GENETIC COUNSELING, FAMILY HISTORY, GENETIC TESTING

How to make the most of these resources

Alicia Gomes, MS, CGC

UAB Department of Genetics

Objectives

- Provide a brief description of genetic counseling
- Discuss useful tools and considerations when reviewing a family history
- Provide a basic understanding for the genetics of NF

Genetic Counseling

- What is it?
  - A bridge between genetics and the general population
  - Provides a patient friendly explanation of genetics and genetic disorders
  - Uses psychosocial cues and interaction to help determine the effects of genetics and genetic disorders on an individual/family

Genetic Counseling

- Who performs genetic counseling?
  - Physicians
  - Nurses
  - Genetic Counselors
- In what settings is this done?
  - Prenatal
  - Pediatric
  - Adult
  - Other

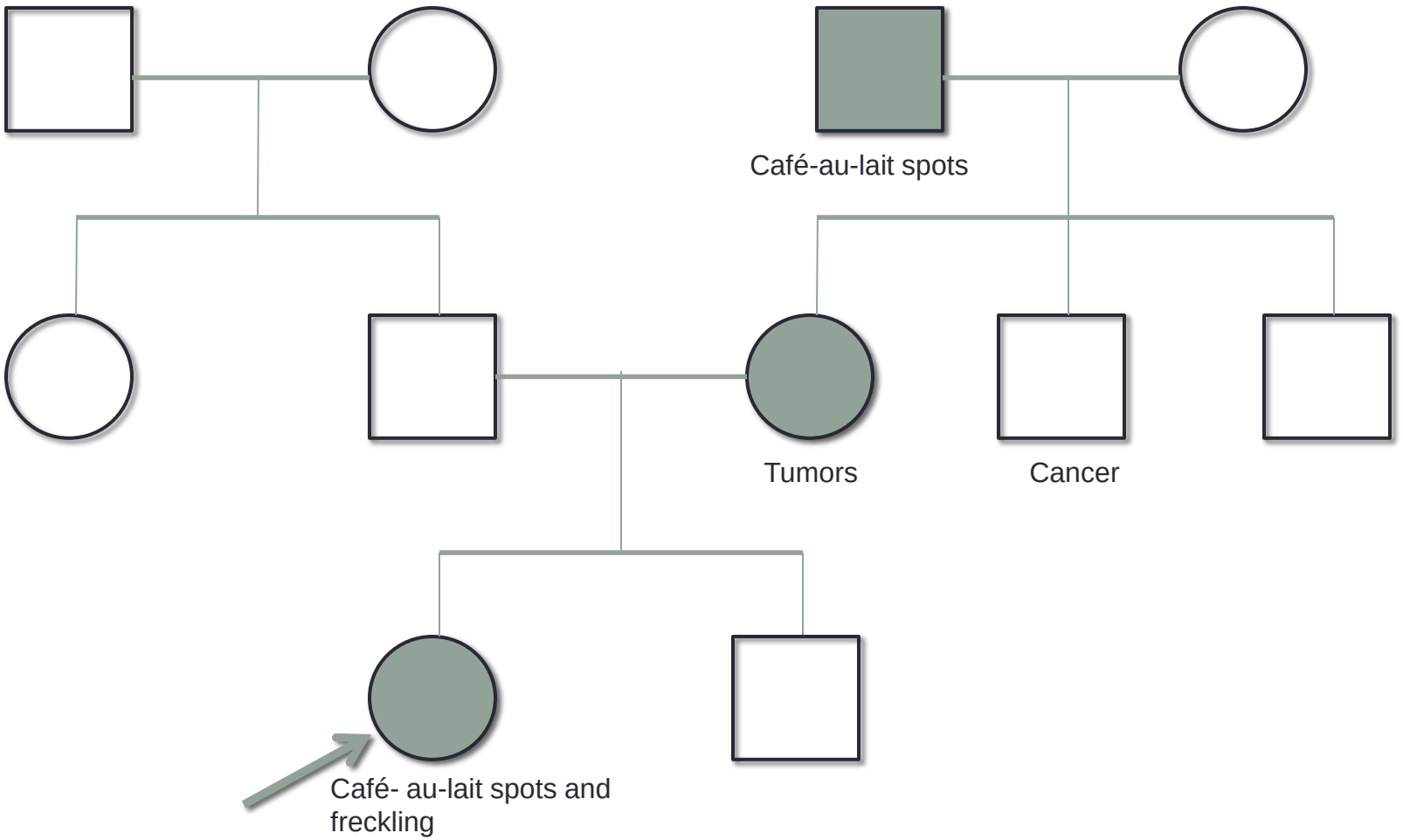
Key Components of Genetic Counseling

- Establish a background on the patient
  - Values and social background for the patient
  - Medical history of the patient
  - **FAMILY HISTORY**
- Explain how genetics currently affects the patient
  - Provide summaries of the genetics and natural history of particular genetic disorders
  - Explain current genetic testing options
  - Provide resources on genetic disorders
- Serve as a resource for any advancements within genetics

Family History

- What is important?
  - Relationships: Different diseases are inherited in different patterns
  - Ages of onset: help to rule in/out genetic disorders
  - Details: medical details can be essential
  - Ancestry: helps to rule in/out genetic disorders

