ECHO IDAHO

Autism

The Genetic Evaluation of Autism, Part 1

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Project ECHO®

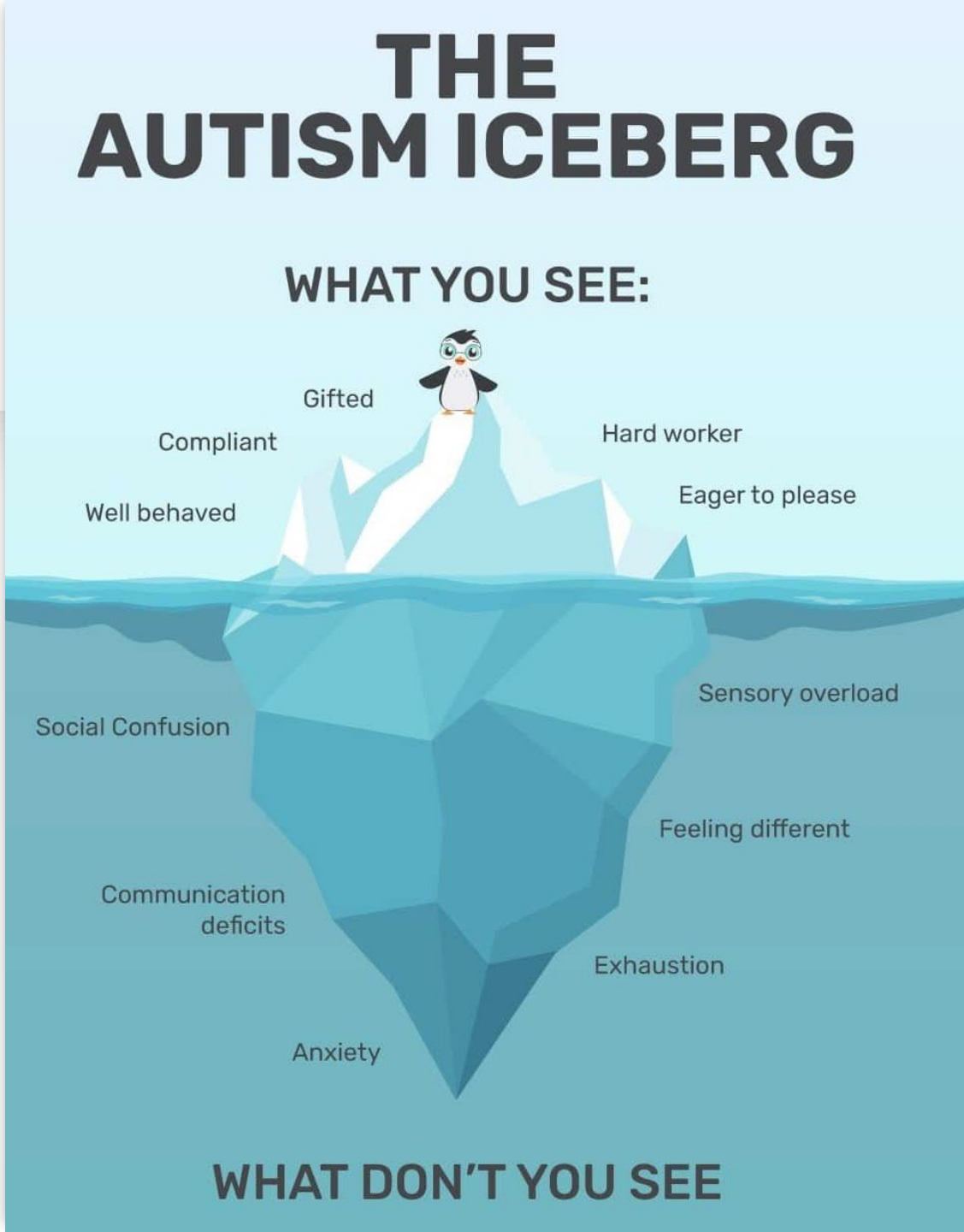
Learning Objectives

- Identify when to offer genetic testing and/or a referral to genetics
- Explain the benefits and limitations of genetic testing in autism
- Describe general elements of consent for genetic testing
- Discuss potential results for cytogenomic microarray
- List necessary steps to send genetic testing
- Develop a plan for communication of genetic results

Background on Autism & Genetics

- Autism affects ~1% of the population[2]
- Heritability of autism: 50-90%[2]
- Genetic causes are found in about 1 in 3 (25-40%) children who have autism or other developmental behavior disorders[7]
- The American Academy of Pediatrics (AAP) recommends genetic testing for all patients with global developmental delay, intellectual disability, and/or autism spectrum disorder[3]

Image: https://www.teeshirtpalace.com/products/aul8869728-accept-understand-love-autism-awareness-autism-iceberg-poster



What does a genetic counselor do?

