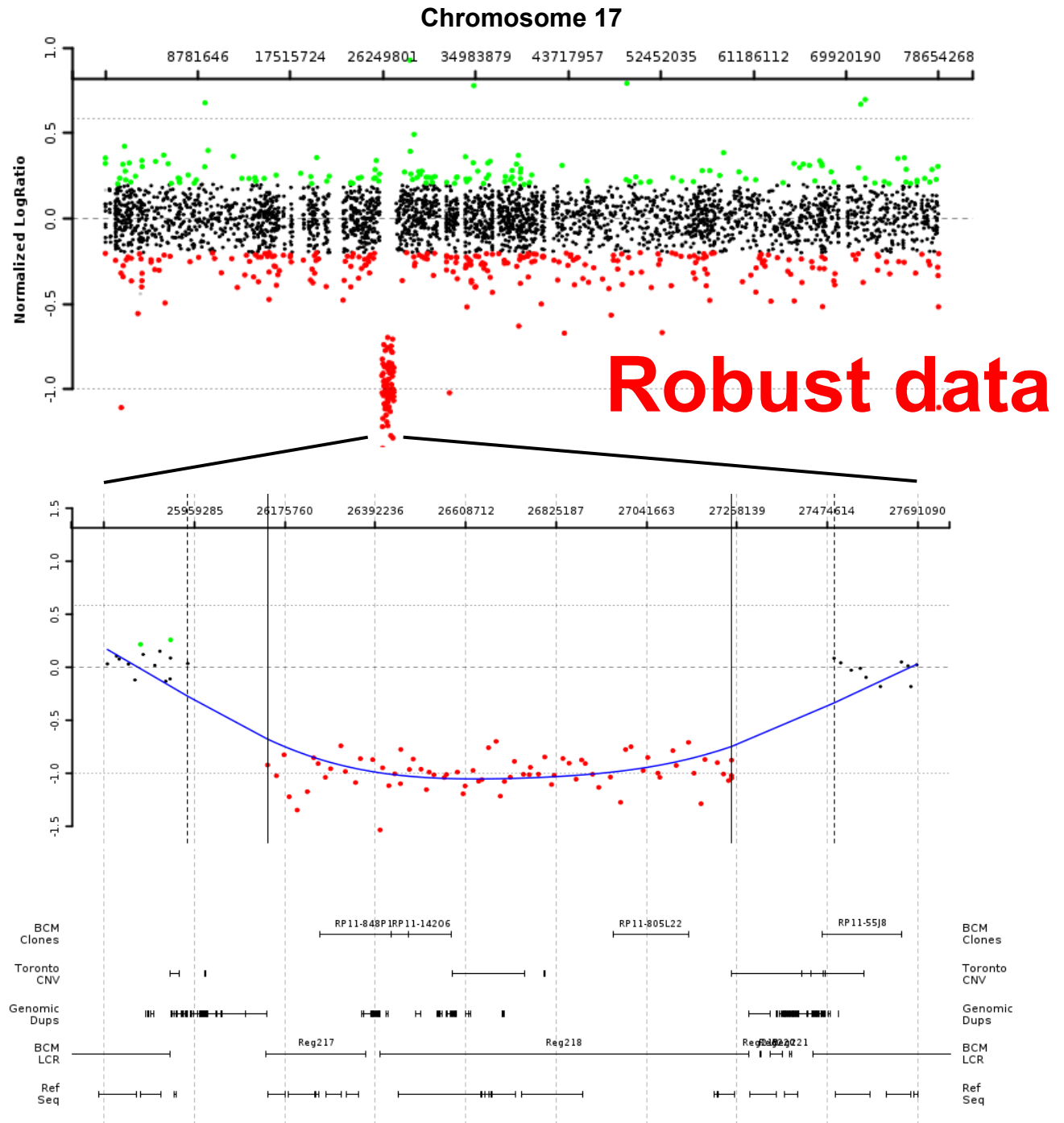


Chromosomal microarray analysis (CMA)