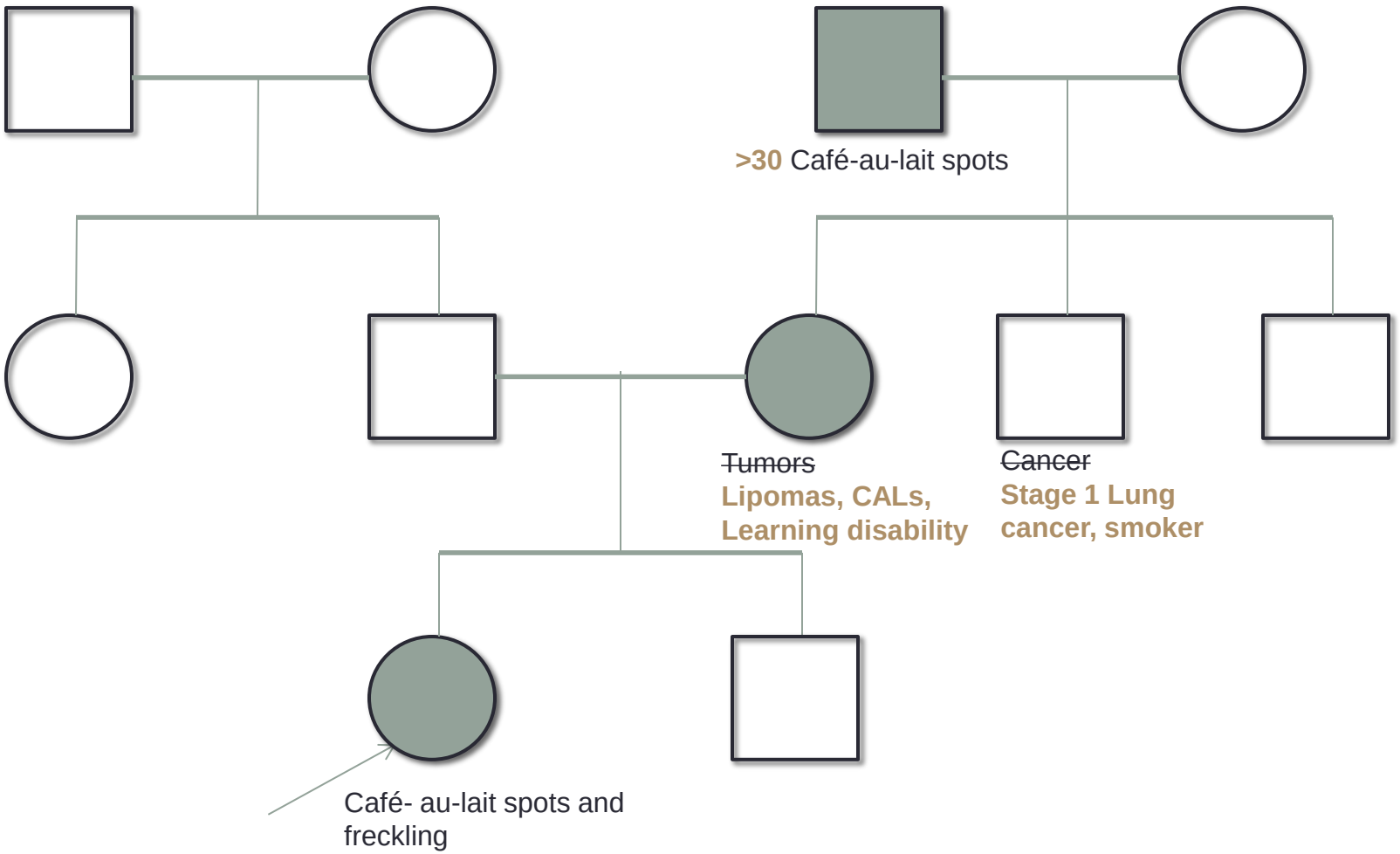
An Example


Café-au-lait spots
Tumors
Cancer
Café- au-lait spots and freckling

Neurofibromatosis Type 1

- Chromosome 17
- *NF1* gene
- Autosomal Dominant
- 1:3,500 incidence
- 50% chance to have a brand new mutation
- Gene change does not provide information on clinical presentation
- >95% detection rate for genetic testing

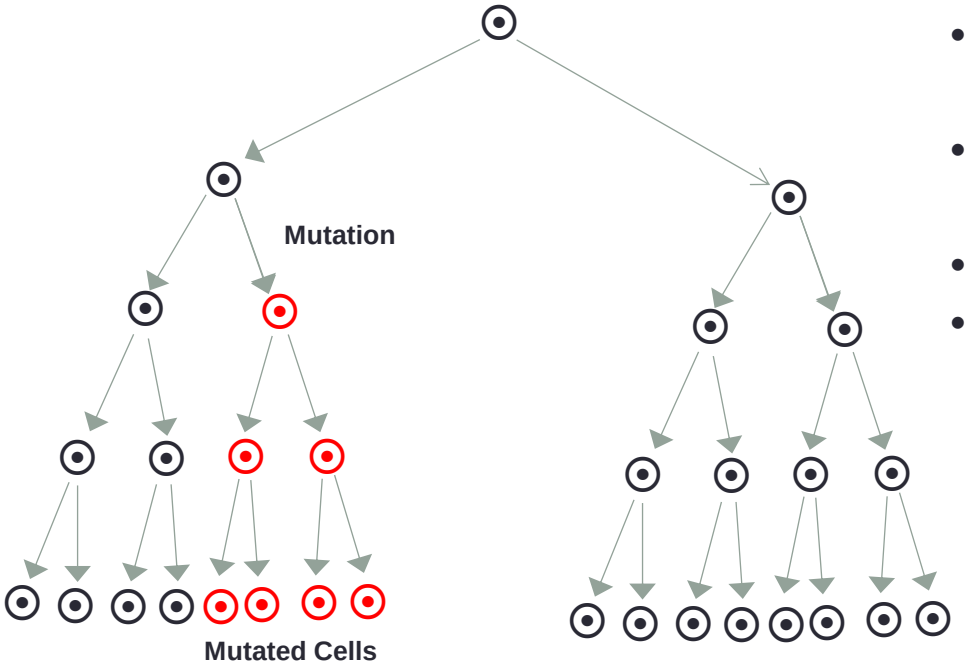
An Example


>30 Café-au-lait spots
~~Tumors~~
Lipomas, CALs,
Learning disability
~~Cancer~~
Stage 1 Lung
cancer, smoker
Café- au-lait spots and
freckling

Legius syndrome

- Chromosome 15
- *SPRED1* gene
- Autosomal Dominant
- No CNS tumors
- Less frequent than NF1
  - ~20% with family history of CAL spots and freckling only
  - ~2% of total population of CAL spots and freckling only

