Genomic Counseling

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HUDSONALPHA
INSTITUTE FOR BIOTECHNOLOGY

Genetic Counseling

common referral indications

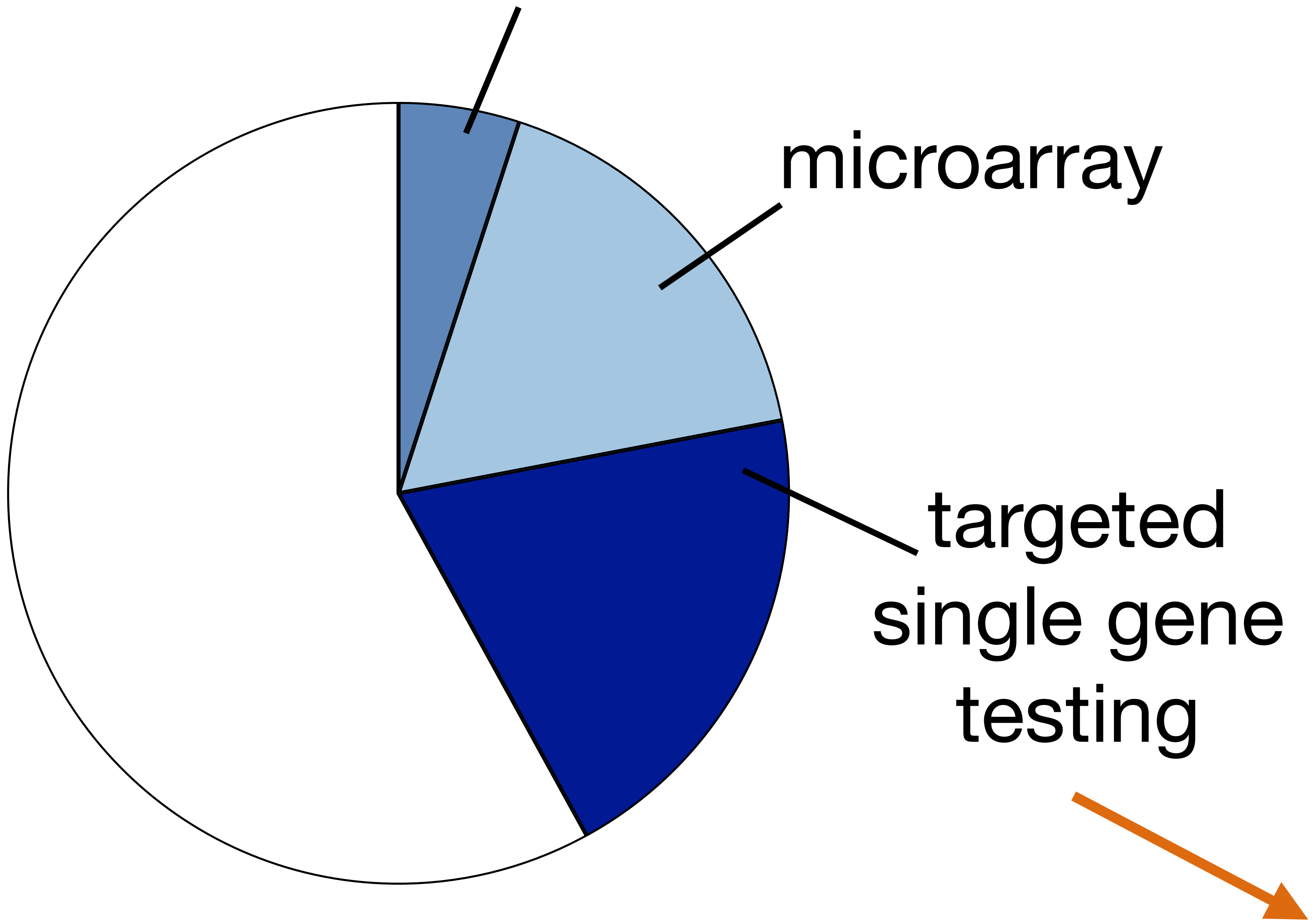
- abnormal prenatal testing (ultrasound, serum screening)
- pediatric undiagnosed disease
- adult undiagnosed disease
- family history of early onset cancer
- family history of known genetic disorder

often includes a discussion of available genetic testing options and the impact of possible results

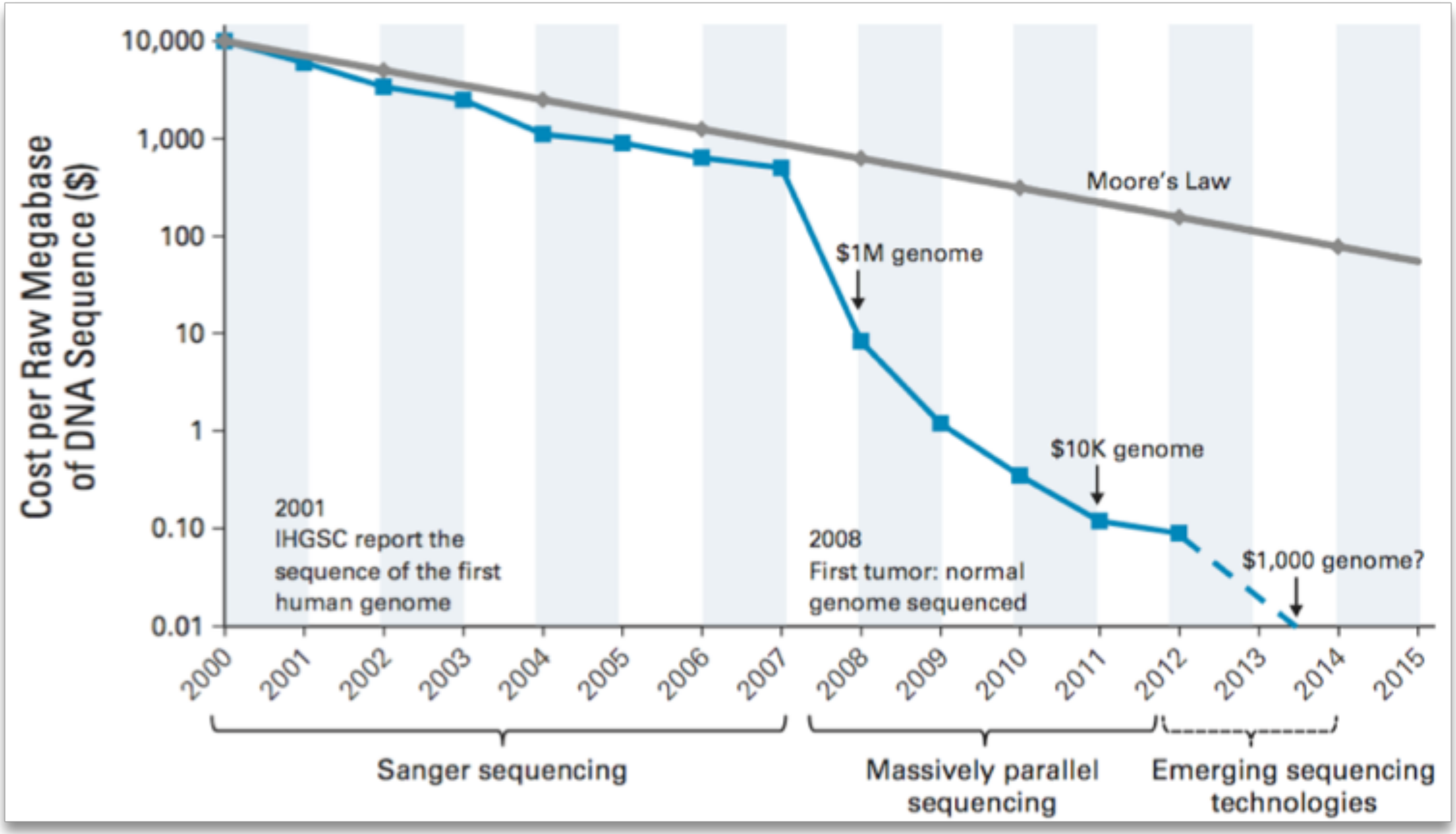
testing options and diagnosis rate

in patients with a suspected genetic condition

2008



problem: have to know what gene to test


Cost per Raw Megabase of DNA Sequence ($)
10,000
1,000
100
10
1
0.10
0.01
Moore's Law
$1M genome
$10K genome
$1,000 genome?
2001
IHGSC report the sequence of the first human genome
2008
First tumor: normal genome sequenced
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
Sanger sequencing
Massively parallel sequencing
Emerging sequencing technologies

