Understanding the Genetic/Genomic Testing Strategy

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INOVA™ TRANSLATIONAL MEDICINE INSTITUTE

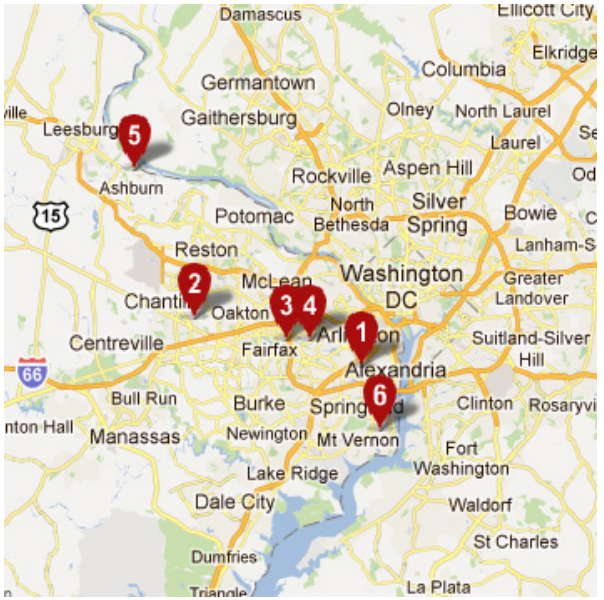
An Overall Theme!

Agenda

- Background
- Cases

Hospital System

- Six hospital + ambulatory healthcare system
- Largest healthcare system in Northern VA
- Two million patient visits/year
- 20,000 deliveries/year
- >5,000 newly diagnosed cancer patients/year



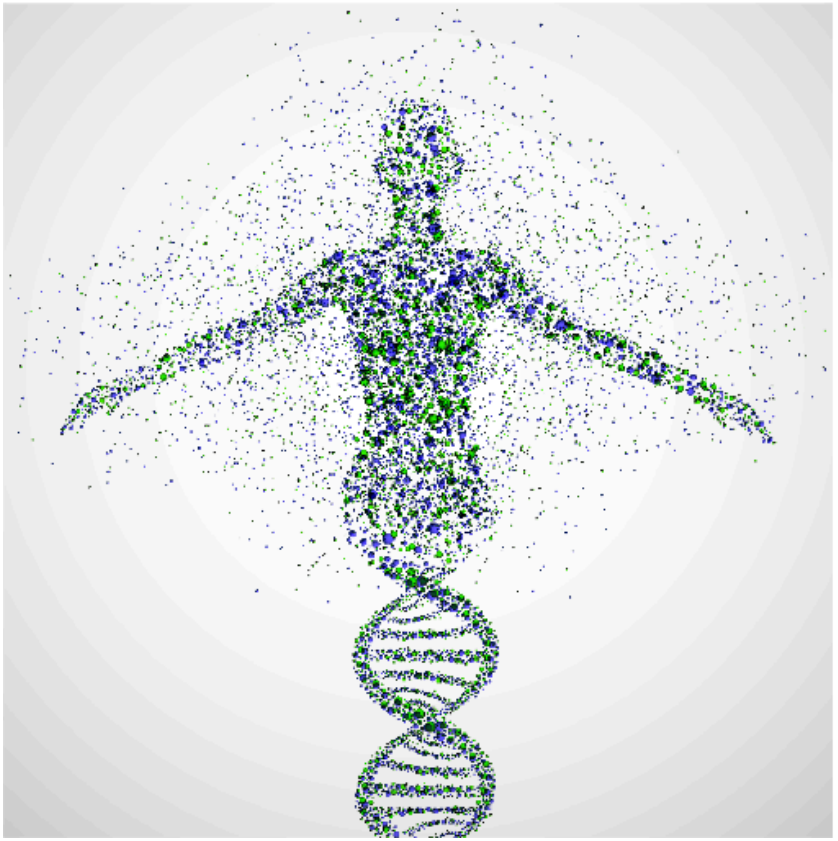
ITMI

- Started: 2010
- Overall goal: research on the integration of genomic information into the practice of medicine
- ~100 members; ~1/3 Clinical, 1/3 IT/Informatic, 1/3 Lab

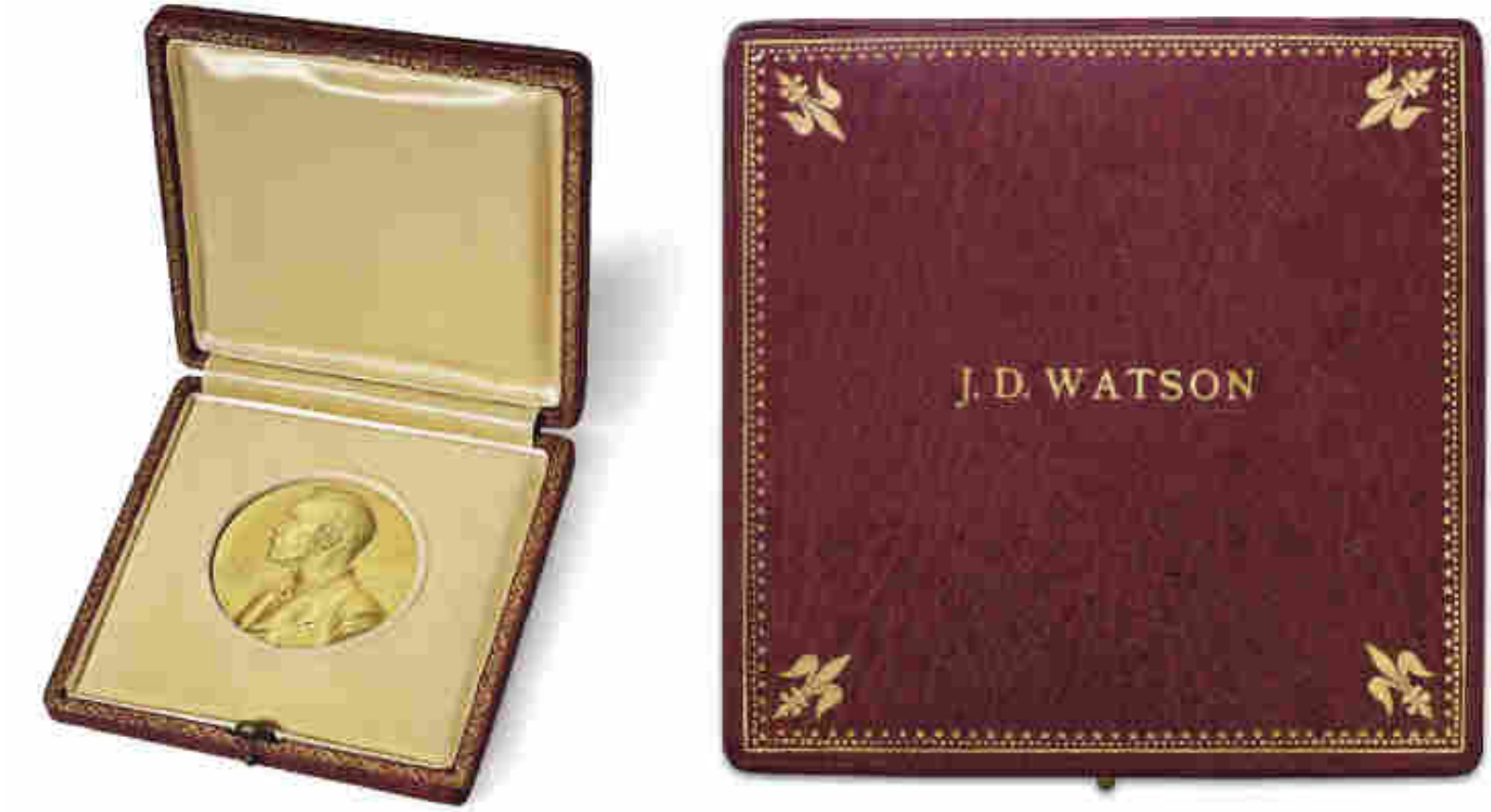
Division of Medical Genomics

- 3 Physician-Scientists
- 8 Genetic Counselors
- 4 PhD Bioinformaticists, Molecular Biologists, etc.