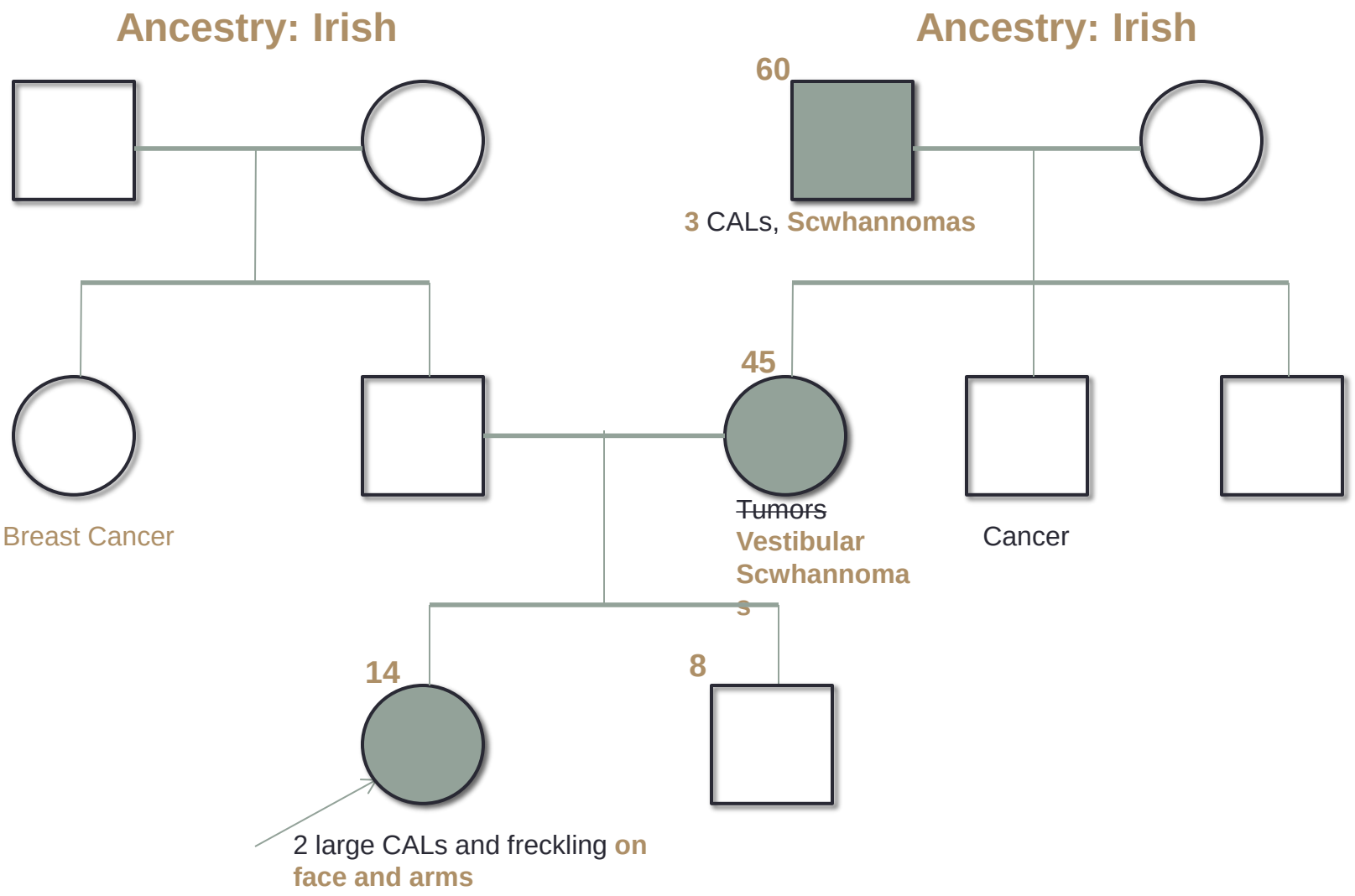
Segmental/Mosaic NF1



- More than one cell line within the body
- May require more complex genetic testing
- Seen in “founder” patients
- Leads to variable risk of inheritance to the next generation

http://carolguze.com/text/442-2-mutations.shtml

An Example


Ancestry: Irish
Ancestry: Irish
60
3 CALs, Scwhannomas
45
Breast Cancer
~~Tumors~~
Vestibular Scwhannomas
Cancer
14
8
2 large CALs and freckling on face and arms