- **ASSESS** – goals of the patient/family
- **DISCUSS** – personal and family history to understand the role of genetics and autism
- **EXPLAIN** – genetics, test implications, informed consent, and education on a diagnosis that's been received
- **GUIDE** – providing families with resources and information

What does a genetic counselor do? And what you can do to

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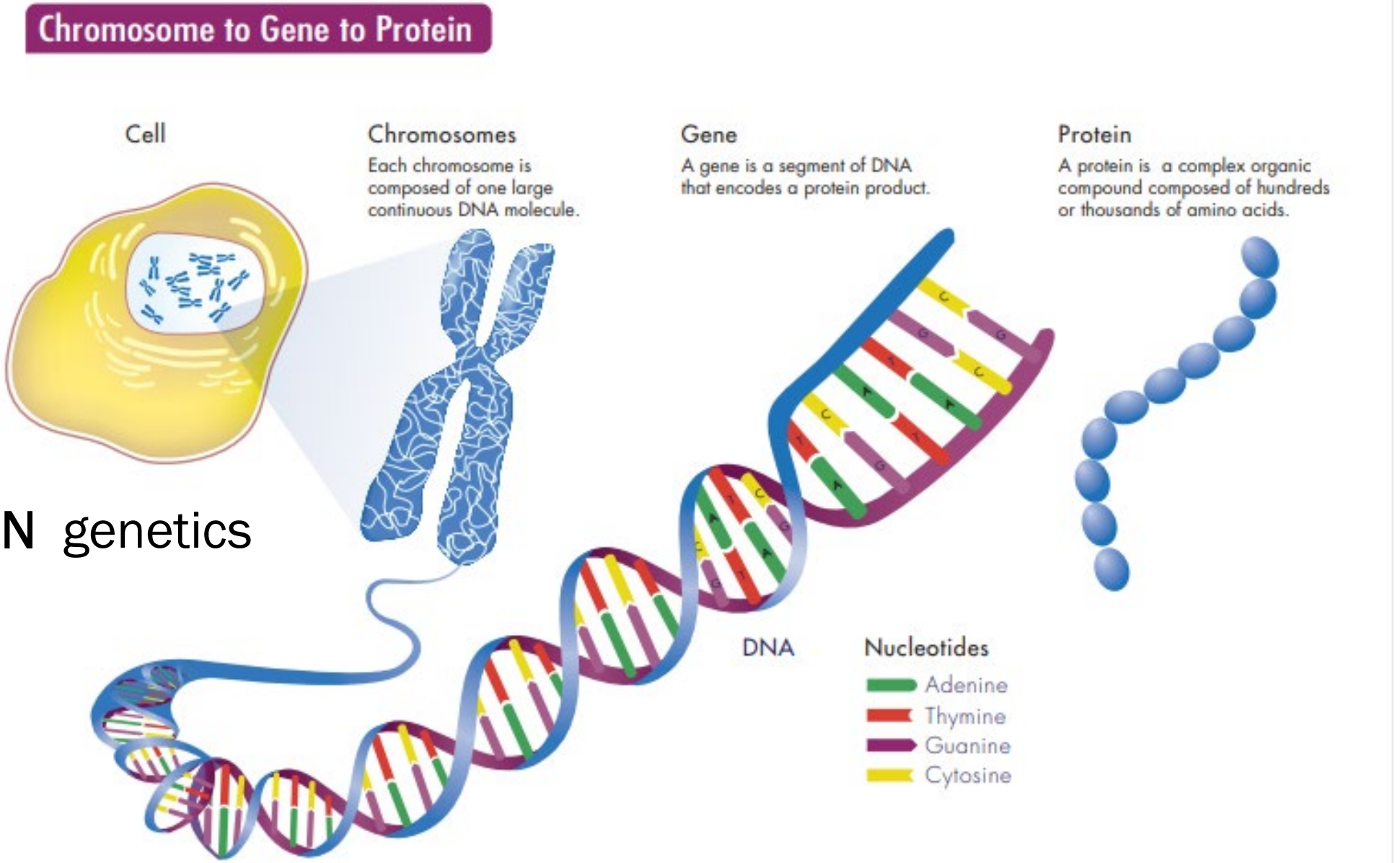
EXPLAIN genetics