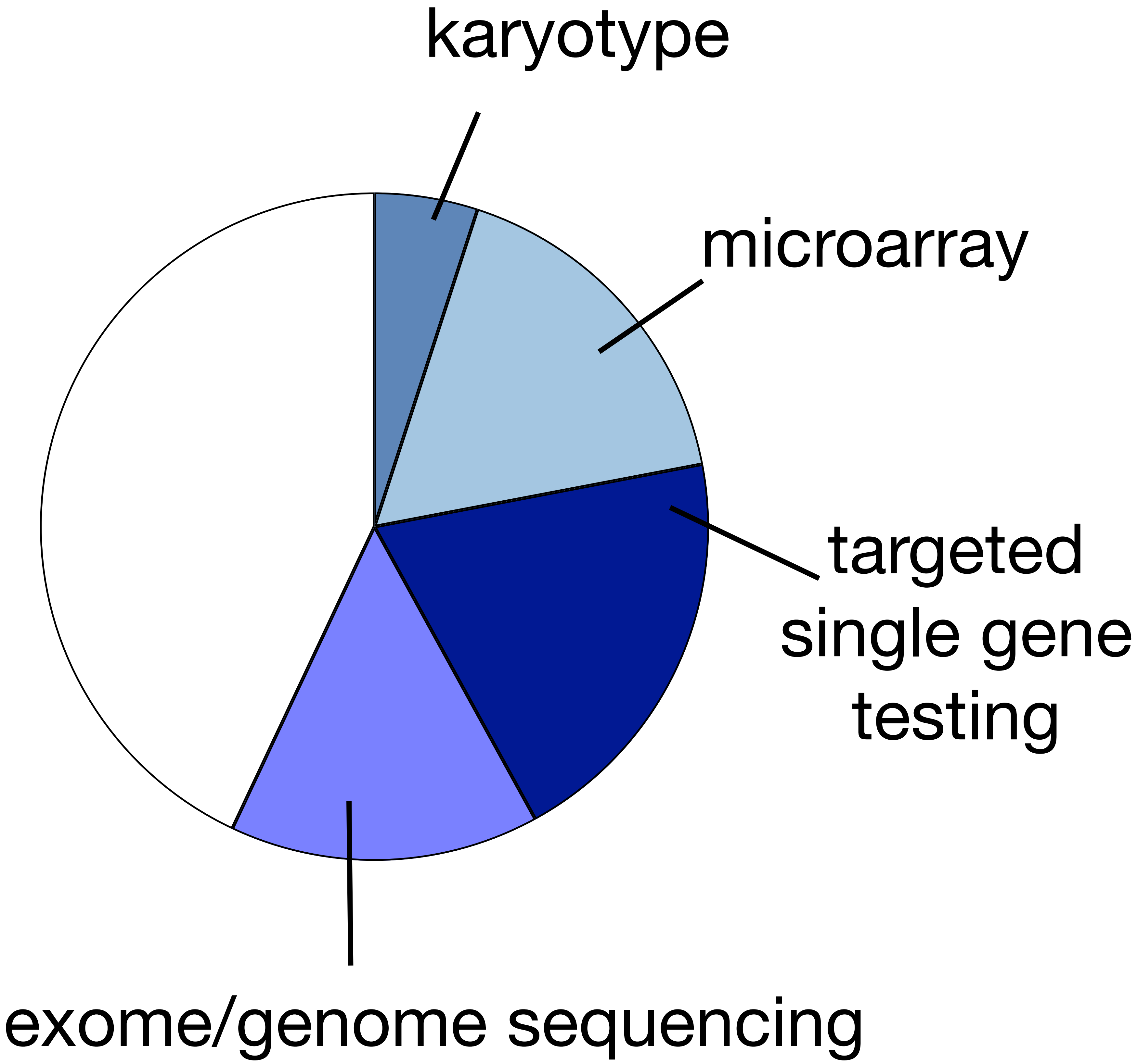
Sequence a single gene

Sequence many genes

Sequence all genes

in patients with a suspected genetic condition

2015



HudsonAlpha Research

Genomic Diagnoses for Children with Developmental Delay

Goals:

1. Utilize new testing technologies to discover genomic causes for pediatric neurological disorders

2. Determine the impact of genomic results on patients and their families

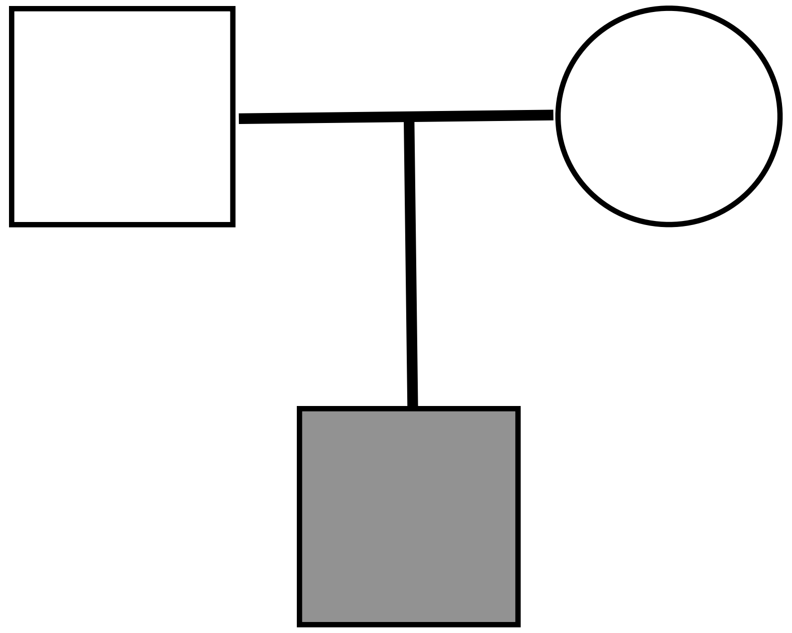
Plan to analyze ~400 families over next four years

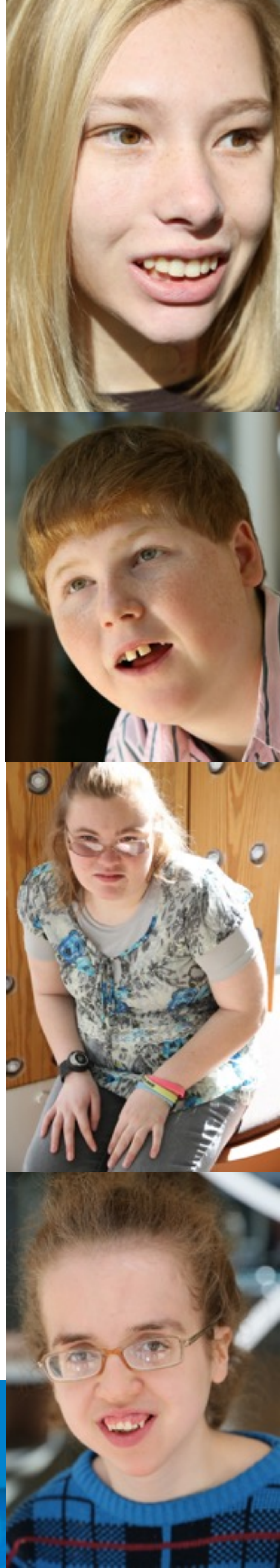
Sequencing of "Trios"

Unaffected Mom

Unaffected Dad

Affected child





clinical genomic testing

- identifies variation across the genome
- wide range of possible results
- many variants cannot be understood

related to symptoms

unrelated to symptoms

Interpretation of findings

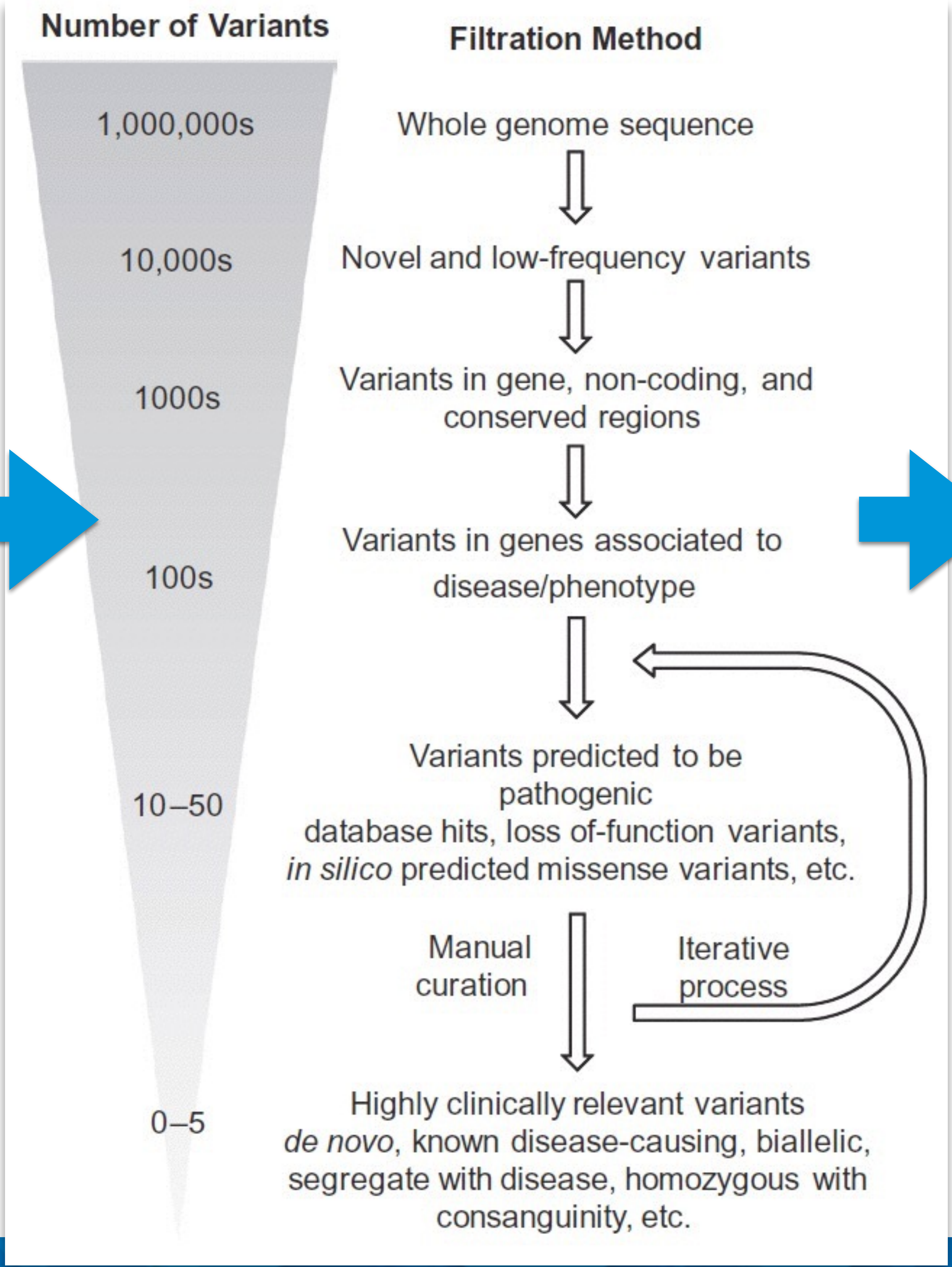
genome sequencing generates massive amounts of data