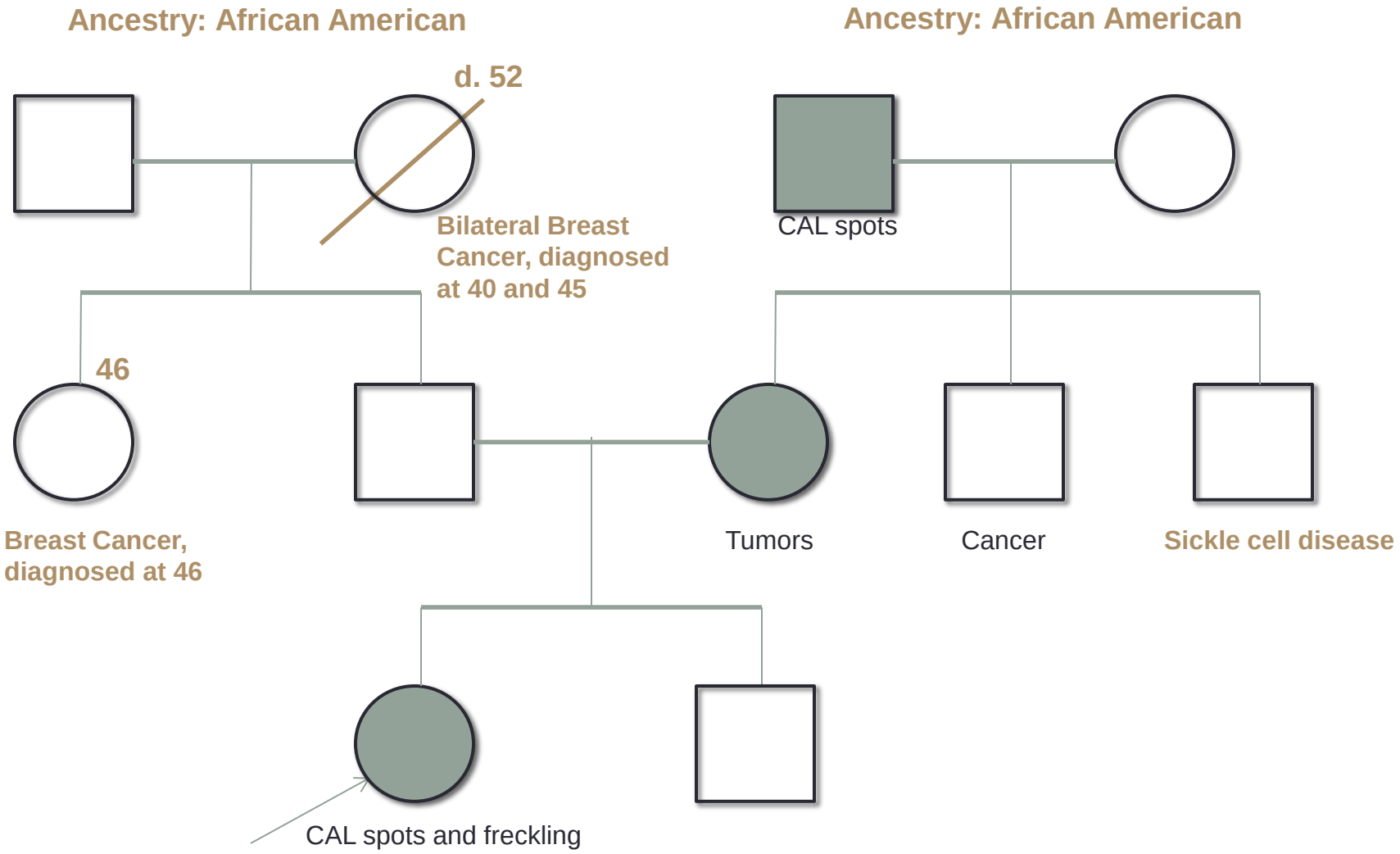
Neurofibromatosis Type 2

- Chromosome 22
- *NF2* gene
- Autosomal Dominant
- Later onset
- 1:33-40,000
- 50% brand new in family
- >92% detection rate with family history
- 25-30% cases can be mosaic

Schwannomatosis

- Chromosome 22
- *SMARCB1* gene
- Adult onset
- Schwannomas
- More compared to NF2
- Low detection rates in blood
- Tumor testing available