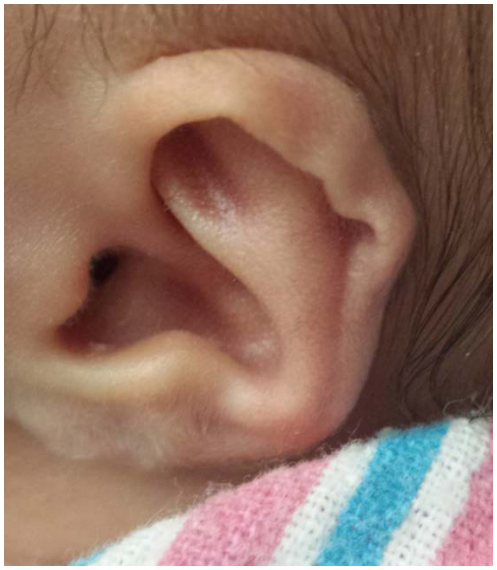
I. Background

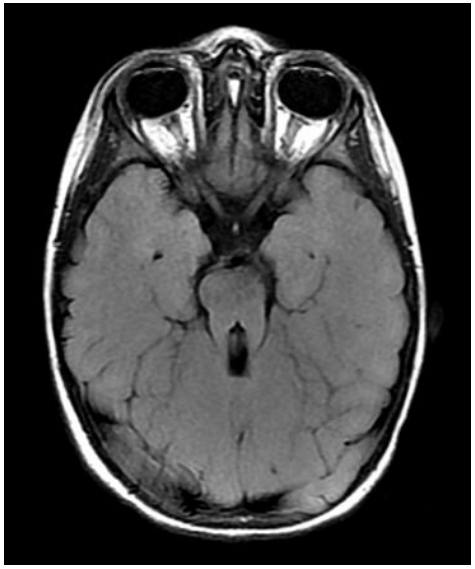


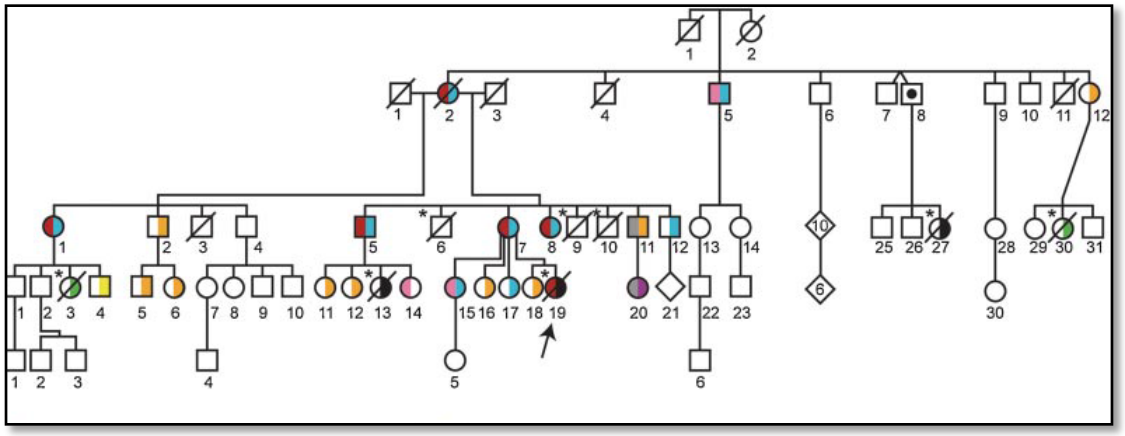
Current Events



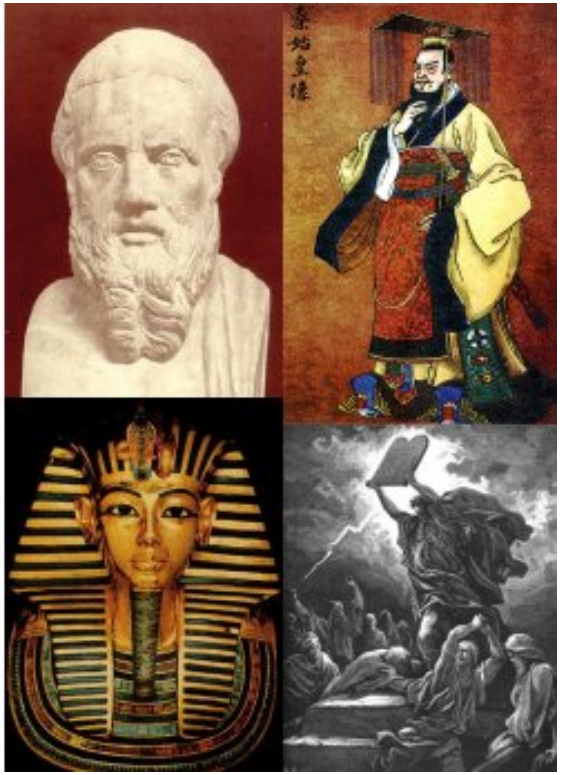
Figuring out the Genetics

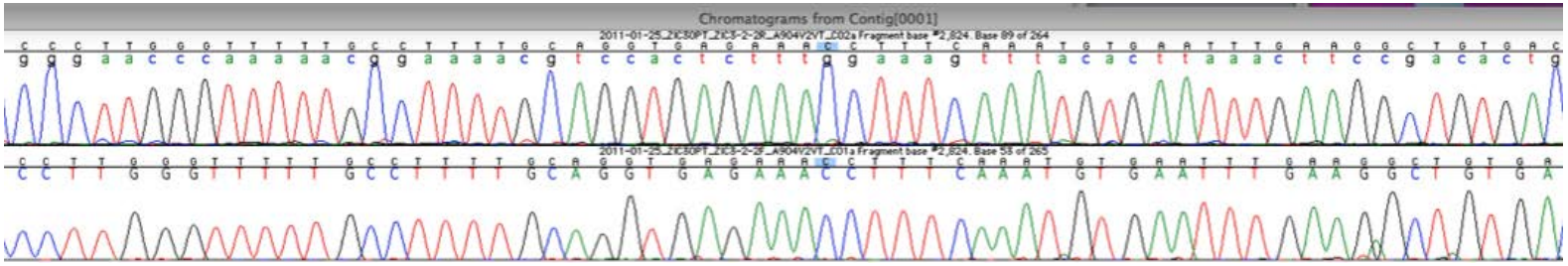




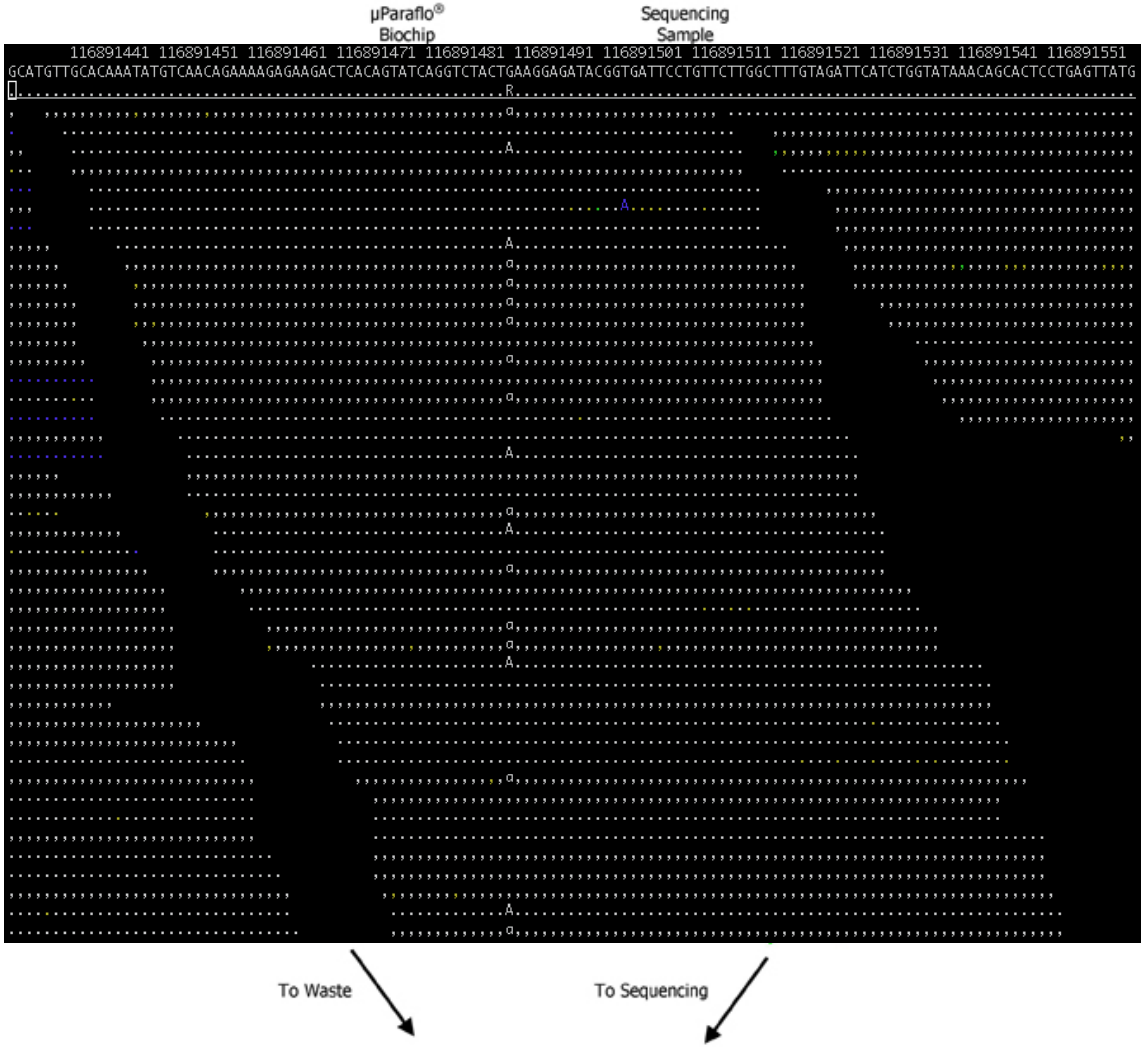


Ancient Times





Current Methods



Genomic Evolution

14 years ago

- ~$2.7 billion
- ~13 years
- 20+ centers (7 countries)