420 terabytes of data generated each year by HudsonAlpha sequencers

- **equivalent to 5 million four-drawer filing cabinets filled with text**

- **840 million songs**
- **20 iTunes stores**
- **and 14,500x english wikipedia**

patient consents to genome sequencing



Number of Variants

Filtration Method

1,000,000s: Whole genome sequence

10,000s: Novel and low-frequency variants

1000s: Variants in gene, non-coding, and conserved regions

100s: Variants in genes associated to disease/phenotype

10–50: Variants predicted to be pathogenic
database hits, loss of-function variants, *in silico* predicted missense variants, etc.

Manual curation

Iterative process

0–5: Highly clinically relevant variants
de novo, known disease-causing, biallelic, segregate with disease, homozygous with consanguinity, etc.

genome results returned to patient

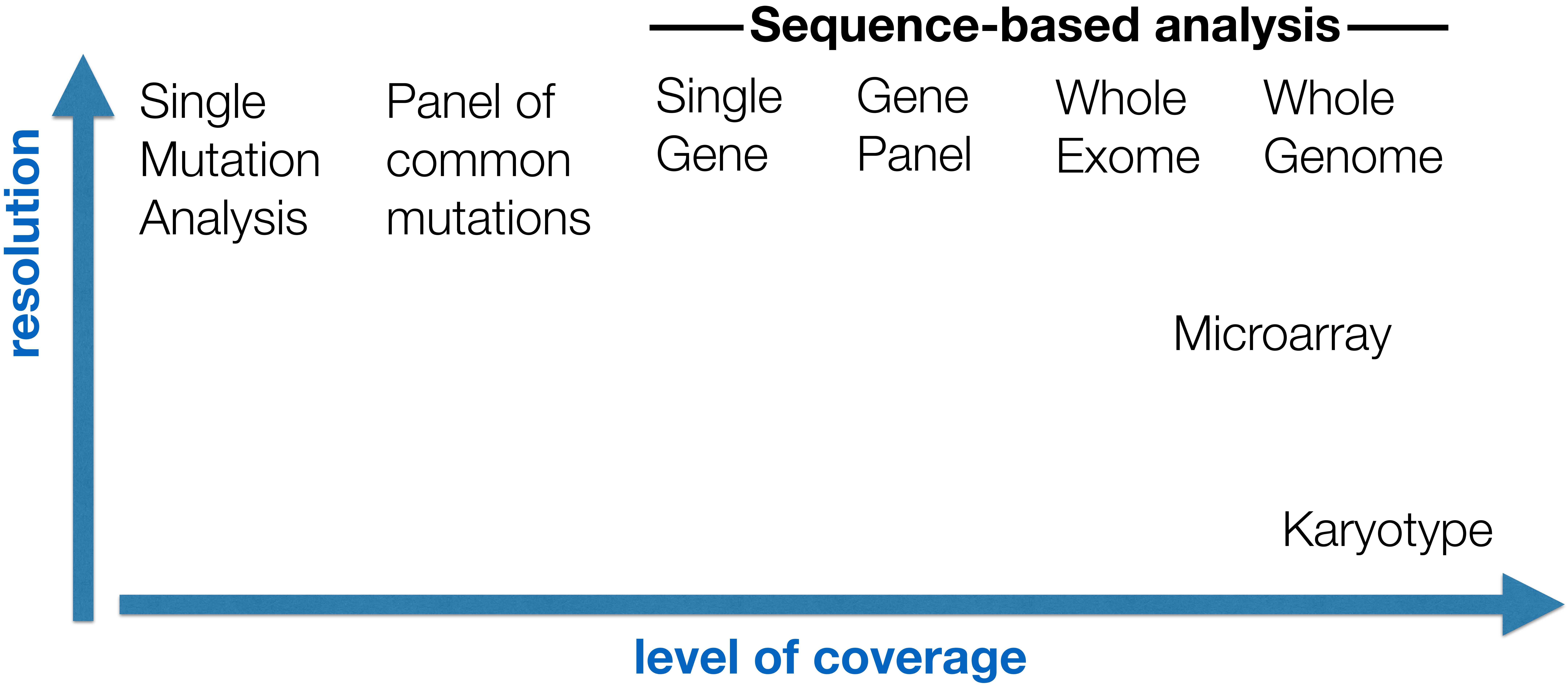
Genomic and Personalized Medicine, Vol I (2nd edition). Ginsburg G. & Willard H (eds). Elsevier 2013

pre-test genetic counseling

- what is a genome
- how genome sequencing is different from other tests
- types of results
- likelihood of getting a result
- risks and benefits
- logistics

Informed Consent: process by which the treating health care provider discloses appropriate information to a competent patient so that the patient may make a voluntary choice to accept or refuse treatment. (Appelbaum, 2007)

genetic testing technologies



Sequence-based analysis

Single Mutation Analysis

Panel of common mutations

Single Gene

Gene Panel

Whole Exome

Whole Genome

Microarray

Karyotype

resolution

level of coverage

types of results

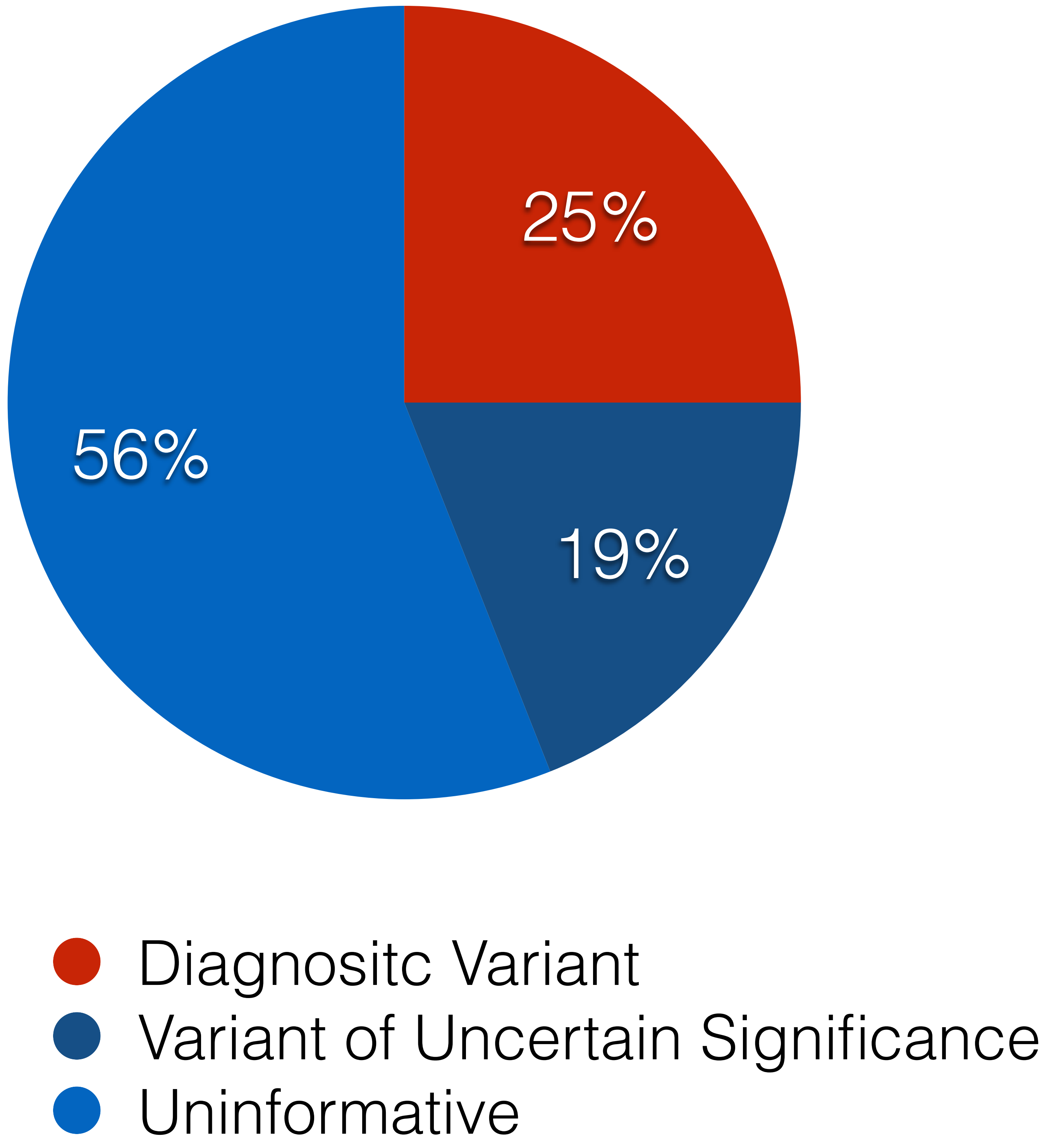
primary related to symptoms or reason for testing