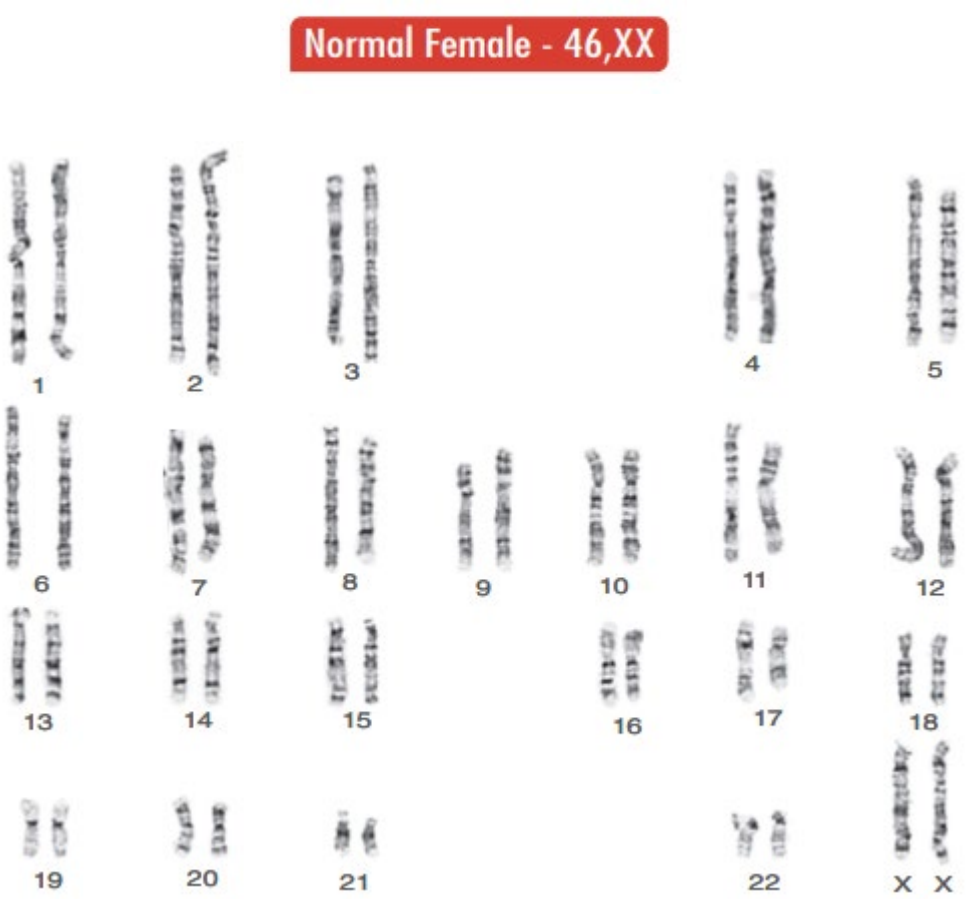


Types of genetic tests

- ~~Karyotype (not for autism dx)~~
- Chromosomal microarray or SNP arrays
- Fragile X
- Whole Exome Sequencing (strongly recommend with involvement of genetic counselor only)

Image: https://www.shutterstock.com/image-vector/bookshelf-books-biography-adventure-novel-poem-2130138842

Chromosomes in a Karyotype



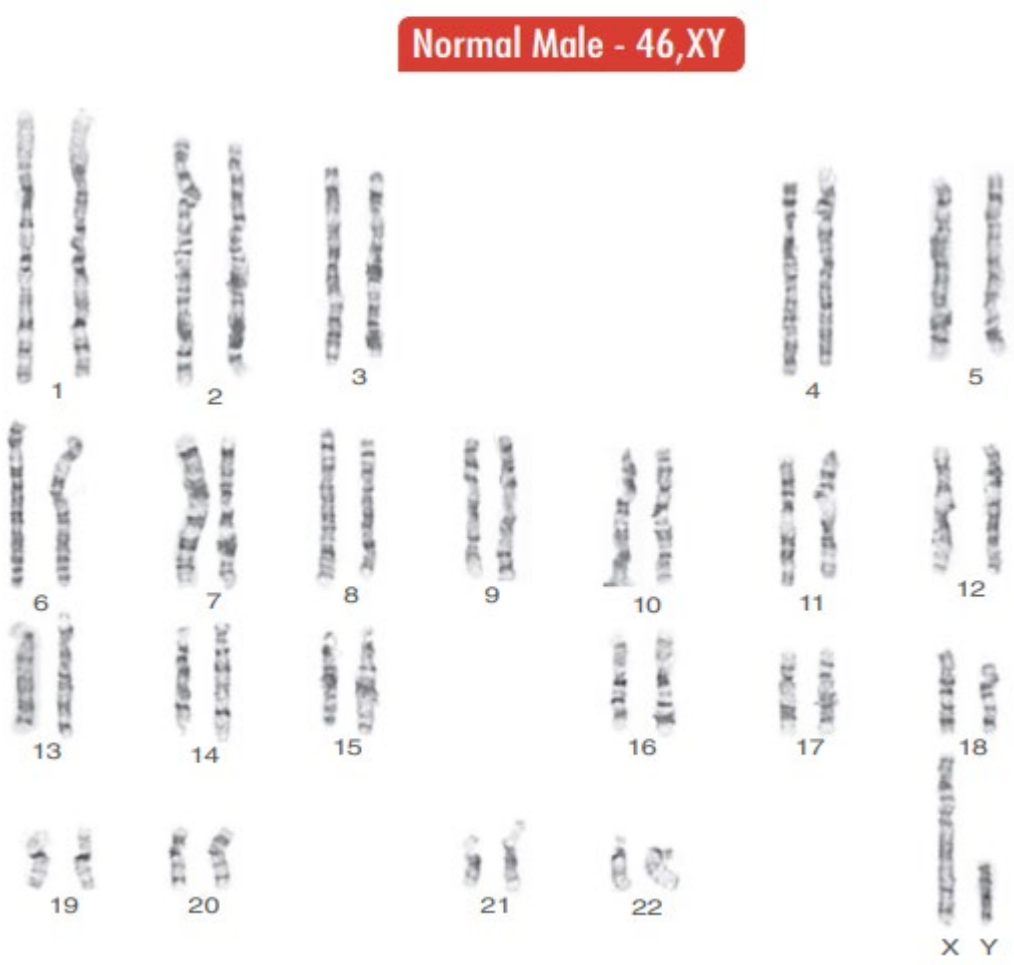


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Image: https://stock.adobe.com/search?k=ripped+book