Now

- ~$1,000
- ~1 week
- 1 machine

14 years from now

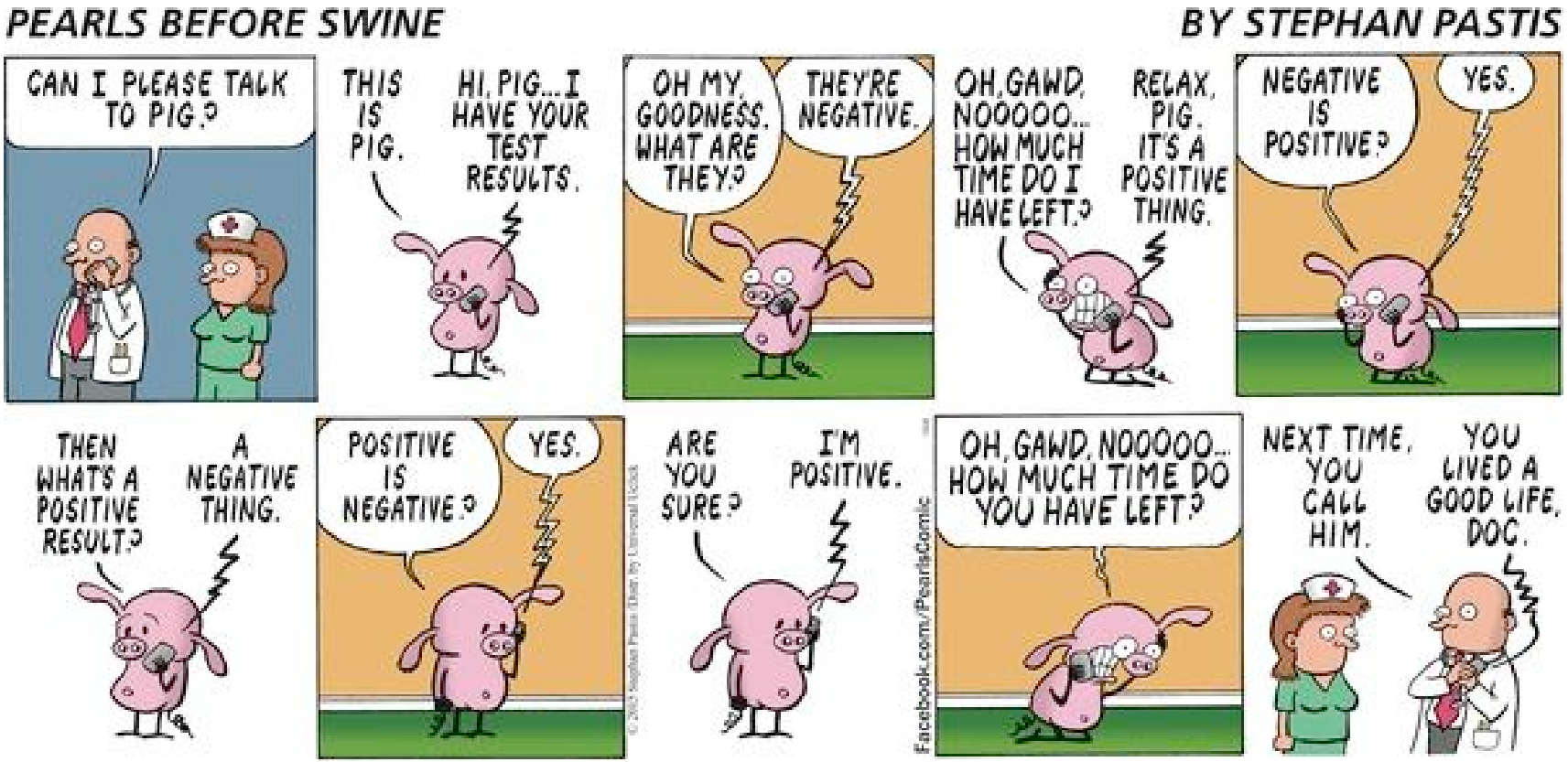
? Few dollars

? Few hours

? 1 (small) machine

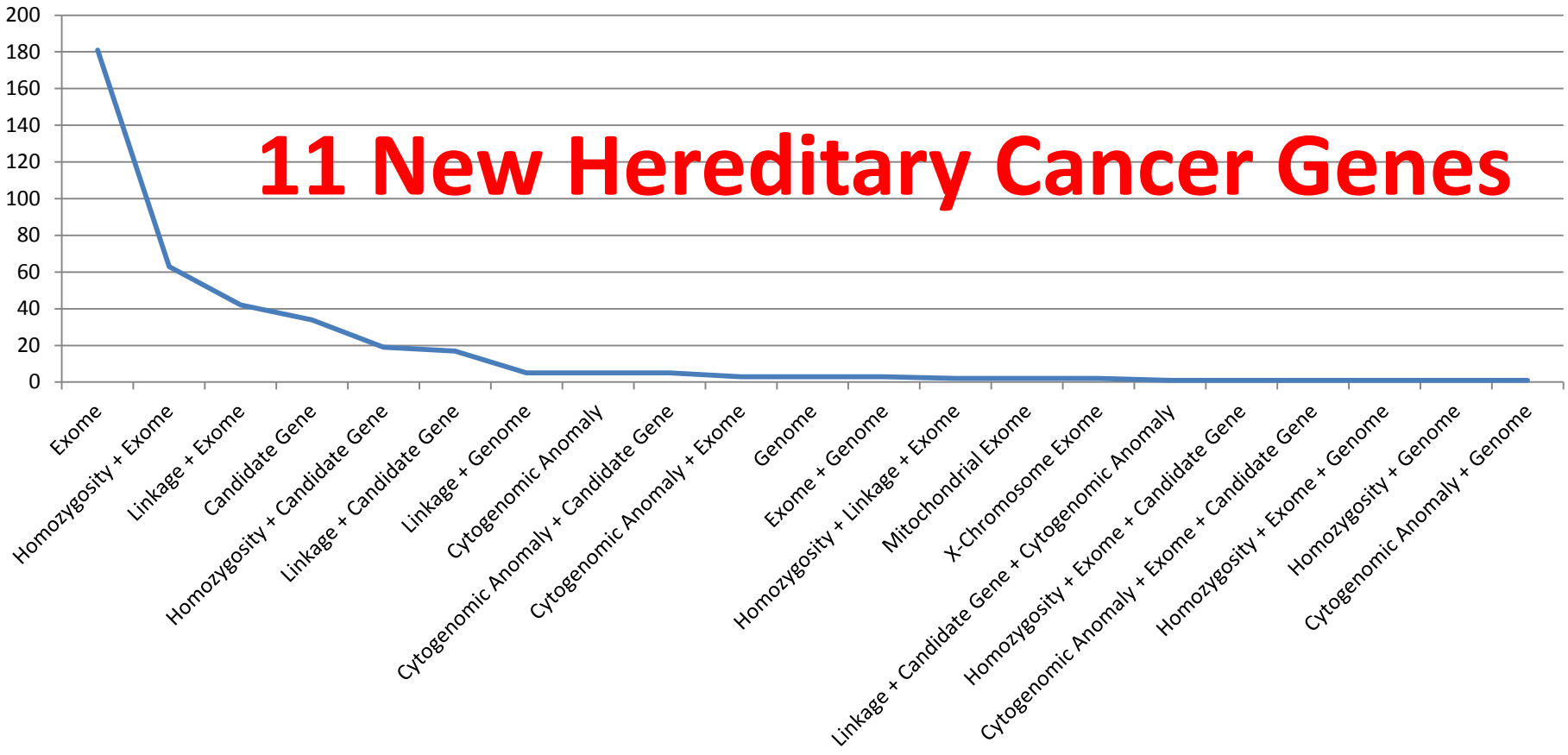

SEAL OF THE PRESIDENT OF THE UNITED STATES

But It’s Complicated…



It’s Almost Impossible to Generalize

The Knowledge Base Keeps Expanding



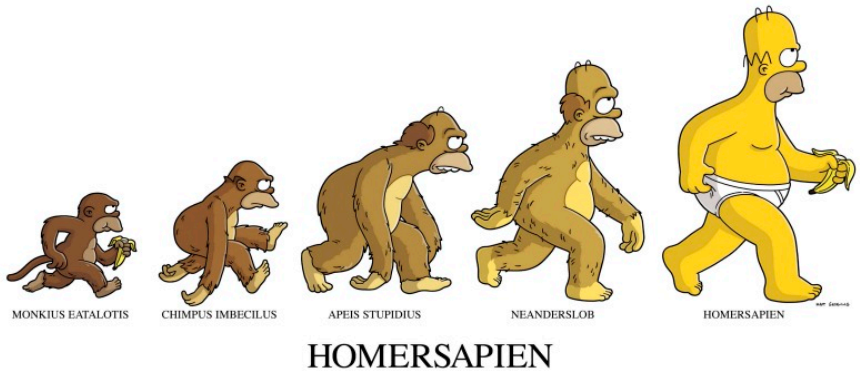
Bornstein et al., [In Preparation]

Different Models!