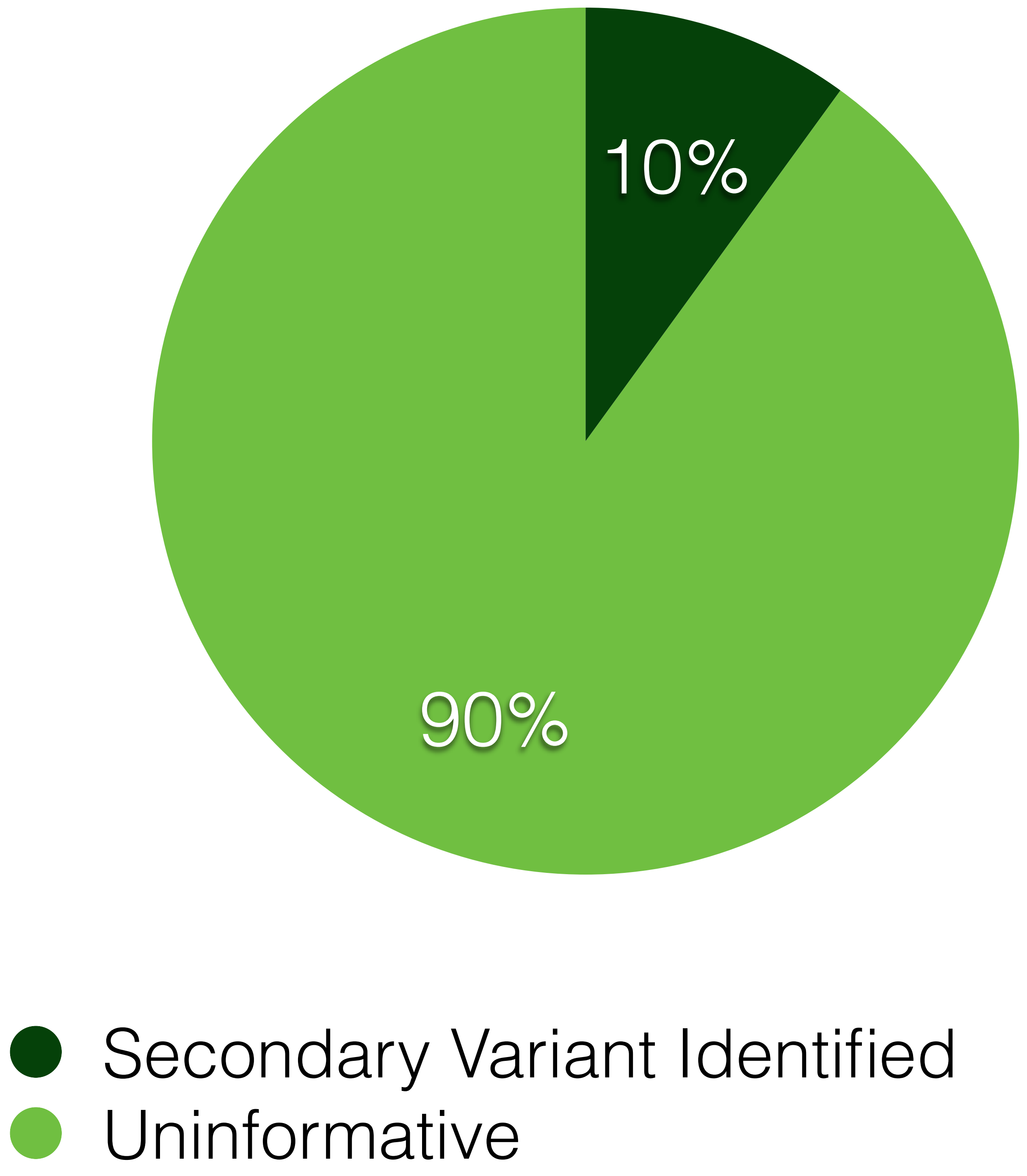
secondary

- disease risk
  - childhood versus adult onset
  - medically actionable versus non
- carrier status
- pharmacogenomics

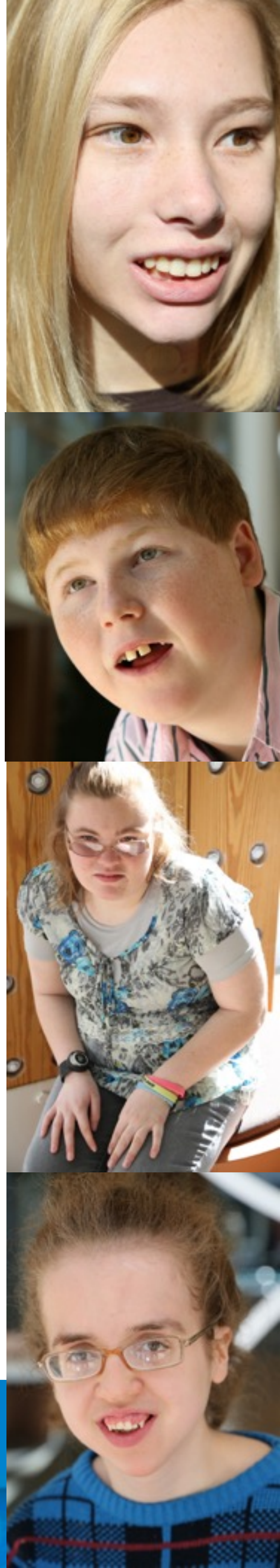
lab or research protocol determines scope of results willing to be returned. patients/participants typically able to opt-out to receiving results

likelihood of getting a result

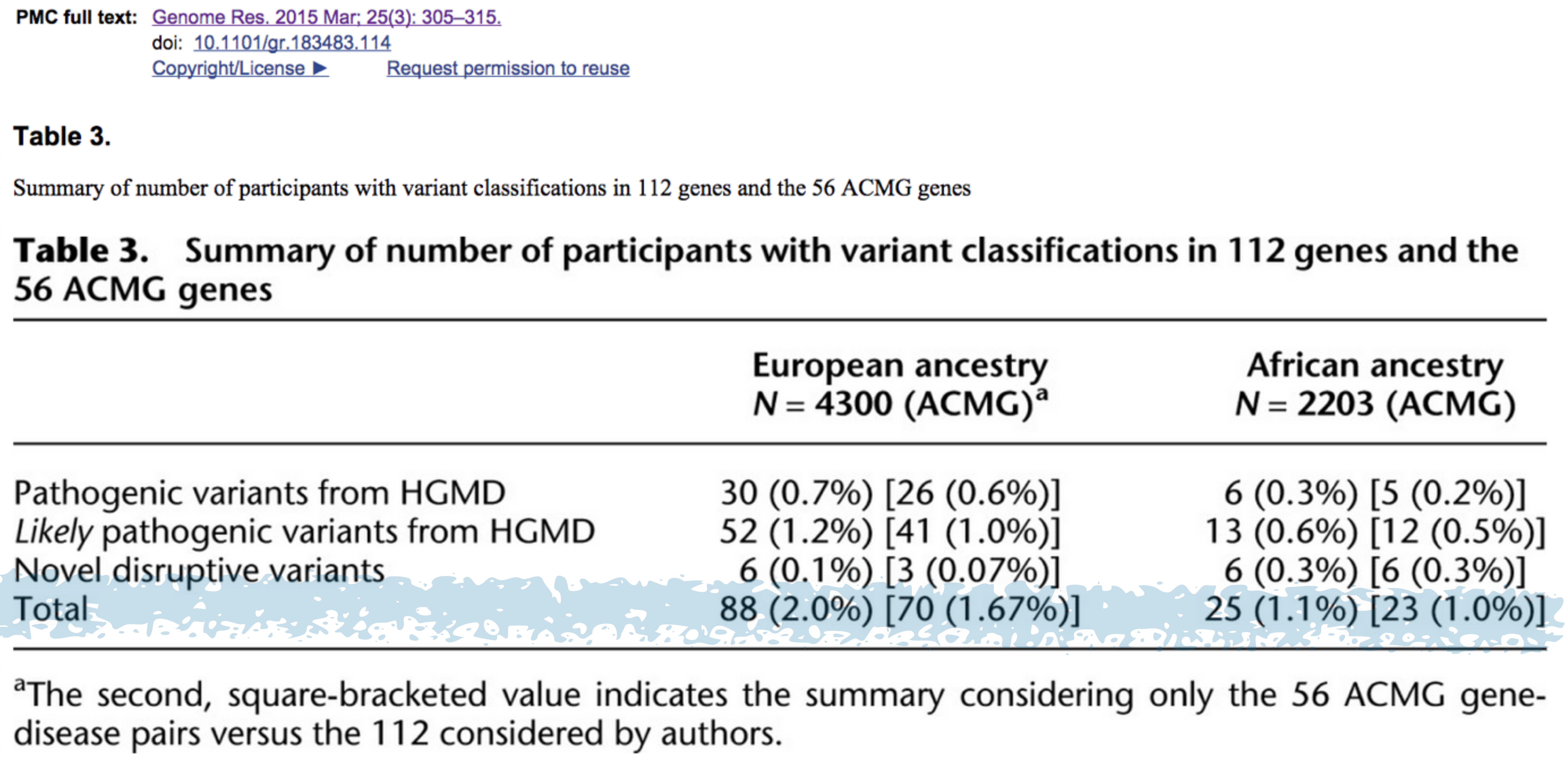




data from first 109 families



Likelihood of a meaningful secondary finding



PMC full text: Genome Res. 2015 Mar; 25(3): 305–315.
doi: 10.1101/gr.183483.114
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Table 3.