Chromosomal microarray or SNP array

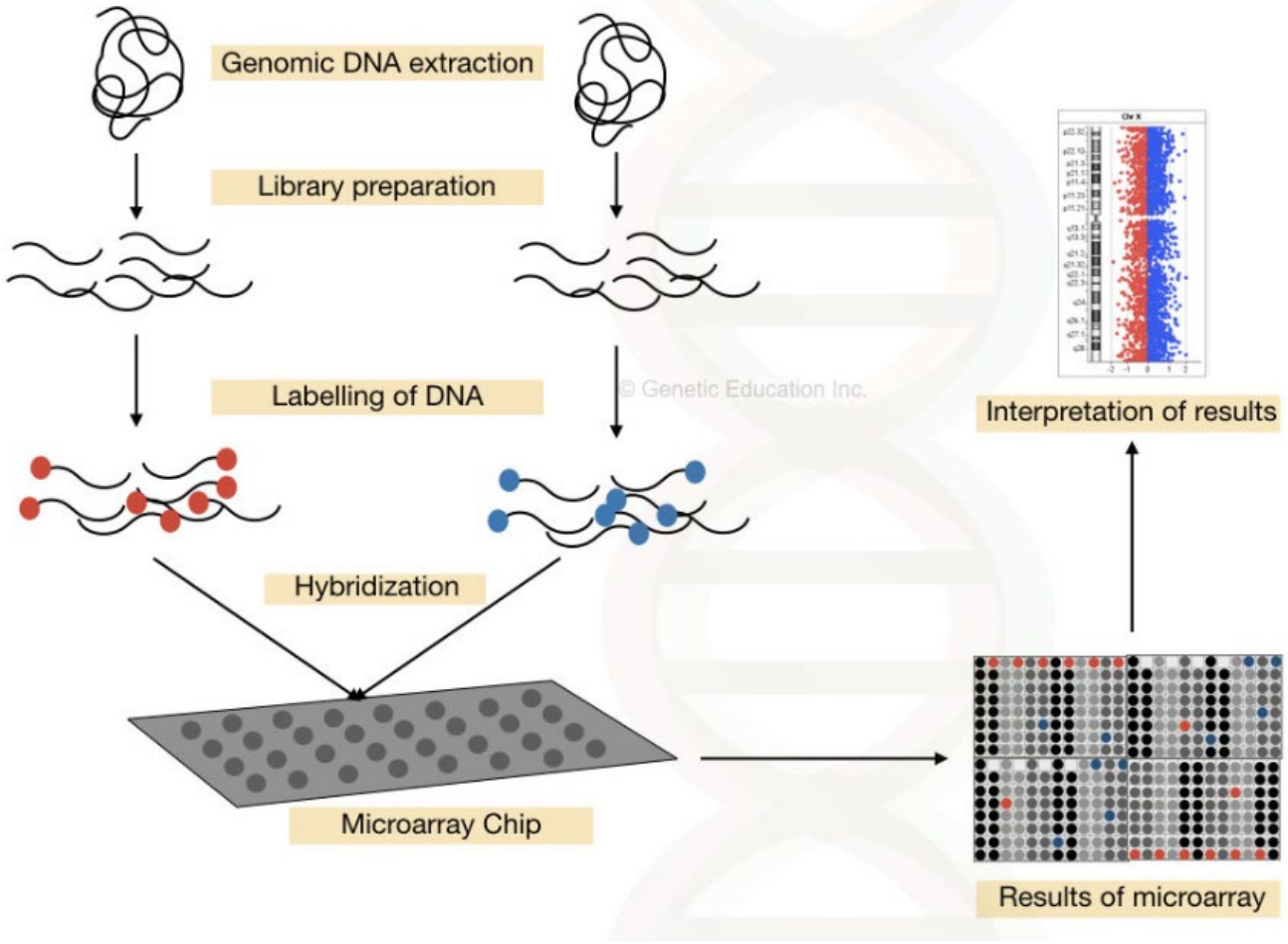

Illustration of Microarray process.

https://geneticeducation.co.in/snp-array-high-throughput-snp-genotyping-technique/

EXPLAIN – genetics

Types of genetic tests

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Fragile X (*FMR1* gene)