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

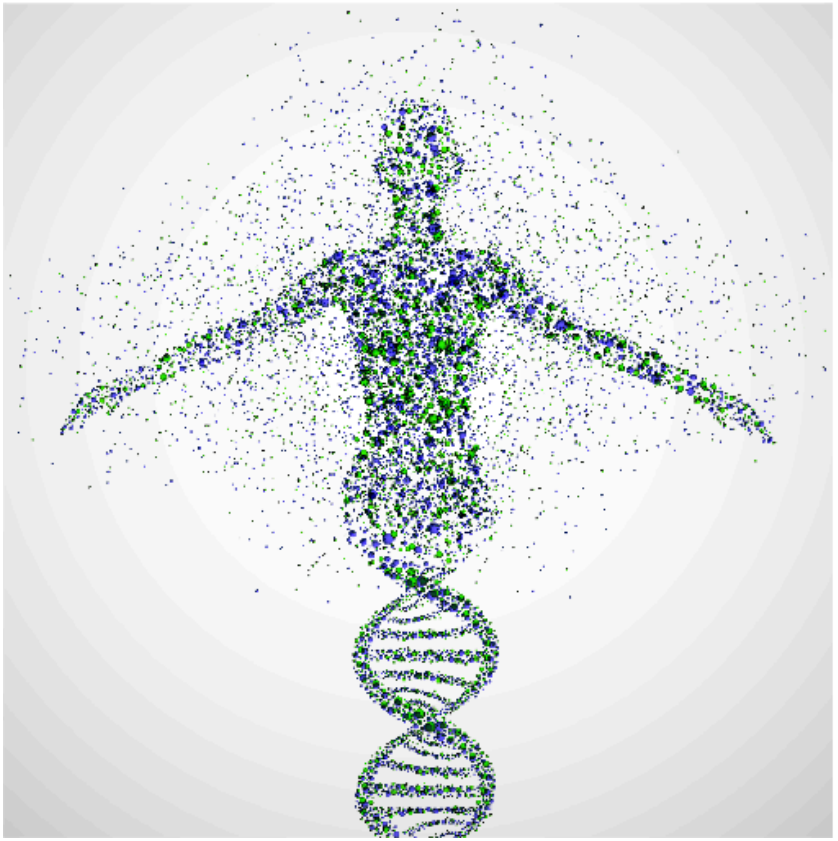
ACMG
American College of Medical Genetics and Genomics
Translating Genes Into Health®

ASHG
THE AMERICAN SOCIETY OF HUMAN GENETICS

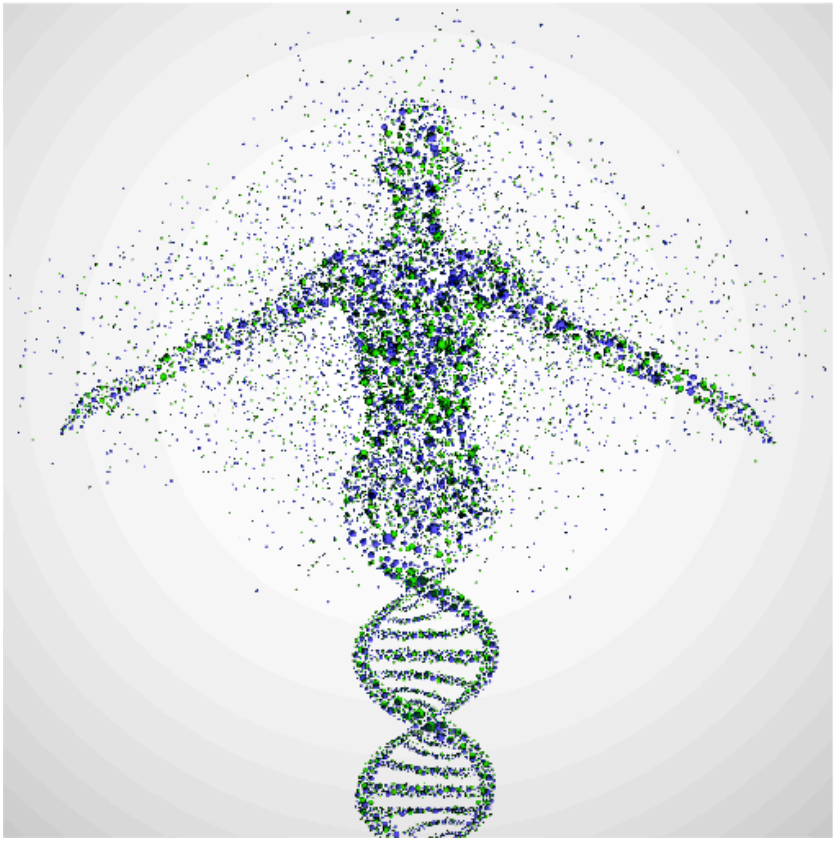


And We Have to be Careful!

II. Cases



A. Cancer Examples



NCCN Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2015
Hereditary Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
Genetics Table of Contents
Discussion

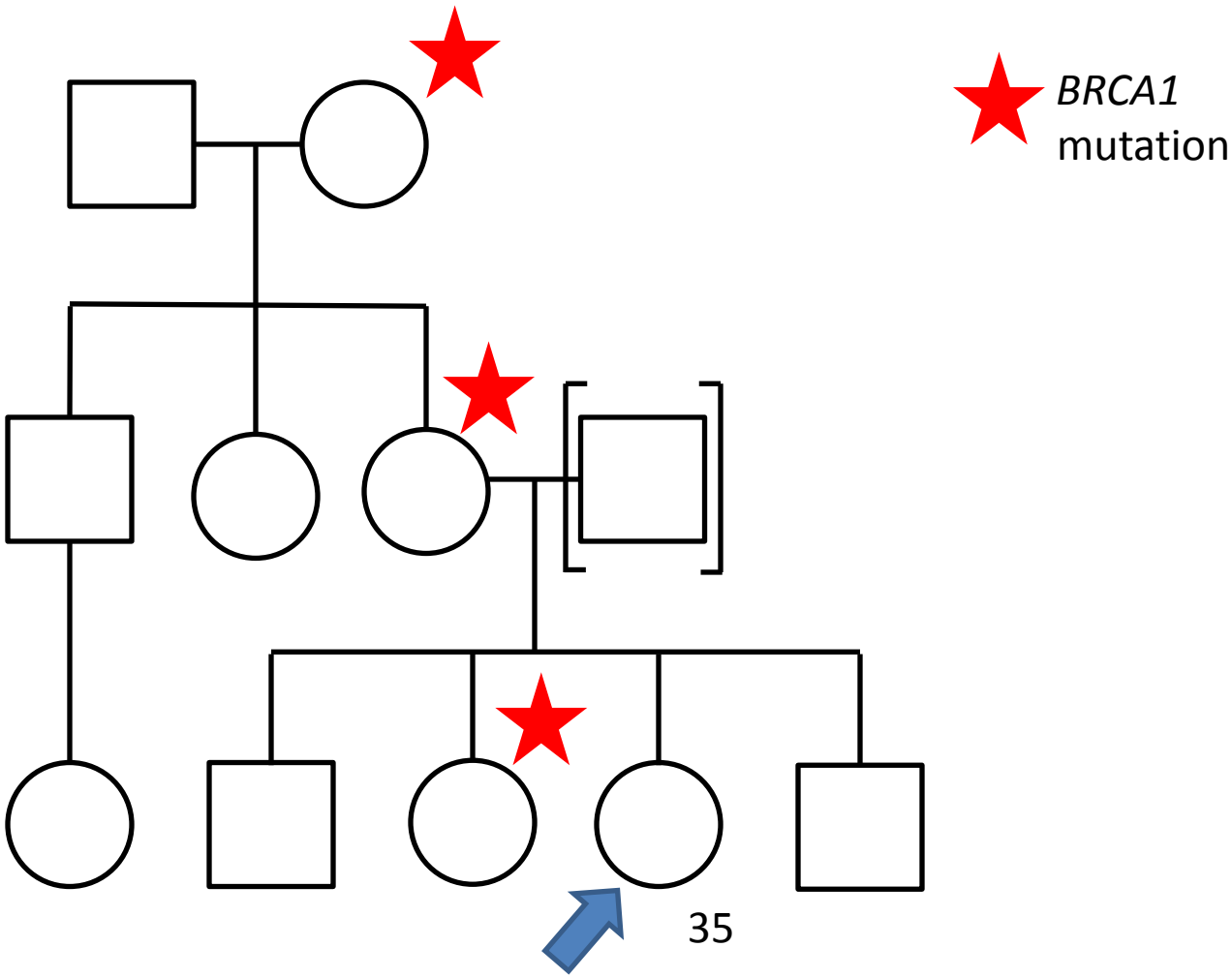
HEREDITARY BREAST AND/OR OVARIAN CANCER SYNDROME TESTING CRITERIA[a,b]