Summary of number of participants with variant classifications in 112 genes and the 56 ACMG genes

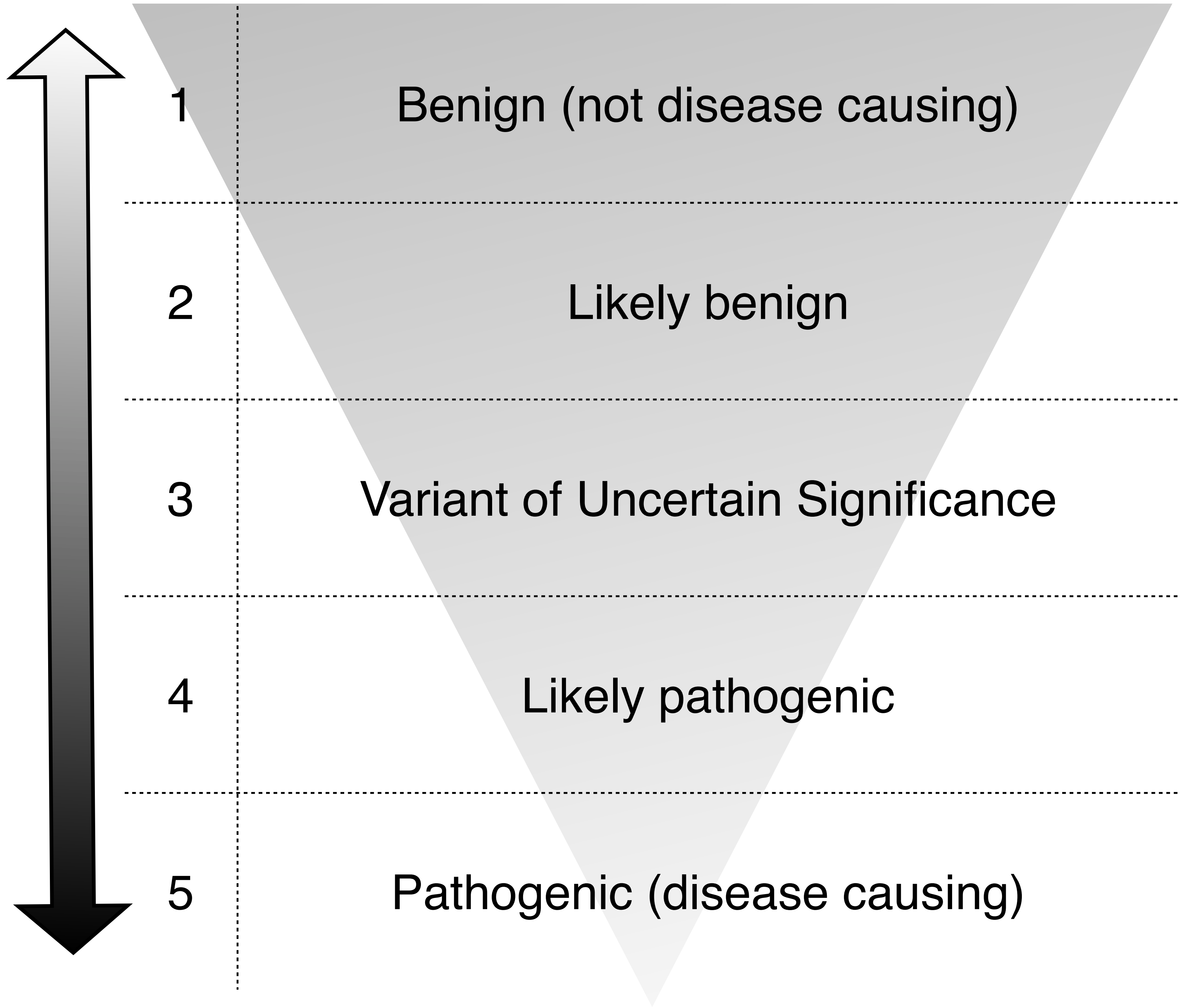
Table 3. Summary of number of participants with variant classifications in 112 genes and the 56 ACMG genes

	European ancestry $N = 4300$ (ACMG)^a	African ancestry $N = 2203$ (ACMG)
Pathogenic variants from HGMD	30 (0.7%) [26 (0.6%)]	6 (0.3%) [5 (0.2%)]
Likely pathogenic variants from HGMD	52 (1.2%) [41 (1.0%)]	13 (0.6%) [12 (0.5%)]
Novel disruptive variants	6 (0.1%) [3 (0.07%)]	6 (0.3%) [6 (0.3%)]
Total	88 (2.0%) [70 (1.67%)]	25 (1.1%) [23 (1.0%)]

[a] The second, square-bracketed value indicates the summary considering only the 56 ACMG gene-disease pairs versus the 112 considered by authors.

variants are not all created equal

most DNA changes have little or no clinical impact



1 Benign (not disease causing)

2 Likely benign

3 Variant of Uncertain Significance

4 Likely pathogenic

5 Pathogenic (disease causing)

depending on what a lab is willing to return, the likelihood of getting a VUS can be high

Benefits

- contribution to science
- information about cause of condition
- reproductive decision making
- possible management/treatment changes
- secondary findings

Risks

- blood draw risks
- psychosocial concerns
- genetic discrimination
- identification, loss of privacy
- inaccurate interpretation

Misconceptions abound

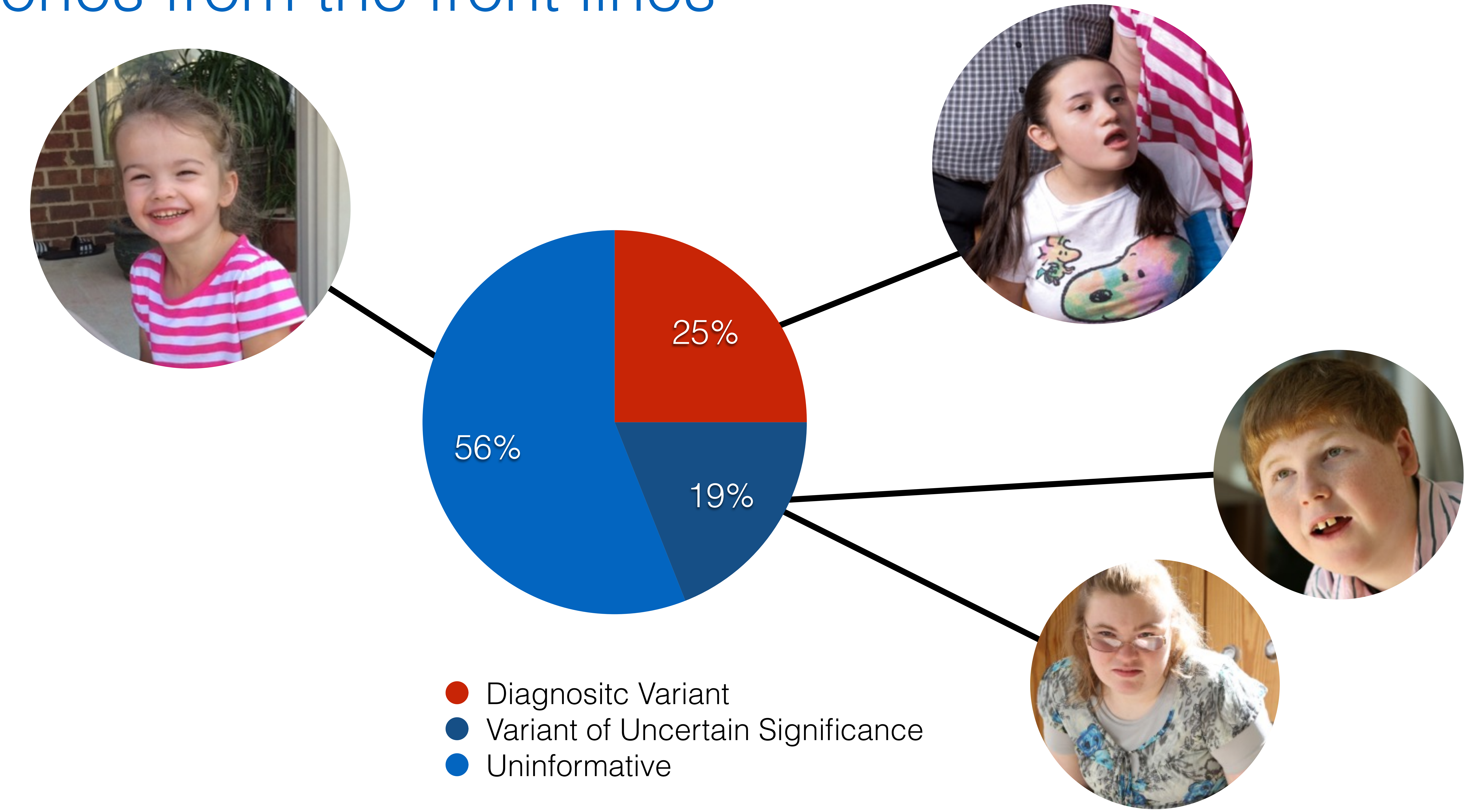
“finally a test that will answer, for once and for all, whether this is genetic”

“every other test was negative, and I know this one will be”