EXPLAIN – genetics

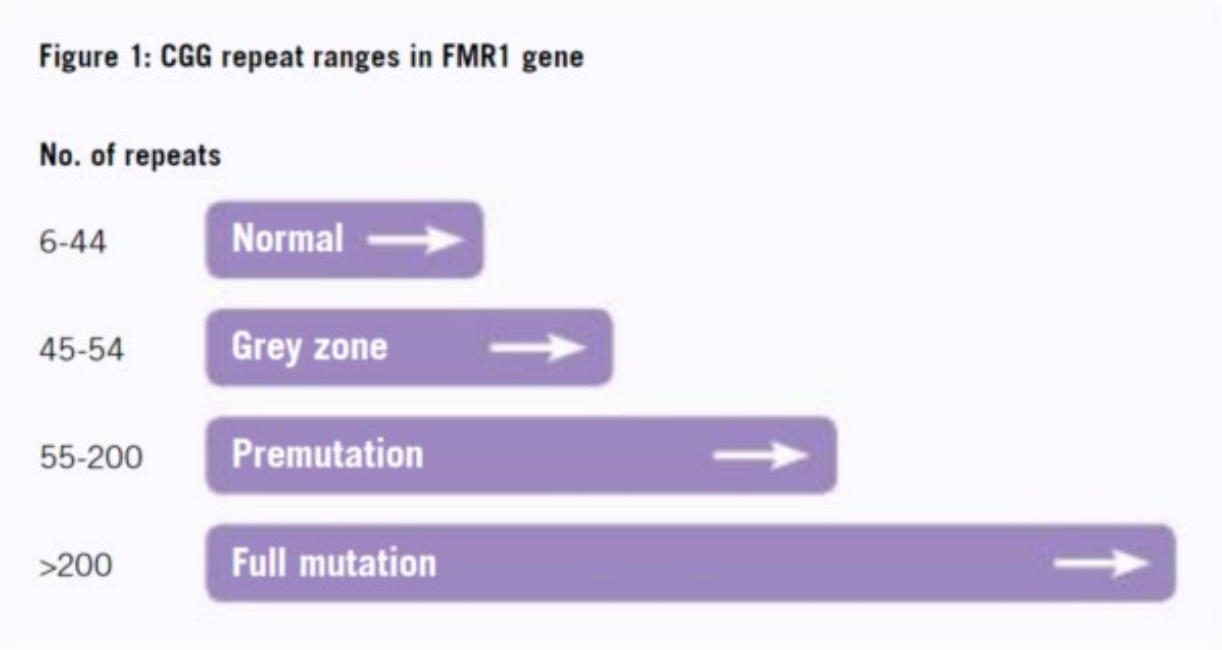


Image: https://www.fragilex.org.au/fragile-x-disorders/fragile-x-syndrome/testing-diagnosis/testing-for-fragile-x/

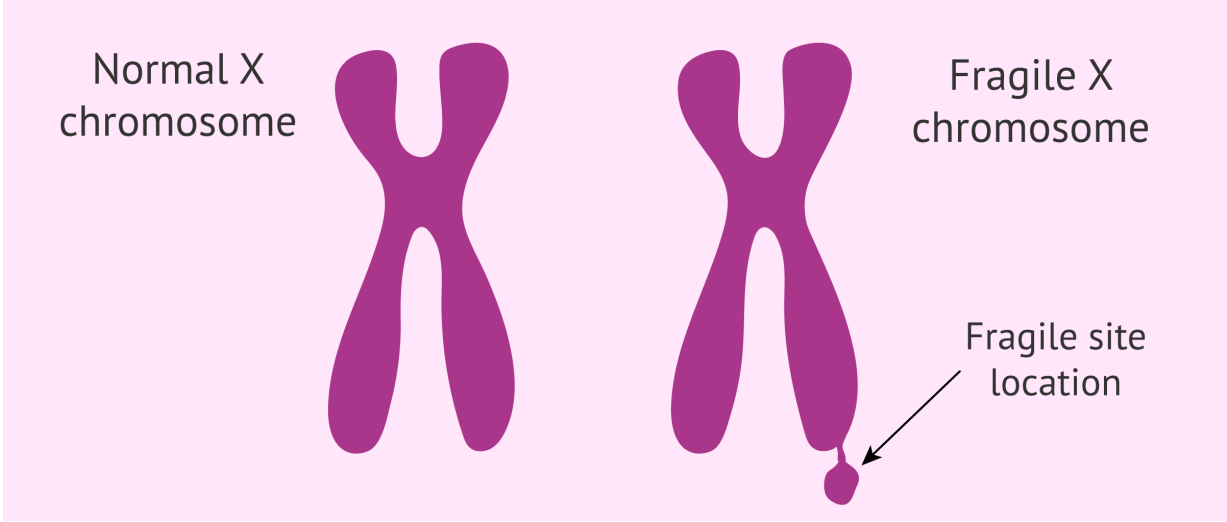
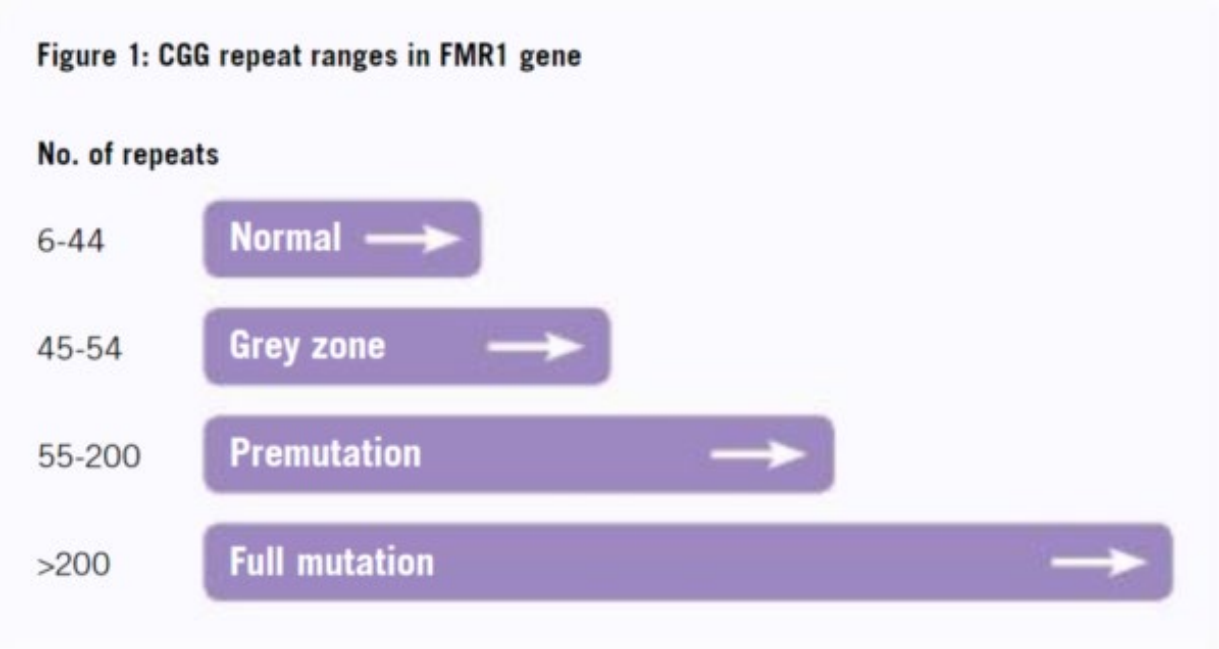