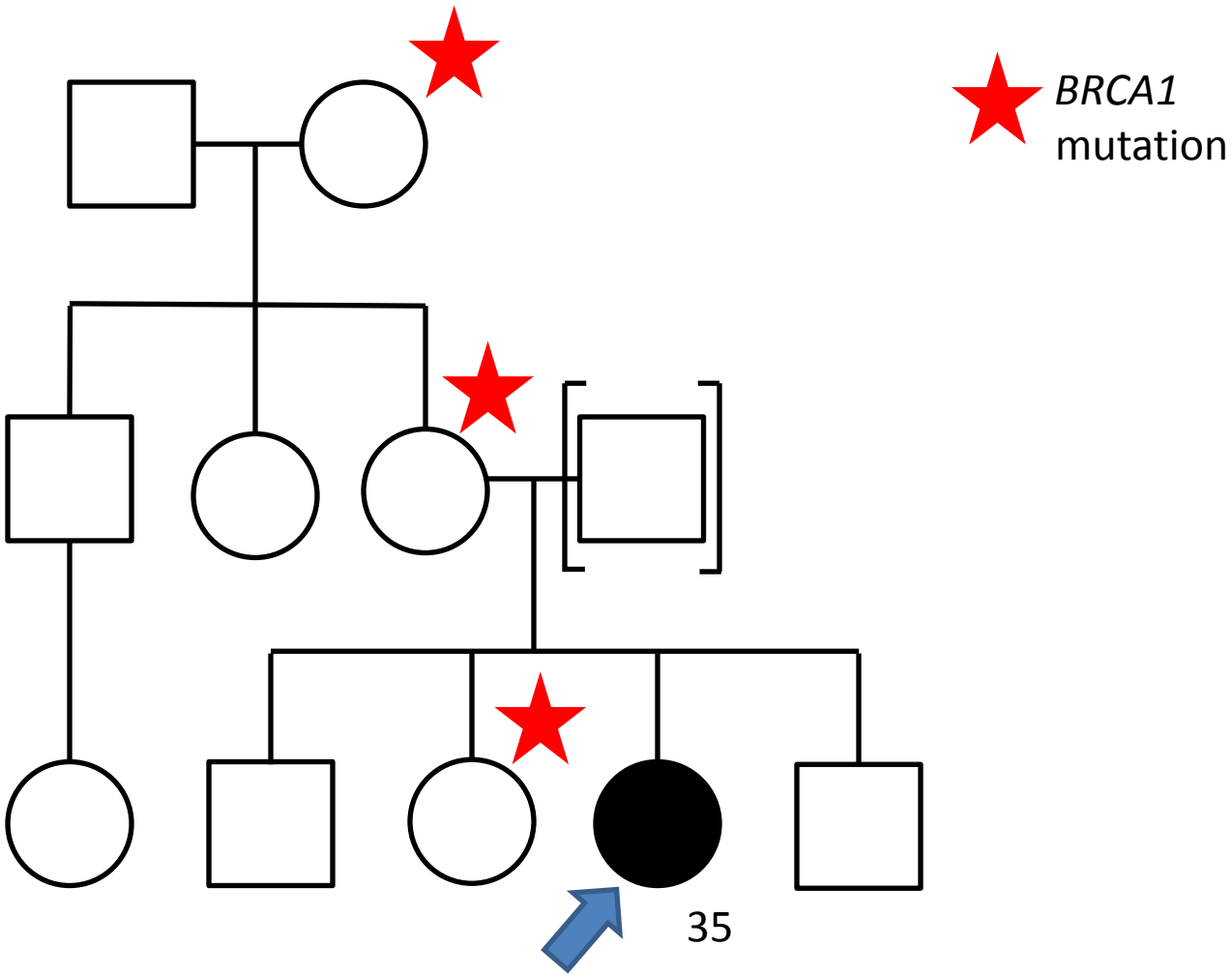
Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management. Testing of unaffected individuals should only be considered when an appropriate affected family member is unavailable for testing.

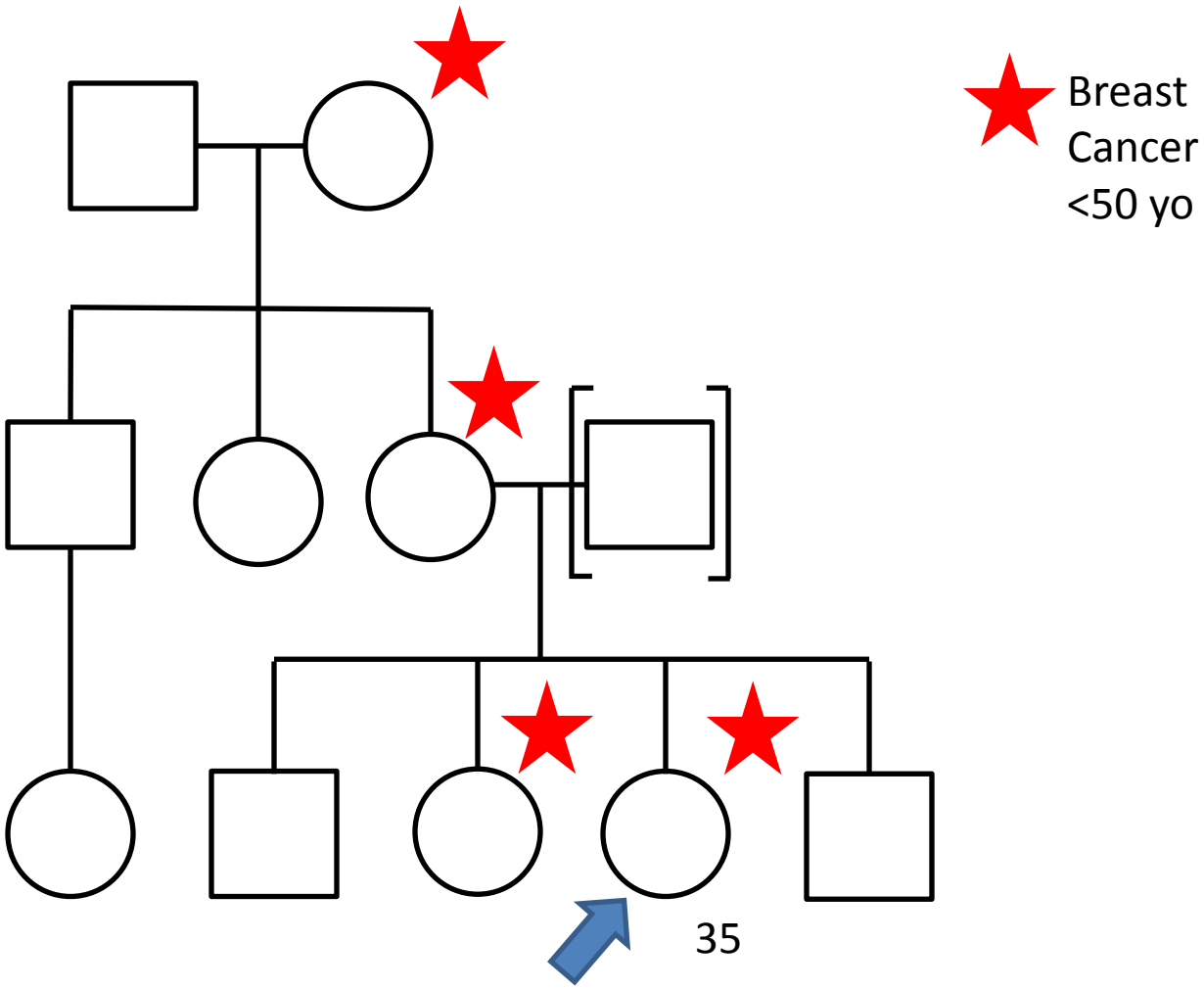
- Individual from a family with a known deleterious *BRCA1/BRCA2* mutation
- Personal history of breast cancer[b] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed ≤50 y with:
    - ◊ An additional breast cancer primary[c]
    - ◊ ≥1 close blood relative[d] with breast cancer at any age
    - ◊ ≥1 close relative with pancreatic cancer
    - ◊ ≥1 relative with prostate cancer (Gleason score ≥7)
    - ◊ An unknown or limited family history[a]
  - Diagnosed ≤60 y with a:
    - ◊ Triple negative breast cancer
  - Diagnosed at any age with:
    - ◊ ≥1 close blood relative[d] with breast cancer diagnosed ≤50 y
    - ◊ ≥2 close blood relatives[d] with breast cancer at any age
    - ◊ ≥1 close blood relative[d] with invasive ovarian[e] cancer
    - ◊ ≥2 close blood relatives[d] with pancreatic cancer and/or prostate cancer (Gleason score ≥7) at any age
    - ◊ A close male blood relative[d] with breast cancer
    - ◊ For an individual of ethnicity associated with higher mutation frequency (eg, Ashkenazi Jewish) no additional family history may be required[f]
- Personal history of invasive ovarian[e] cancer
- Personal history of male breast cancer
- Personal history of prostate cancer (Gleason score ≥7) at any age with ≥1 close blood relative[d] with breast (≤50 y) and/or invasive ovarian[e] and/or pancreatic or prostate cancer (Gleason score ≥7) at any age
- Personal history of pancreatic cancer at any age with ≥1 close blood relative[d] with breast (≤50 y) and/or invasive ovarian[e] and/or pancreatic cancer at any age
- Personal history of pancreatic cancer, and Ashkenazi Jewish ancestry
- Family history only (significant limitations of interpreting test results for an unaffected individual should be discussed):
  - First- or second-degree blood[d] relative meeting any of the above criteria
  - Third-degree blood[d] relative who has breast cancer[b] and/or invasive ovarian[e] cancer and who has ≥2 close blood relatives[d] with breast cancer (at least one with breast cancer ≤50 y) and/or invasive ovarian[f] cancer