“We have no family history, so it can't be genetic”

“If we identify the gene, we will know how to treat it”

Stories from the front lines



Jessi

ental delay,
elay,
autism

history

fragile X
e testing

Jessi has a de novo pathogenic variant in MECP2 that leads to atypical Rett syndrome

Mutation Spectrum in Patients With Rett Syndrome in the German Population: Evidence of Hot Spot Regions

F. Laccone,[1*] P. Huppke,[2] F. Hanefeld,[2] and M. Meins[1]

[1]*Institute of Human Genetics, Georg-August-University Göttingen, Göttingen, Germany*

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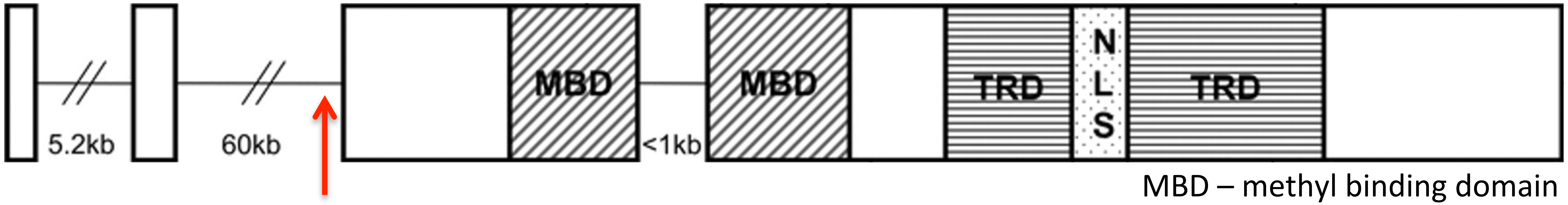

chrX:153298014 C>G
a.a. R9fs24X

MBD – methyl binding domain
TRD – transcriptional repressor domain
NLS – nuclear localization signal

Rett syndrome

caused by mutations in the MECP2 gene on the X chromosome

progressive, neuro-degenerative disorder in 1/10,000 females

- develop typically for first 6 months
- loose skills previously acquired
- problems with movement, coordination and muscle control
- seizures and intellectual disability

typically lethal in males

often no family history, >99% of mutations are sporadic

posttest genetic counseling

- review what the test looked for
- discuss what was found (or not found)
- impact on diagnosis, prognosis, treatment, recurrence risk
- who to share information with
- assess psychosocial issues
- support community and other resources
- whats next

sometimes a definite diagnosis still does not give all the answers…

atypical presentation of well known disorders

atypical Rett syndrome
unclear prognosis,
recurrence risk

Mutation Spectrum in Patients With Rett Syndrome in the German Population: Evidence of Hot Spot Regions

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[1]*Institute of Human Genetics, Georg-August-University Göttingen, Göttingen, Germany*
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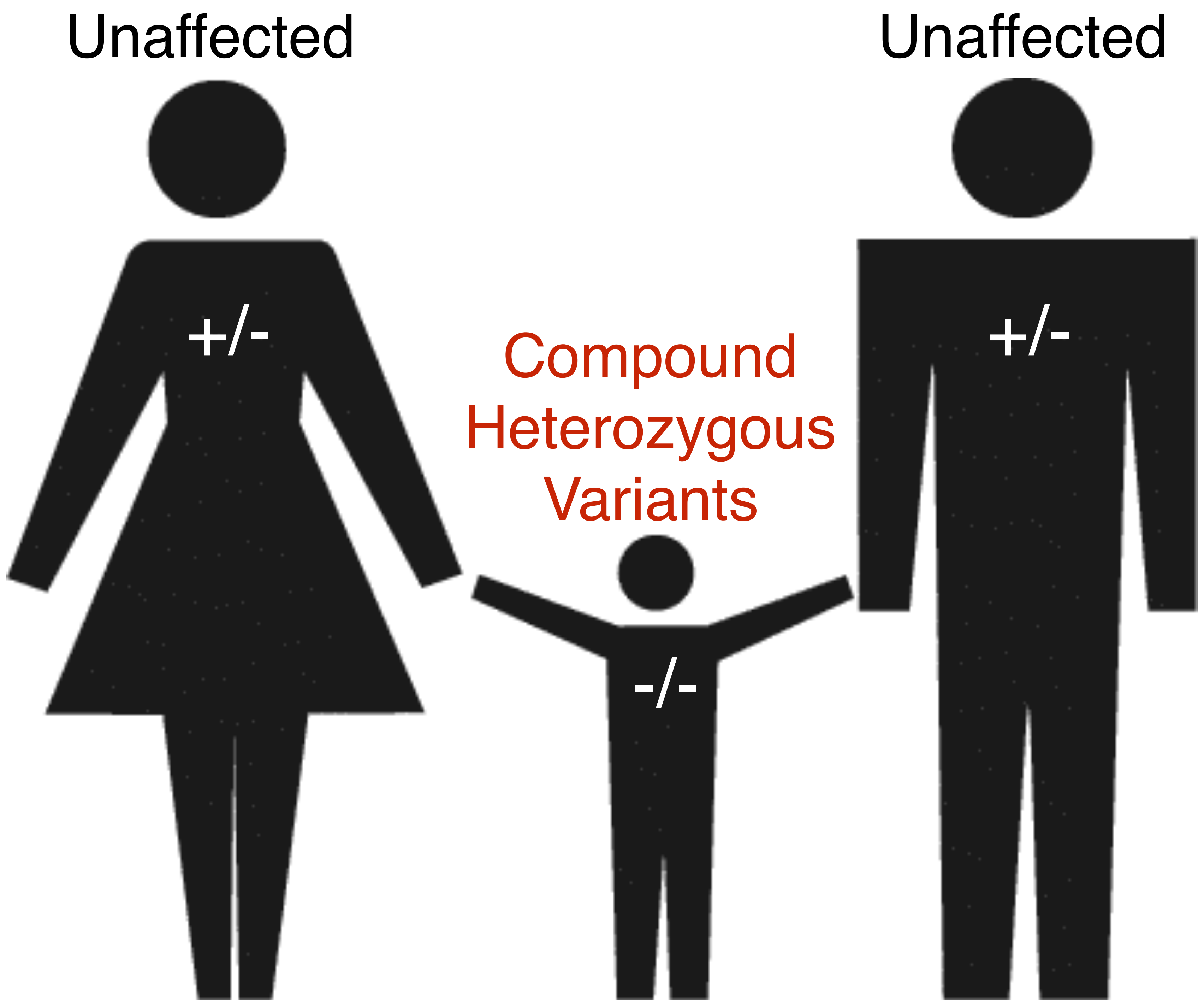
Brandon and Beth

dev
sei

no

neg
Pra
sy

Brandon and Beth inherited variants in PCNXL2 from their parents that are of uncertain significance



- Both variants appear to be detrimental to gene function
- Very little is known about the function of PCNXL2
- One report in the literature suggests that PCNXL2 functions in the nervous system (model organism study)

Will future studies inform to the pathogenicity of these variants?
Do they contribute to DD/ID?

handling the inevitable VUS

VUS = “variant of uncertain significance”

Laboratory did not have enough data to determine whether variant is benign or pathogenic.

Clinically, should be treated like an uninformative result. Management dictated by personal and family history.

- request re-interpretation of the variant periodically by the testing laboratory
- some, but not all, clinical labs routinely try to reclassify VUS’s and automatically update reports

burden of re-analysis and re-interpretation by research laboratories?

Alaina

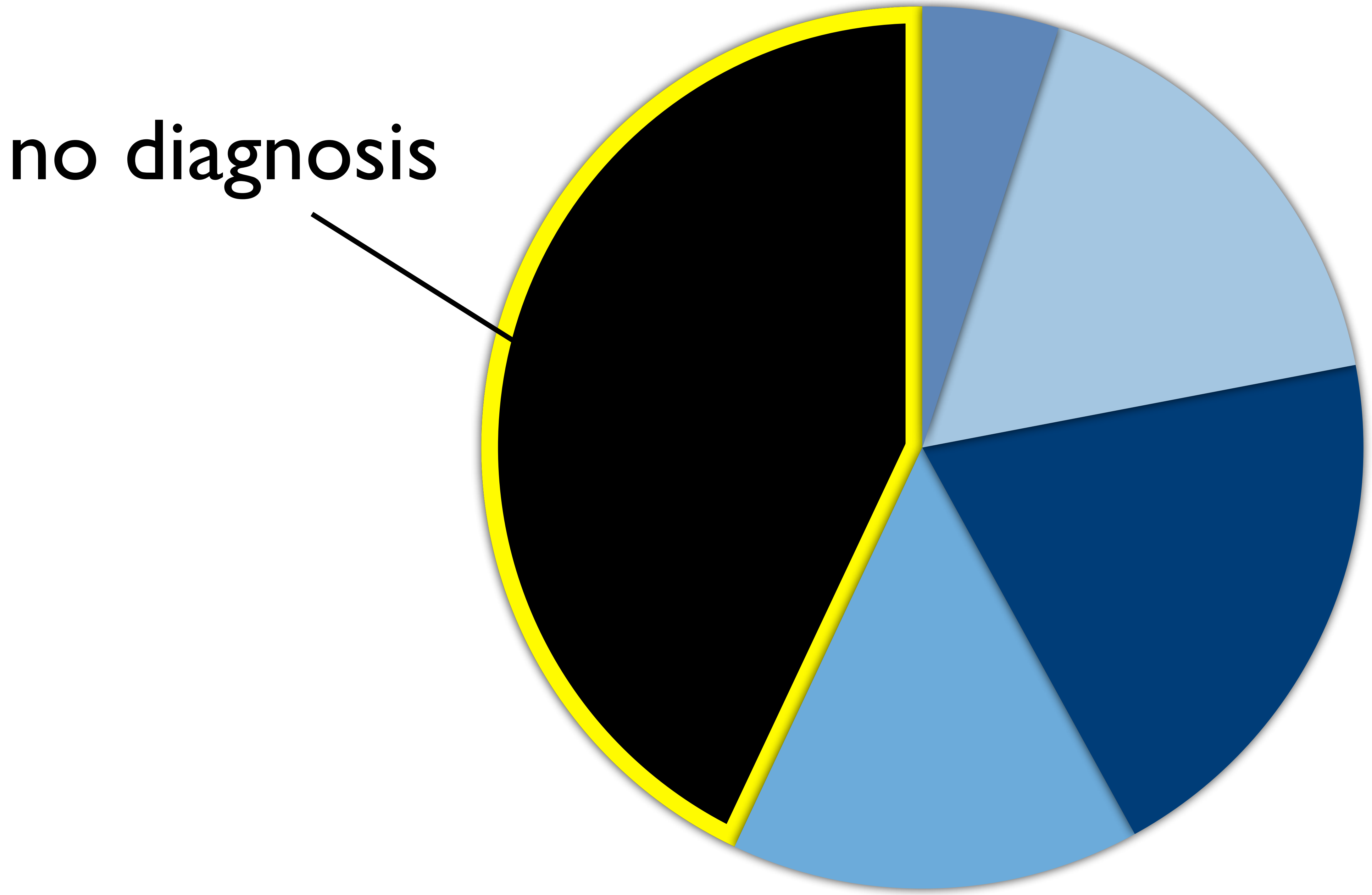
developmental delay, speech delay, hypotonia, mild ventriculomegaly