NF1 Deletion



NF1 Deletion





Case 1: del 4q21



Case 7: del 1q36



Case 9: del 21q22



Case 12: dup Xq25



Case 14: dup 1q31



Case 16: del 7q11



Case 28: dup 15q11-q13



Case 29: del 3q27.2-q29

D-MR
Mostly *de novo*
M:F = ~1.5:1

25-30% CNV
Future 80-90%
genetic

Jacquemont et al.
PMID: 16840569

WHOLE EXOME SEQUENCING

Sign Out Conference

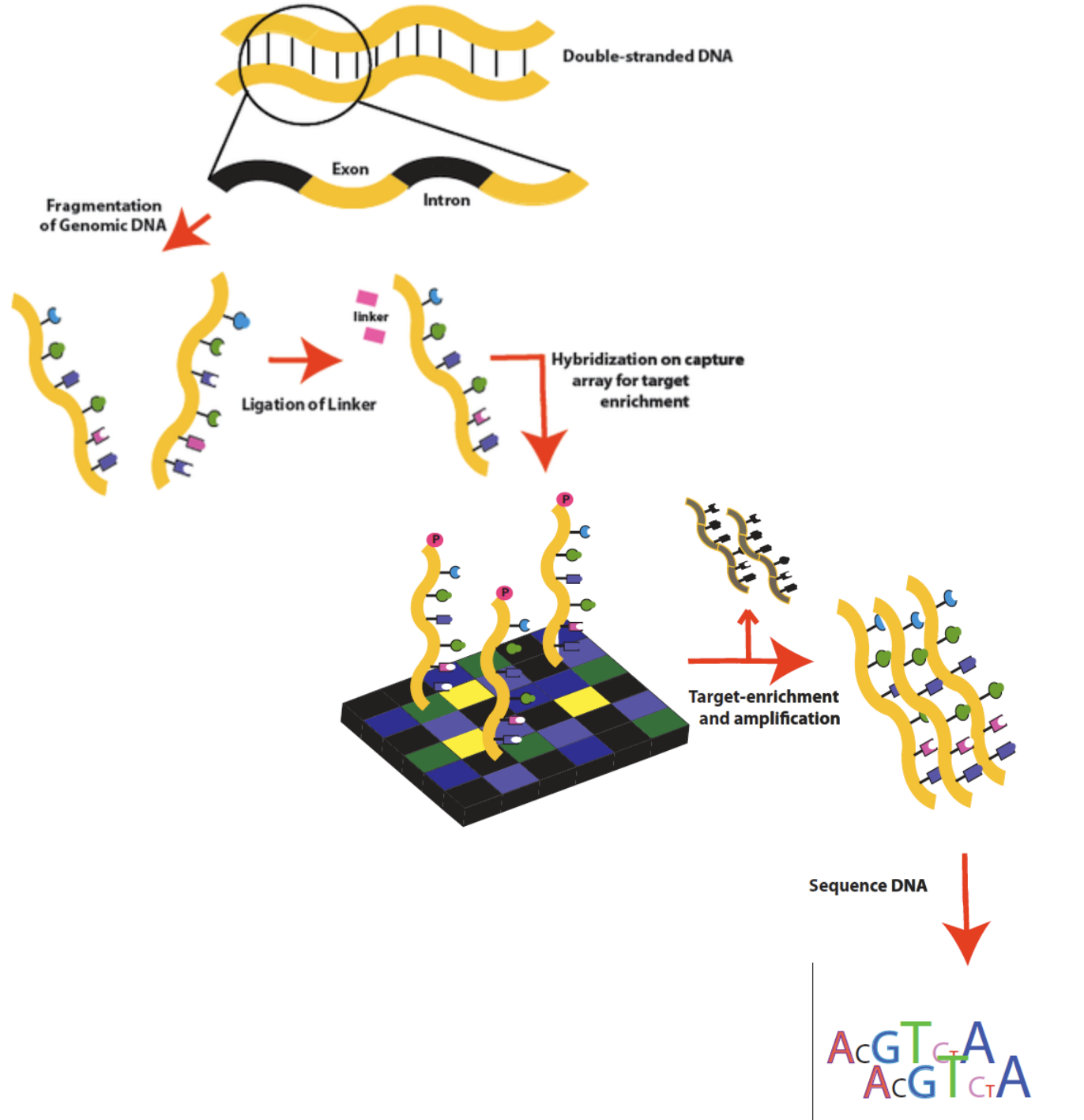
1/27/2012

MGL

MEDICAL GENETICS LABORATORIES

WGL

WHOLE GENOME LABORATORY



ARID1B & ID



Low-set, posteriorly rotated ears; Frontal bossing;
Downslanting palpebral fissures; Bulbous nasal tip; Thin upper lip;
Psychomotor retardation, speech delay