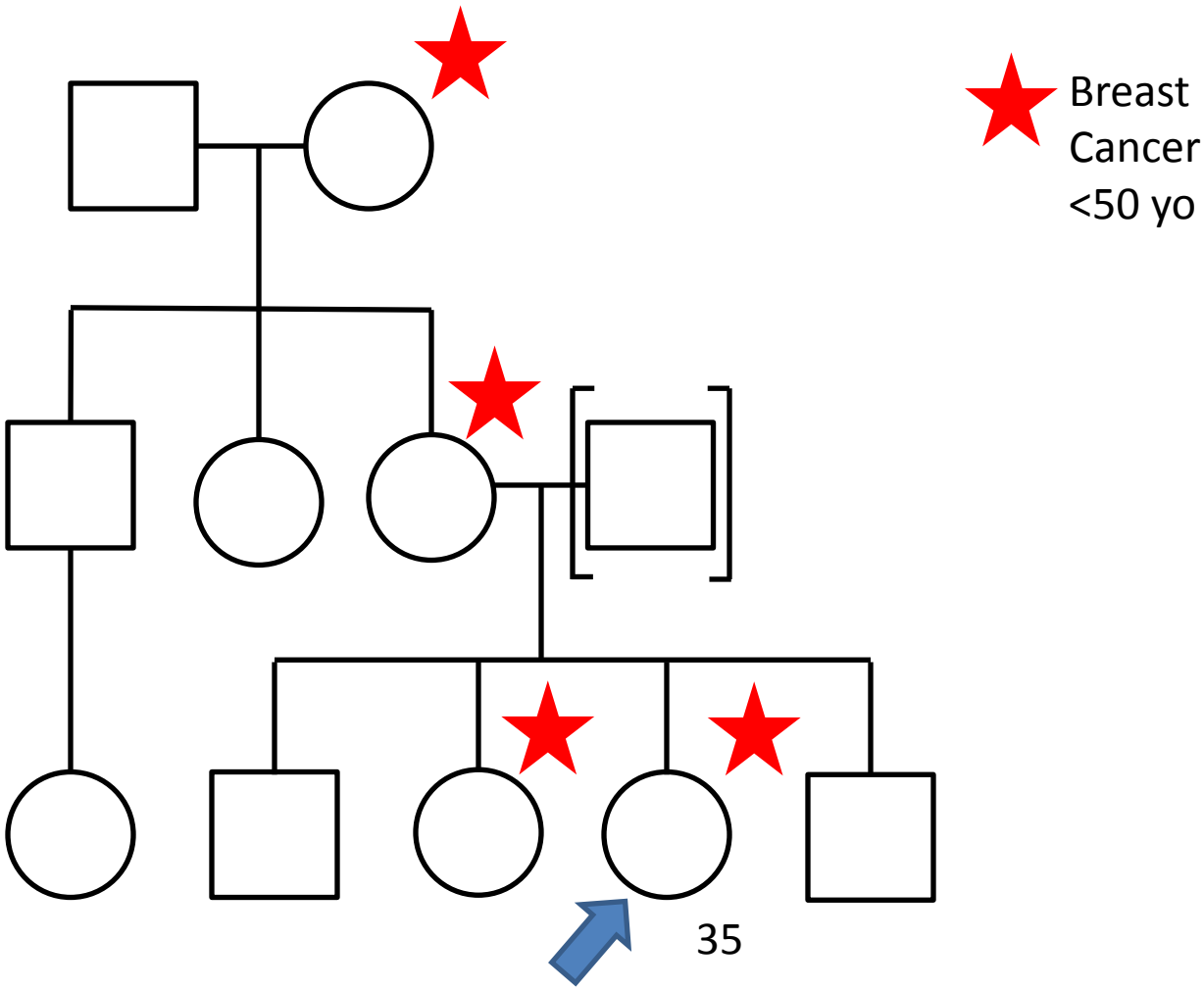
HBOC testing criteria met → See Follow-up (HBOC-2)

If HBOC testing criteria not met, consider testing for other hereditary syndromes → If criteria for other hereditary syndromes not met, then cancer screening as per NCCN Screening Guidelines