Image: https://www.invitra.com/en/fragile-x-syndrome/

Fragile X (*FMR1* gene)

EXPLAIN – test implications



- Pre-mutation carriers
  - Male
  - Female
- Full mutation carrier
  - Male
  - Female

Image: https://www.fragilex.org.au/fragile-x-disorders/fragile-x-syndrome/testing-diagnosis/testing-for-fragile-x/

https://fragilex.org/understanding-fragile-x/fragile-x-101/

Informed Consent

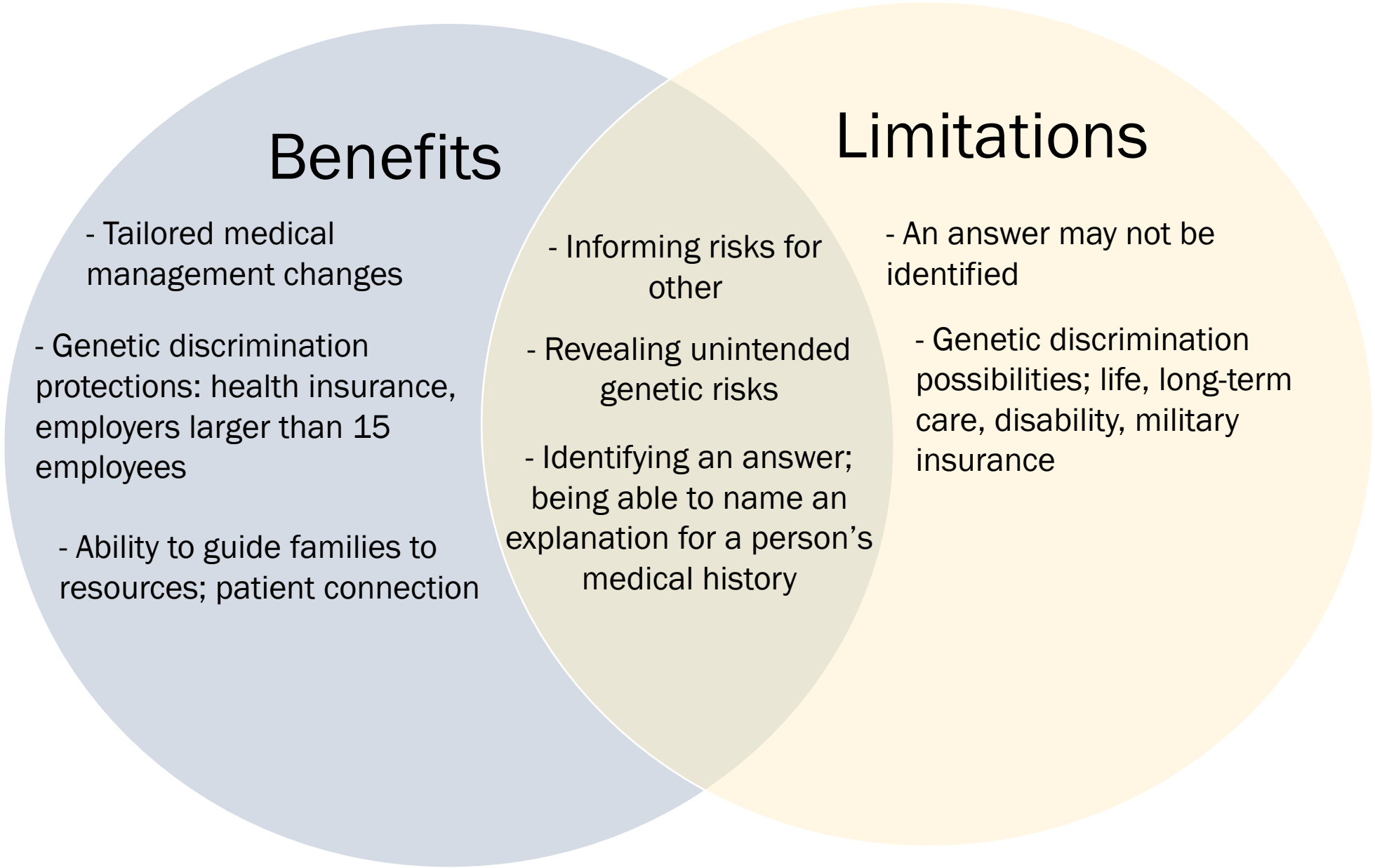
EXPLAIN – informed consent

- Participation is voluntary
- Inform about possible results
  - Intended
  - Unintended
- Discussion about risks and benefits of testing
- Documentation of informed consent can also help with insurance approval

Genetic Information Nondiscrimination Act (GINA) (Public Law 110-233)

- Federal law to prohibit health insurers and employers from discriminating based on genetic information