Universal carrier detection plus

```
graph TD; A[Universal carrier detection plus] --> B[PGD Pre-implantation genetic diagnosis]; A --> C[Prenatal diagnosis]; A --> D[Newborn screening]; C --> E[Termination of pregnancy]; C --> F[Early prenatal or postnatal treatment];
```

**PGD Pre-
implantation
genetic
diagnosis**

**Prenatal
diagnosis**

**Newborn
screening**

**Termination
of
pregnancy**

**Early
prenatal or
postnatal
treatment**

WHAT IS PGD?

- Couple desires to avoid an inherited genotype in offspring.
- Dominant (BRAC1/2 breast cancer) or recessive (cystic fibrosis).
- In vitro fertilization.
- Grow embryos 3 or 5 days.
- Genotype embryos with arrays or sequencing.

Universal carrier detection plus

**Already
pregnant**

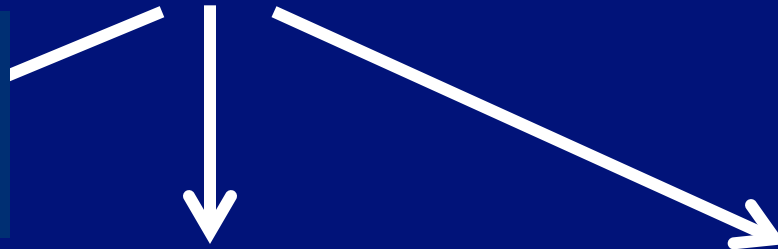
~~PGD Pre-
implantation
genetic
diagnosis~~

**Prenatal
diagnosis**

**Newborn
screening**

**Termination
of
pregnancy**

**Early
prenatal or
postnatal
treatment**



OPTIONS PRIOR TO NBS

- **Universal carrier detection.**
- **Preimplantation genetic diagnosis.**
- **First trimester noninvasive prenatal diagnosis and selective termination of pregnancy.**
- **Early prenatal or postnatal treatment.**
- **Is there an ongoing pregnancy or not?**

INHERITED VERSUS DE NOVO MUTATIONS

- Many options for inherited mutations including PGD, donor sperm or egg, and NIPD.
- For de novo mutations, NIPD is the most relevant option.
 - Intervention could include abortion, prenatal treatment, or treatment at birth.

ABORTION AS A LAST OPTION

- **Already pregnant and fetus has**
 - Tay Sachs disease
 - DiGeorge syndrome deletion
 - Lethal osteogenesis imperfecta, not NBS
 - Duchenne muscular dystrophy
 - Cystic fibrosis

DETECTING DE NOVO POINT MUTATIONS BY NGS

- Rett syndrome
- Lethal osteogenesis imperfecta
- Lethal skeletal dysplasias, thanatophoric
- Angelman mutation cases
- Cornelia de Lange syndrome
- Rubinstein-Taybi syndrome
- ARID1B Coffin-Siris syndrome
- SHANK3, NRXN1

WHAT DOES EXPERIENCE TELL US?

- Tay-Sachs disease
- Thalassemia in Mediterranean countries
- Cystic fibrosis
- Sickle cell anemia
- Broader Ashkenazi Jewish testing

CONCLUSIONS

- Expanded testing may be preferable prior to conception and in the first trimester.
- Preconception testing can detect inherited but not de novo risks.
- Newborn screening will not go away in the foreseeable future.

QUESTIONS

- Will universal carrier testing become routine?
- Will it be combined with healthy exomes?
- What will be the role of direct to consumer?
- Can cost of PGD be justified?
- Noninvasive genomic analysis of all pregnancies, CNV and sequence?

END

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<http://www.bcm.edu/geneticlabs/>