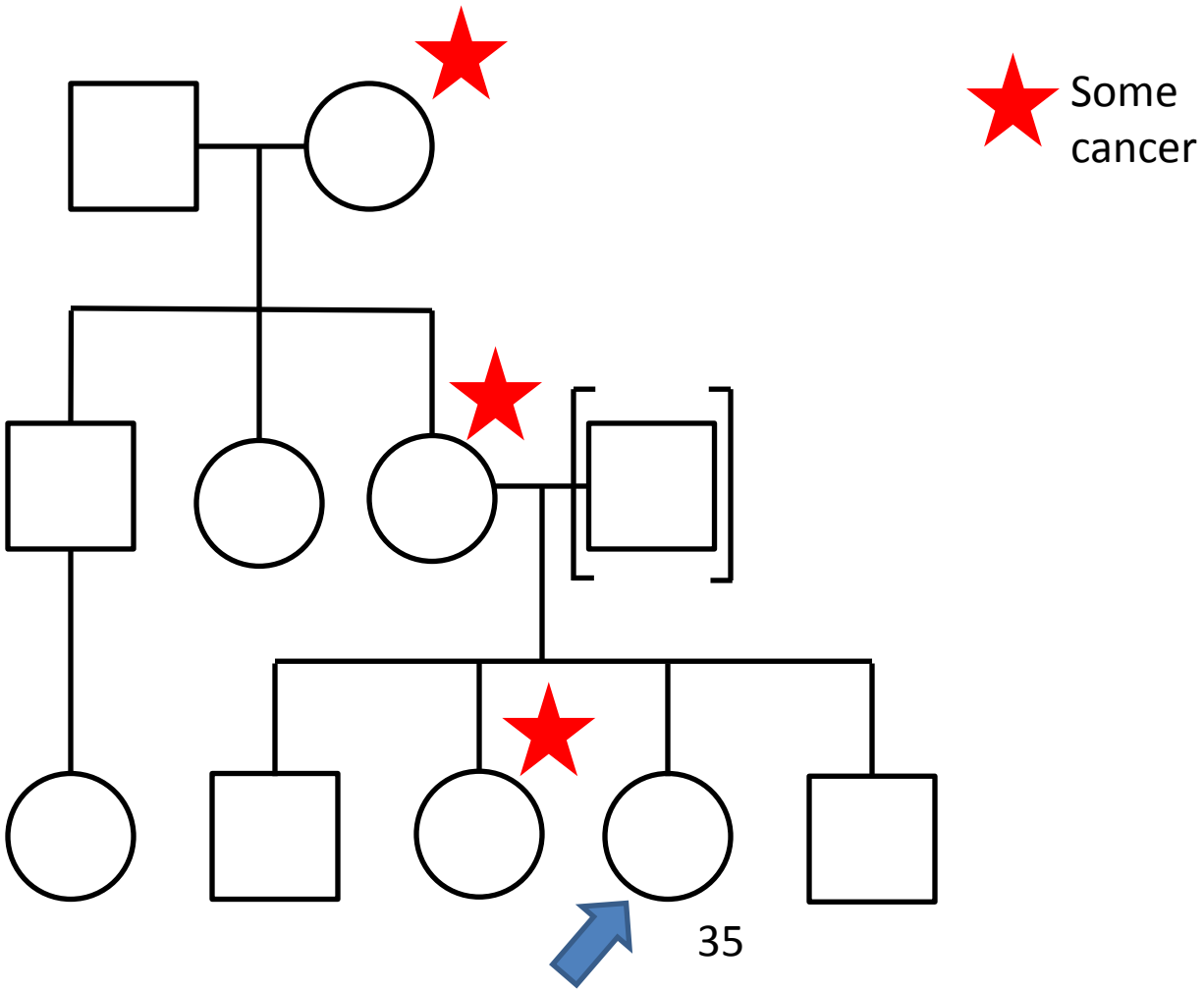

BRCA1
mutation
35

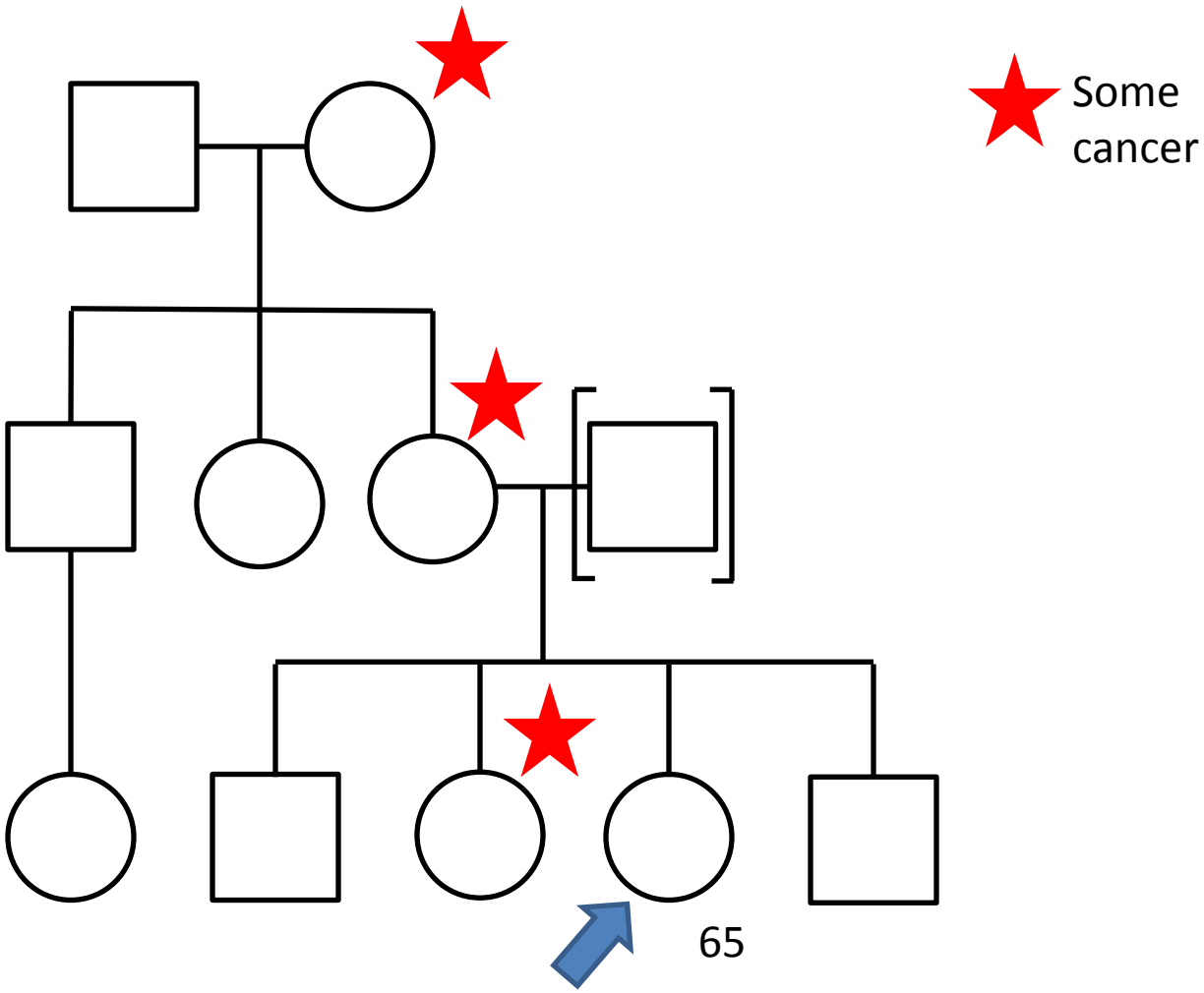

BRCA1
mutation
35


Breast
Cancer
<50 yo
35

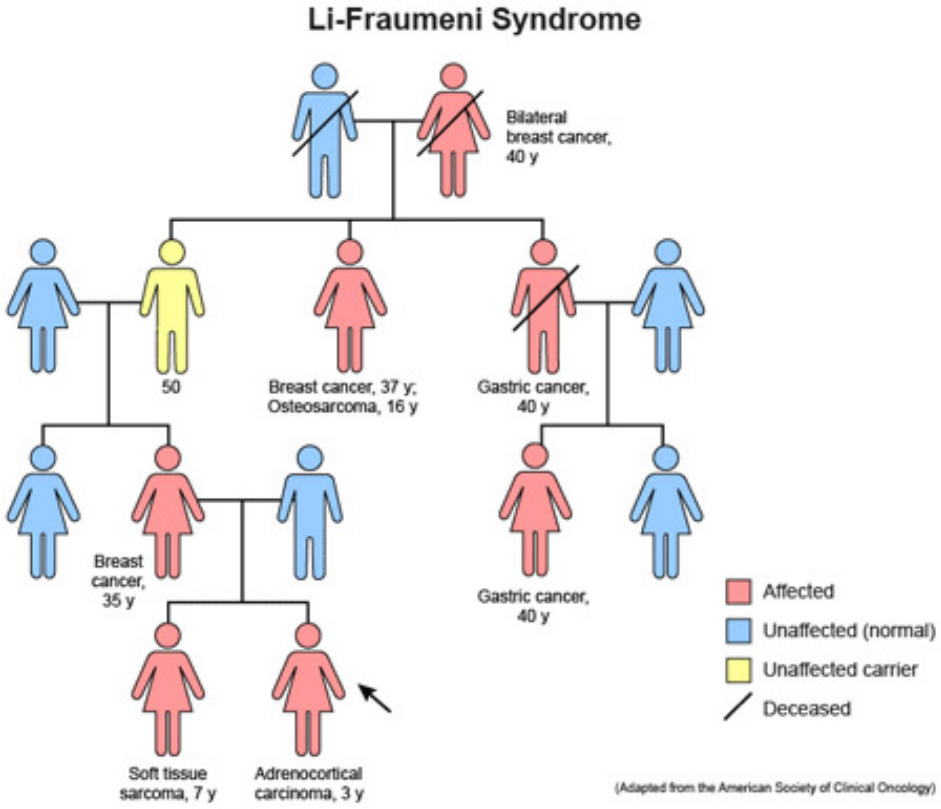


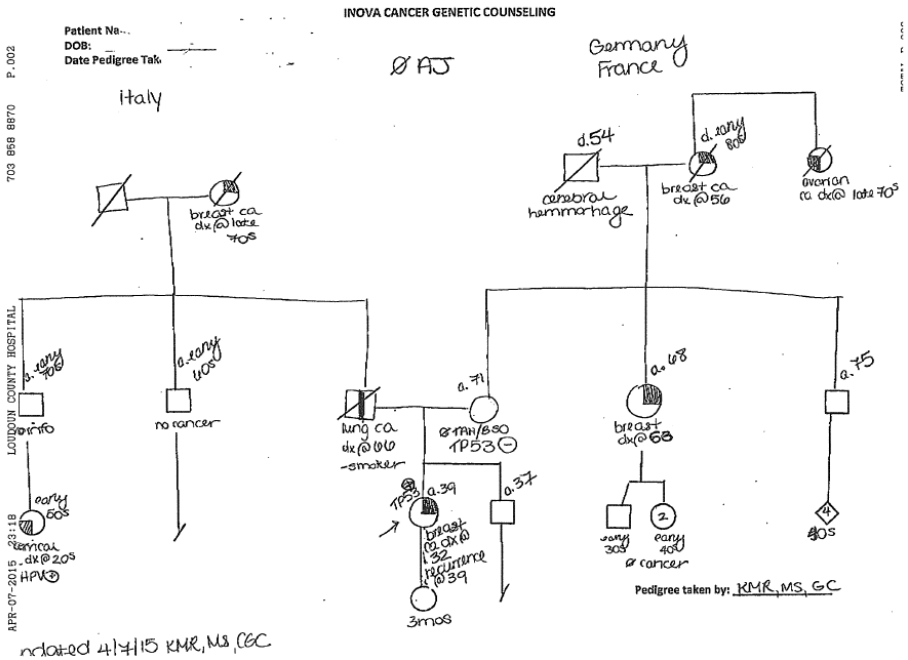
Previous BRCA1/BRCA2 testing negative (4 years ago)