- Limitation: does NOT extend to life, long term care, or disability insurance
  - State law may have more comprehensive laws for this coverage area
  - Idaho has protections for life, disability, and group health insurance
  - See: Triage Cancer Chart for information per state


Benefits
- Tailored medical management changes
- Genetic discrimination protections: health insurance, employers larger than 15 employees
- Ability to guide families to resources; patient connection
- Informing risks for other
- Revealing unintended genetic risks
- Identifying an answer; being able to name an explanation for a person's medical history
Limitations
- An answer may not be identified
- Genetic discrimination possibilities; life, long-term care, disability, military insurance

Chromosomal microarray/ SNP array

EXPLAIN – test implications

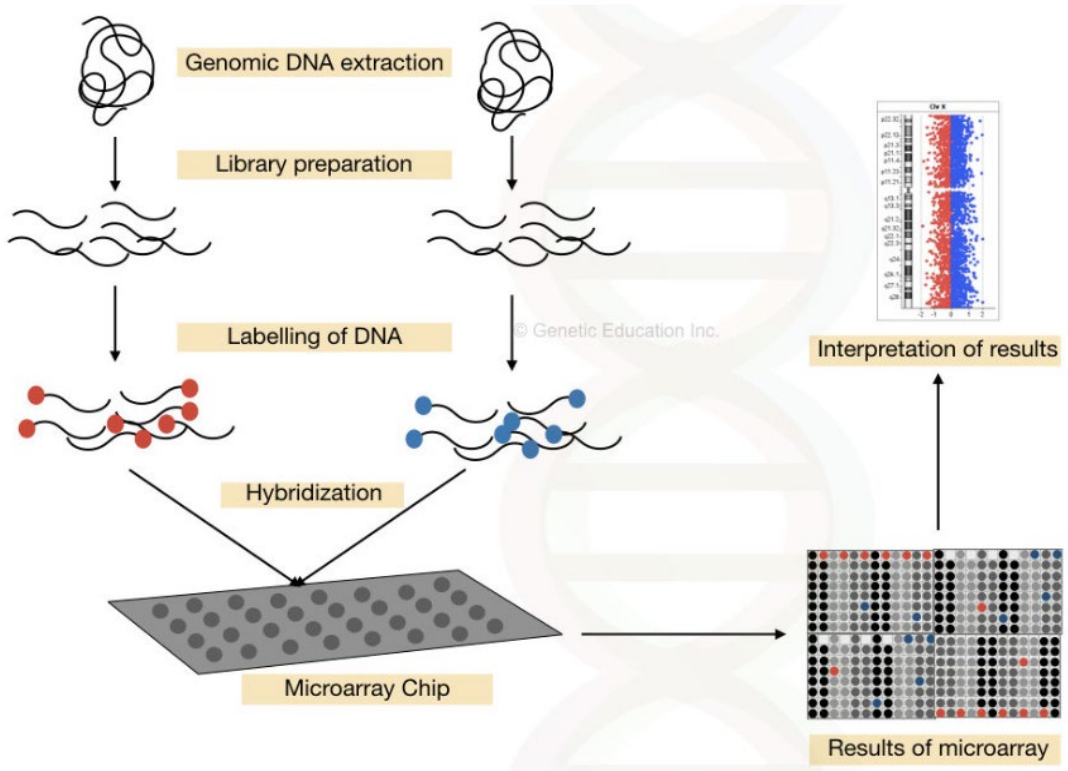


Illustration of Microarray process.