An Example


Ancestry: African American
Ancestry: African American
d. 52
Bilateral Breast Cancer, diagnosed at 40 and 45
CAL spots
46
Breast Cancer, diagnosed at 46
Tumors
Cancer
Sickle cell disease
CAL spots and freckling

Importance of Genetic Testing

Beneficial in making a diagnosis

- Helpful for those with:
  - Unclear clinical presentations
  - Mild clinical presentations
  - Mosaicism

REPORT MUTATION ANALYSIS NEUROFIBROMATOSIS TYPE1 – .TODAY

Patient Name: Doe, John

Date of Birth 1/2/03	**Family #** NF456	**Lab ID#** M123456	**Date Collected – Date Initiated** 7/8/09-7/9/09
Referred by Dr. Genetics	**Address** 720 20th St. South Birmingham, AL 35294		**Telephone / Fax Number** 205-999-9999 /205-555-5555

MRN#	123-45-6789	**ACCN#**	7787	**PT#**	5250

Indications for testing: 7.5yo boy presenting with >6 CALs and bilateral inguinal and axillary freckling. Father is reported to have several CALs.

Result and interpretation:

A heterozygous truncating mutation in the *NF1* gene was identified in the patient Doe, John : i.e. c.6709C>T (p.Arg2237*). No other possibly damaging alteration was found after comprehensive *NF1* mutation analysis.

This finding confirms the diagnosis of NF1 in this patient.

Comprehensive *NF1* mutation analysis detects the pathogenic mutation in >95% of non-founder NF1 patients fulfilling the NIH diagnostic criteria.

Genetic counseling should be offered to explain the implication of the test result. Counseling should include information about the implications of testing, residual risks, reproductive and medical options.

Method:

Comprehensive *NF1* mutation analysis starts with extraction of DNA from the blood sample of the patient. Another aliquot of the blood sample is used to start a short term culture of phytohaemagglutinin stimulated lymphocytes. Total RNA is extracted from puromycin-treated cultures and cDNA is prepared.
Four intragenic microsatellite polymorphisms, i.e., IVS27 CAGT (Lazaro et al, 1993), AAAT-Alu IVS27 (Xu et al., 1991), IVS27 GT (Lazaro et al., 1994), IVS38 TG53.0 (Lazaro et al., 1993) and 1 extragenic marker, i.e. 3'NF1-1, are analyzed as a first approach to determine whether 2 copies of the *NF1* gene are likely to be present. If no heterozygous signal is observed for any of these markers, FISH analysis is performed using PACs 926B9 and 1002G3 to confirm or rule out the presence of a total gene deletion.
Thereafter, the total coding region of the *NF1* gene is analyzed by long-range RT-PCR and direct cycle sequencing, starting from 3 overlapping RT-PCR fragments, spanning exons 1-27b, 12b-34 and exons 22-49. Sequencing is performed using dye-terminator chemistry on an ABI PRISM 3730*xl* capillary sequencer. *NF1* exon 1 is hereafter sequenced at the gDNA level.
If no mutation is identified by direct cycle sequencing, a multiple-ligation-probe assay (MLPA) is performed in order to detect copy number changes (deletions/duplications) in the coding region of the *NF1* gene.
A routine cytogenetic analysis is NOT performed.
Mutations are described to conform to the HGVS recommendations with nucleotide 1 being the A of the ATG translation initiation codon in the *NF1* REFSEQ **NM_000267.3**, and corresponding *NF1* protein REFSEQ **NP_000258.1**.

This test was developed and its performance determined by the Medical Genomics Laboratory. It has not been cleared or approved by the U.S. Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This test is used for clinical purposes. Pursuant to the requirements of CLIA '88, this laboratory has established and verified the test's accuracy and precision.