no family history

negative microarray analysis, Rett syndrome and Prader-Willi/Angelman syndrome testing

negative exome sequencing

in patients with a suspected genetic condition



Misconceptions abound

Positive:

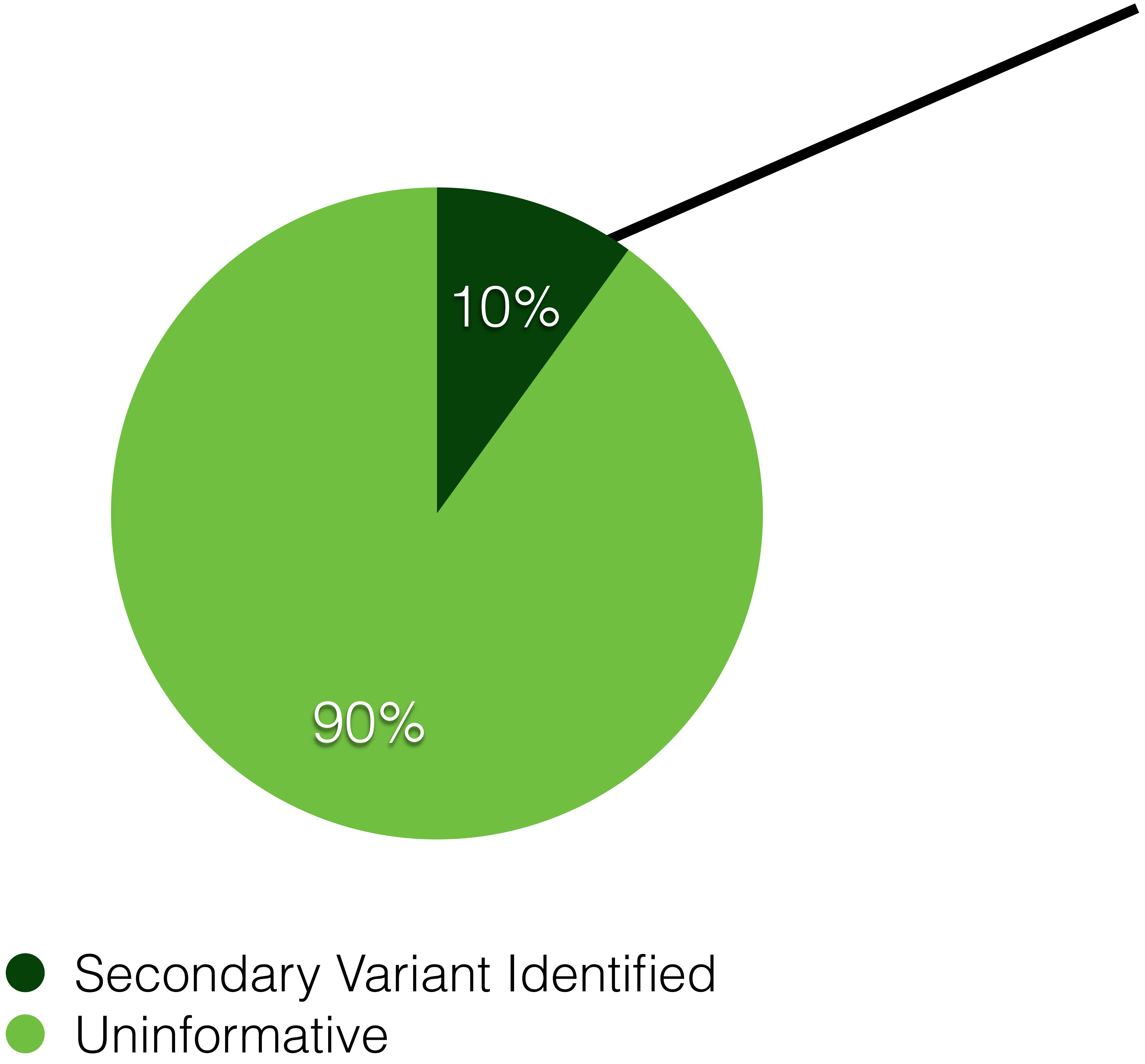
“Can’t you just go in and fix the mutation?”

Negative:

“does this mean it is environmental?”

[illegible]

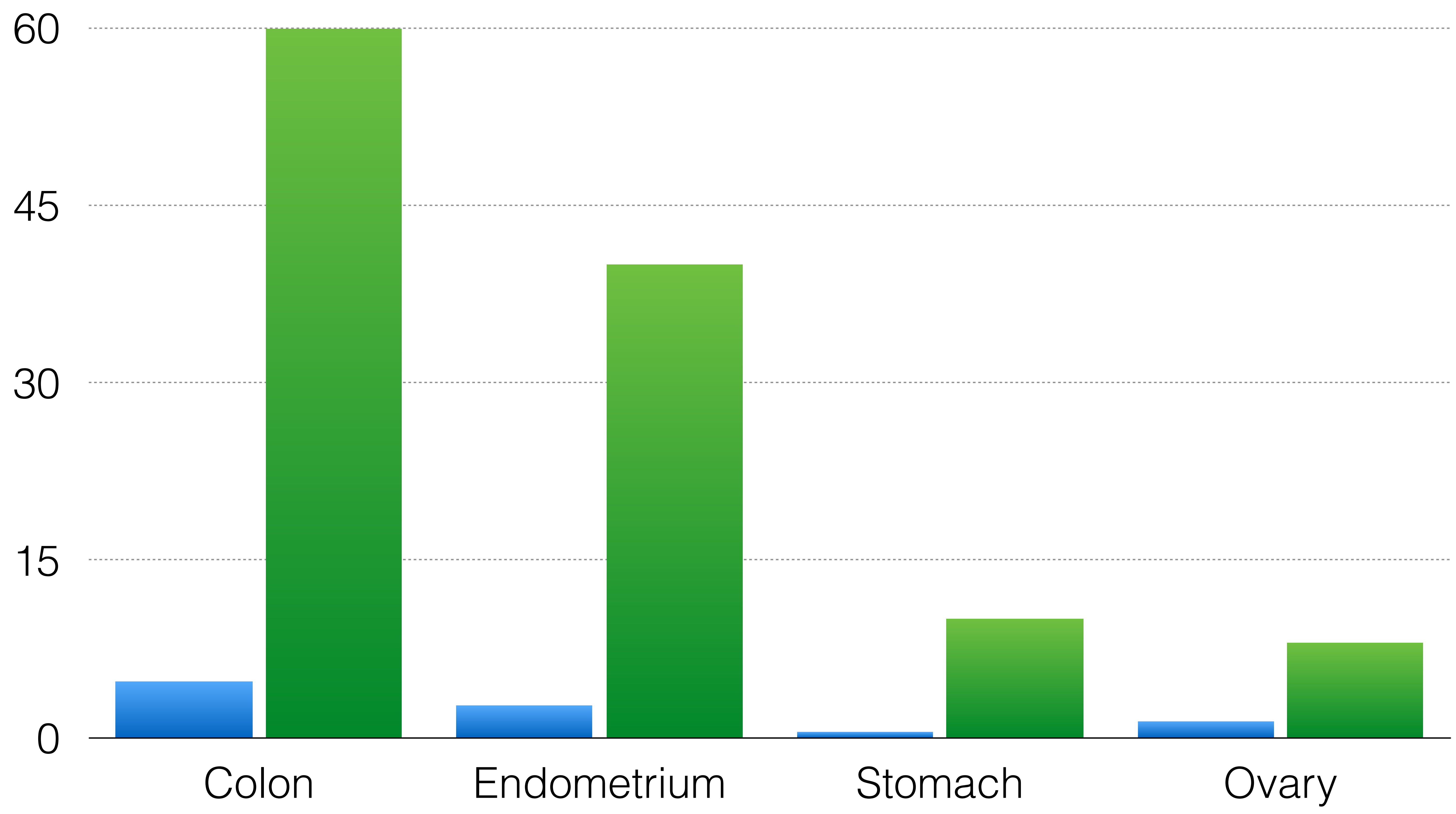
Stories from the front lines



genetic analysis of 242 CSER project parents

- Cystic Fibrosis carrier (6)
- Long QT syndrome (3)
- Sickle Cell carrier (2)
- Tay-Sachs carrier (2)
- Wilson disease carrier* (2)
- Malignant Hyperthermia (2)
- Lynch syndrome (2)
- Hereditary Breast Cancer
- Marfan syndrome
- Oculocutaneous Albinism
- Carnitine Deficiency