Copy number variation
Duplications and Deletions
Regions of homozygosity

https://geneticeducation.co.in/snp-array-high-throughput-snp-genotyping-technique/

Possible Results

EXPLAIN – test implications

POSITIVE

Yes, identified likely pathogenic or pathogenic finding

- Confirmation of a person affected with a genetic condition
- Risk for developing a genetic condition
- Carrier of a recessive condition

NEGATIVE

No, did not identify reportable finding

- person was not identified with any concerning genetic changes HOWEVER; this does not exclude the possibility of being affected with a condition

UNCERTAIN

Yes, identified a finding, unclear about impact of the finding

- Uncertainty isn't about whether a genetic variant is present
- Needs additional evidence to support pathogenicity or benign impact

INCIDENTALS

- Identifying unintended/unrelated genetic risk
- Predicting another family member's risk or is a carrier of a genetic condition
- Non paternity, non maternity
- Regions of homozygosity/consanguinity

Classification of Genetic Variants

EXPLAIN – test implications

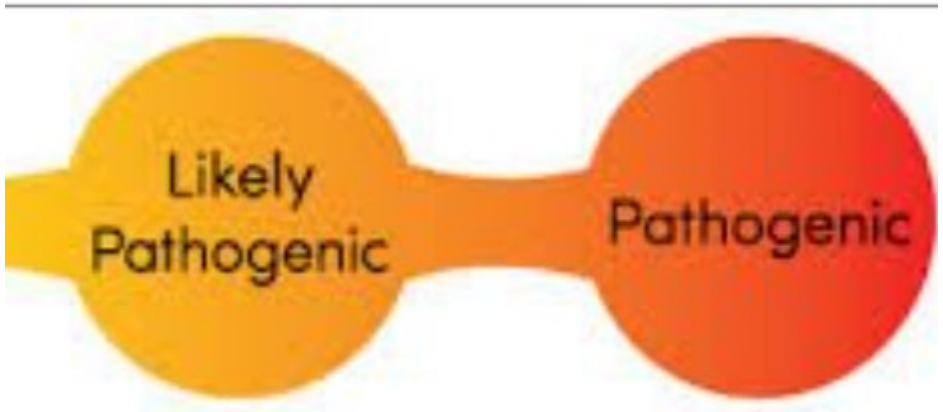
NEGATIVE/NORMAL

POSITIVE/ABNORMAL

Image: https://www.genome.gov/sites/default/files/media/files/2020-04/Guide_to_Interpreting_Genomic_Reports_Toolkit.pdf

Test Reports

EXPLAIN – test implications



POSITIVE/ABNORMAL

- Pathogenic or likely pathogenic refers to the VARIANT
- Before deciding if causative: Is the condition recessive, dominant or X-linked?

Image: https://www.genome.gov/sites/default/files/media/files/2020-04/Guide_to_Interpreting_Genomic_Reports_Toolkit.pdf

Billing: Questions to Consider

- What is the test most likely to reveal an answer for my patient?
- What testing labs offer this genetic test?
- What type of insurance does my patient have?
  - e.g., private, Medicaid, Medicare
- Are there cost considerations based on the lab?
  - No balance billing for Medicaid patients
  - Self-pay options
- What sample type is required and accepted?
  - Blood, buccal, saliva

What does a genetic counselor do? And what you can do to

- **GUIDE** – provide families with resources and information
  - Use the resources offered by the testing lab
  - Refer your patients with ASD Level 3 and/or IDD to Genetics Clinic at the SAME time you are sending testing and referring to Developmental Pediatrics
  - Websites:
    - Genetic and rare Disease Information Center https://rarediseases.info.nih.gov/diseases

GUIDE: **Cascade testing**
(testing other potentially affected family members)

- OPTIONS
  1. Send the testing yourself
  2. Directly refer at risk family members to Genetic Counseling
  3. Send a communication to the patient's PCP recommending testing
  4. Write a short letter that at risk family members can take to the PCP.
     - *** was diagnosed with X *(write out exactly what was seen)*. At risk family members should be referred for Genetic Counseling and testing.

Resources

- To find a genetic counselor in your area, visit: http://findageneticcounselor.nsgc.org/
- There may be ways for your patients to be involved in research. To learn more about research studies, visit: http://autismsciencefoundation.org/get-involved/participate-in-research/
- Good web site on Fragile X: https://fragilex.org/understanding-fragile-x/fragile-x-101/
- Video consent for chromosomal microarray https://www.youtube.com/watch?v=ZrDANI0KSNU&t=3s
- Detailed – how to take a pedigree https://humangenetics.medicine.uiowa.edu/resources/how-draw-pedigree

Resources

- Glossary of genetic terms https://www.genome.gov/genetics-glossary
- Genetic and rare Disease Information Center https://rarediseases.info.nih.gov/diseases
- GeneReviews
- https://medlineplus.gov/ - a medical encyclopedia

References

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Links to Common Testing Lab Consent Forms

- Default – google lab name and “consent form”
  - Most labs have options for consent forms in multiple languages
  - Labs typically do NOT require a wet signature on consent forms, if documentation of the consent conversation is sent
- Ambry: https://www.ambrygen.com/file/material/view/1903/Comprehensive%20Consent%20Form%20%2817707_0%29.pdf
- ARUP Labs: https://ltd.aruplab.com/api/ltd/pdf/245
- Baylor: https://www.baylorgenetics.com/wp-content/uploads/2021/12/baylor-genetics-informed-consent-for-genetic-testing-form.pdf
- GeneDx: https://www.genedx.com/wp-content/uploads/2024/11/Informed-Consent-ENG-20241029.pdf
- Invitae: https://view.publitas.com/invitae/fm104_invitae_patient_consent_form/page/1
- Prevention Genetics: https://assets.preventiongenetics.com/documents/patient-informed-consent.pdf