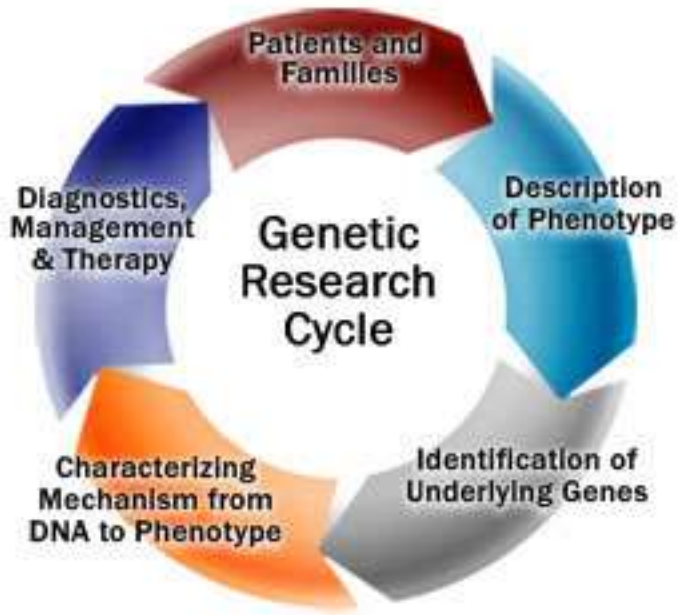
Ludwine Messiaen, Ph.D.
Director, Medical Genomics Laboratory

Bruce Korf, M.D., Ph.D.
Chairman, Department of Genetics

Importance of Genetic Testing

Can help with future research studies

- Genotype-phenotype correlations
- Clinical trials

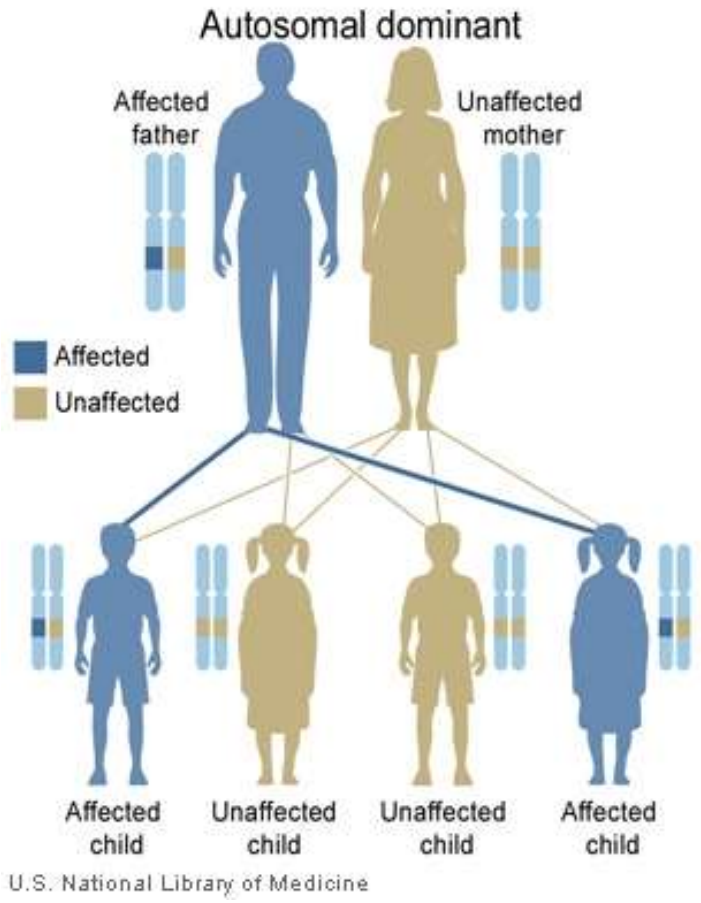


http://chgr.org/about.html

Importance of Genetic Testing

Can help with assessing recurrence risk

- Risks for:
  - Parents
  - Siblings
  - Children



http://ghr.nlm.nih.gov/handbook/illustrations/autodominant

Importance of Genetic Testing

Can help with assessing recurrence risk for future pregnancies

- Testing options:
  - Chorionic villus sampling (CVS)
    - 10-13 weeks gestation
  - Amniocentesis
    - 15-21 weeks gestation
  - Pre-implantation genetic diagnosis
    - Before the embryo is implanted into the uterus

In Summary

- Check on the details!
- Think “outside” box
- Know your relationships
- Be sure to update your physician
- Talk with your family about important medical diagnoses
- Share your testing results with relevant family members