Lynch syndrome



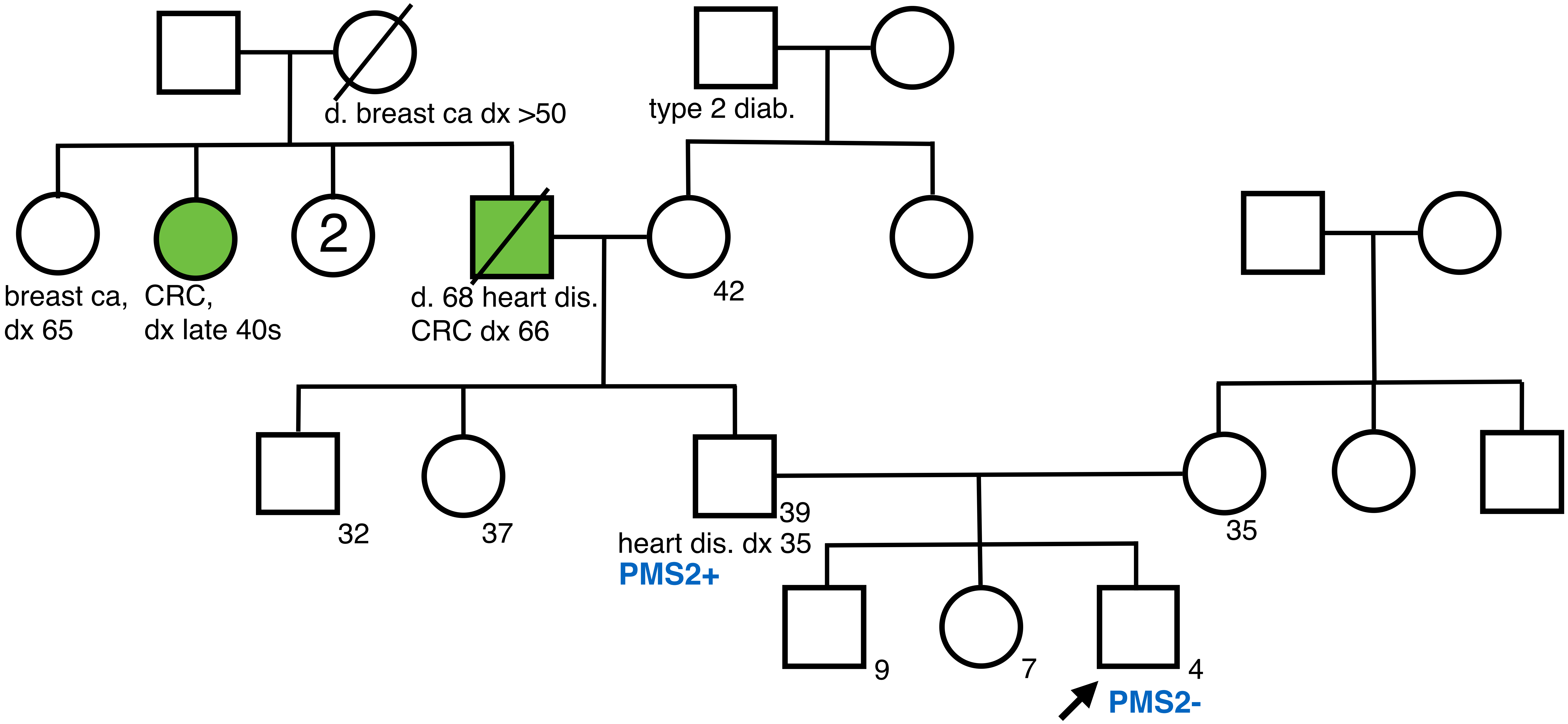
also known as
Hereditary Non
Polyposis Colorectal
Cancer

caused by mutations in:
MLH1
MSH2
MSH6
PMS2

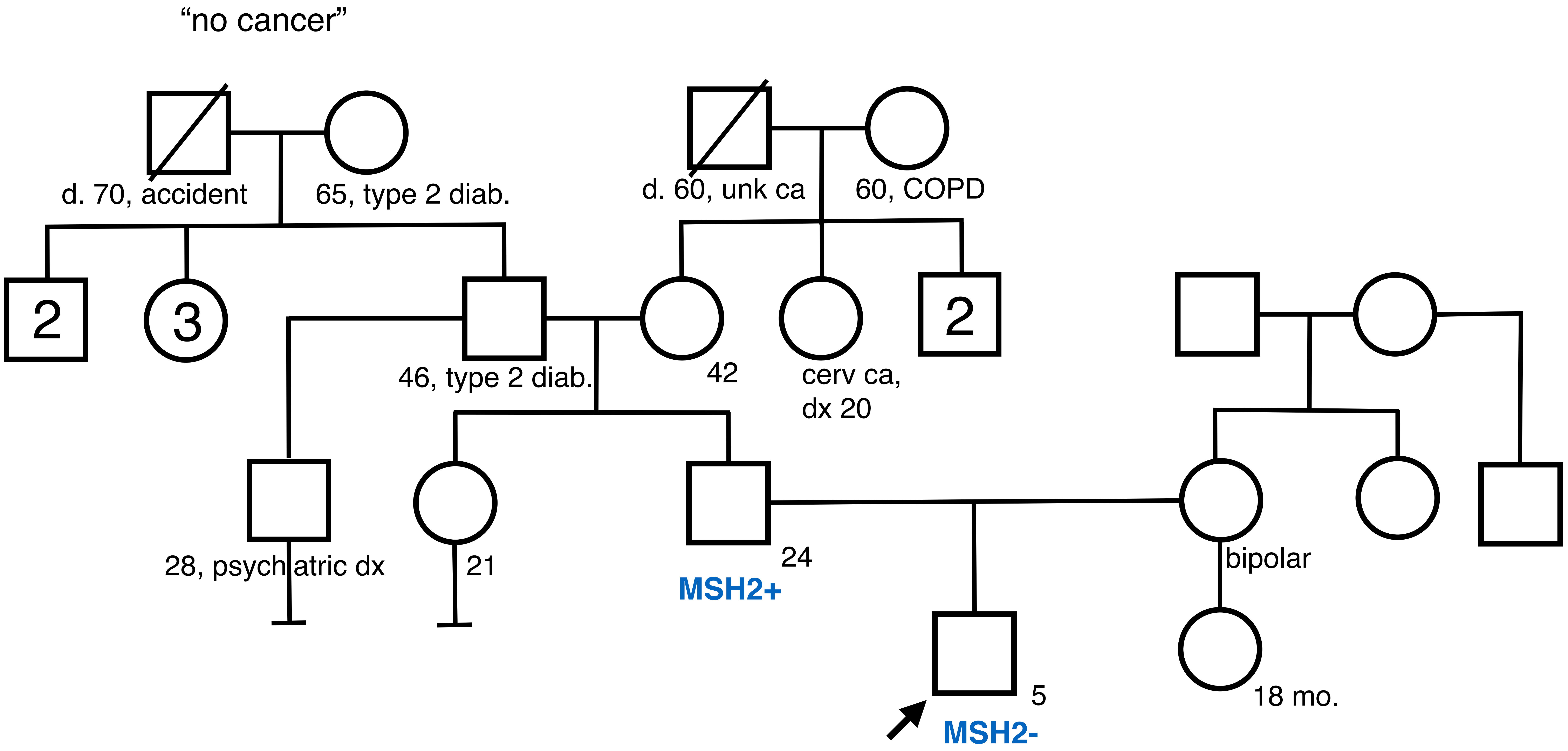
also increased risks of hepatobiliary tract, urinary tract, small bowel, brain and sebaceous neoplasms

Hereditary Non Polyposis Colorectal Cancer Genereviews [Internet]

Family A


d. breast ca dx >50
type 2 diab.
2
breast ca,
dx 65
CRC,
dx late 40s
d. 68 heart dis.
CRC dx 66
42
32
37
39
heart dis. dx 35
PMS2+
35
9
7
4
PMS2-

Family B


"no cancer"
d. 70, accident
65, type 2 diab.
d. 60, unk ca
60, COPD
2
3
46, type 2 diab.
42
cerv ca, dx 20
2
28, psychiatric dx
21
24
MSH2+
bipolar
5
MSH2-
18 mo.

Misconceptions abound

negative:

“ok, tell me how I am going to die”

"whew, glad to know I don’t have any genetic risk factors”

no secondary findings does NOT mean “no risk” or “not at increased risk “

Genetic Counseling → Genomic Counseling

description of testing
types of results and likelihood
VUSs
secondary findings*
expectation setting
cost/access issues
benefits/limitations
potential impacts
misconception probing
pyschosocial counseling

Thanks!

CSER Team
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