Some cancer
35


Some cancer
65

Sometimes (Often Not) Obvious





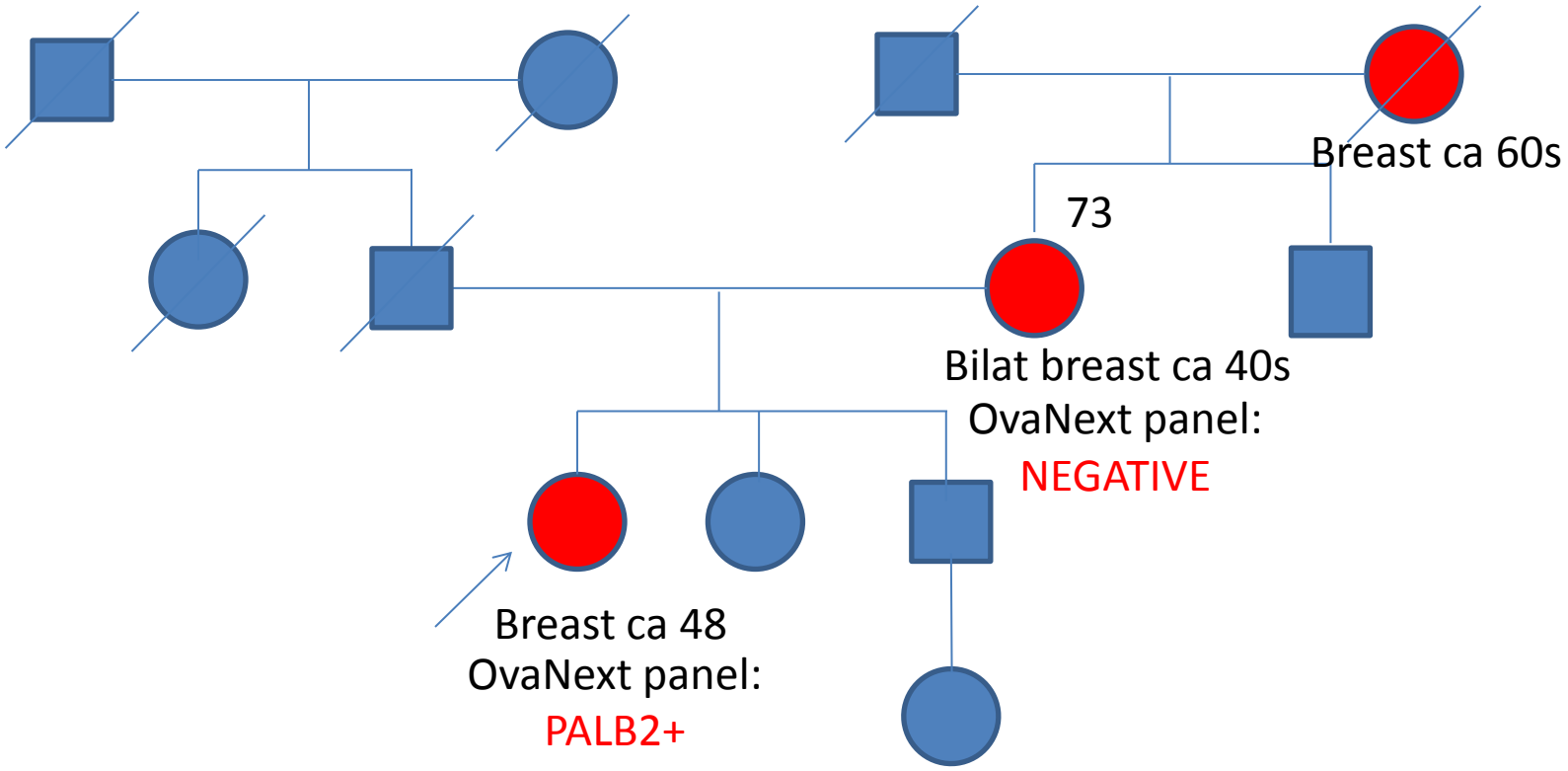
Factors

- Types of cancer (including pathology)
- Ages of onset
- Ancestry (e.g., Ashkenazi)
- Availability and informativeness of family history
- Patient preference (how extensive testing will be)
- Previous genetic testing in family members
- Urgency of testing (e.g., are the results needed prior to a surgical decision)?
- Etc.

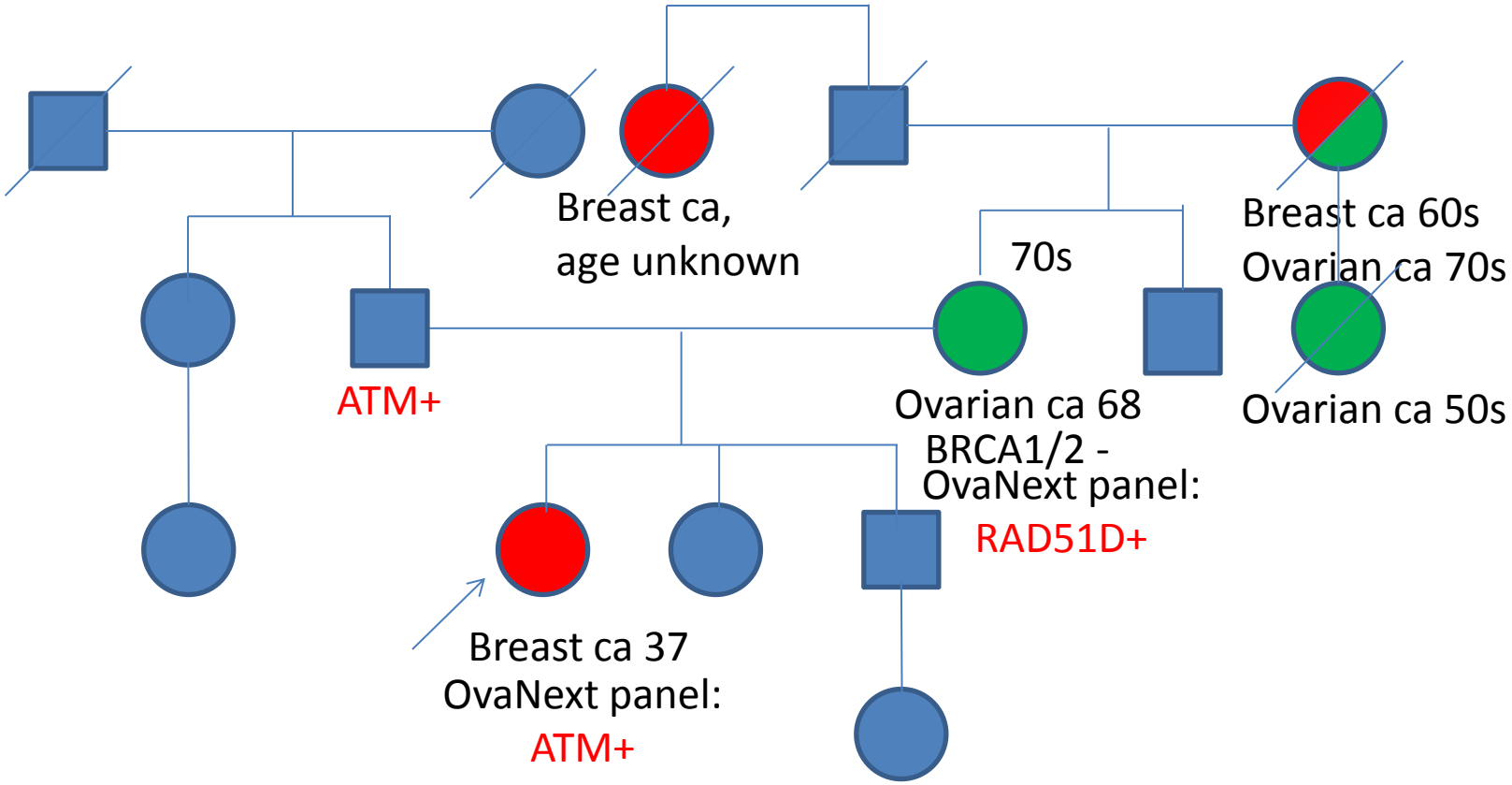
Choices and the Spiderman Effect

- Specific familial (or ancestral) variant
- BRCA1/BRCA2
- Large panel
- Very large panel
- Exome/Genome
- Research participation
- Etc.

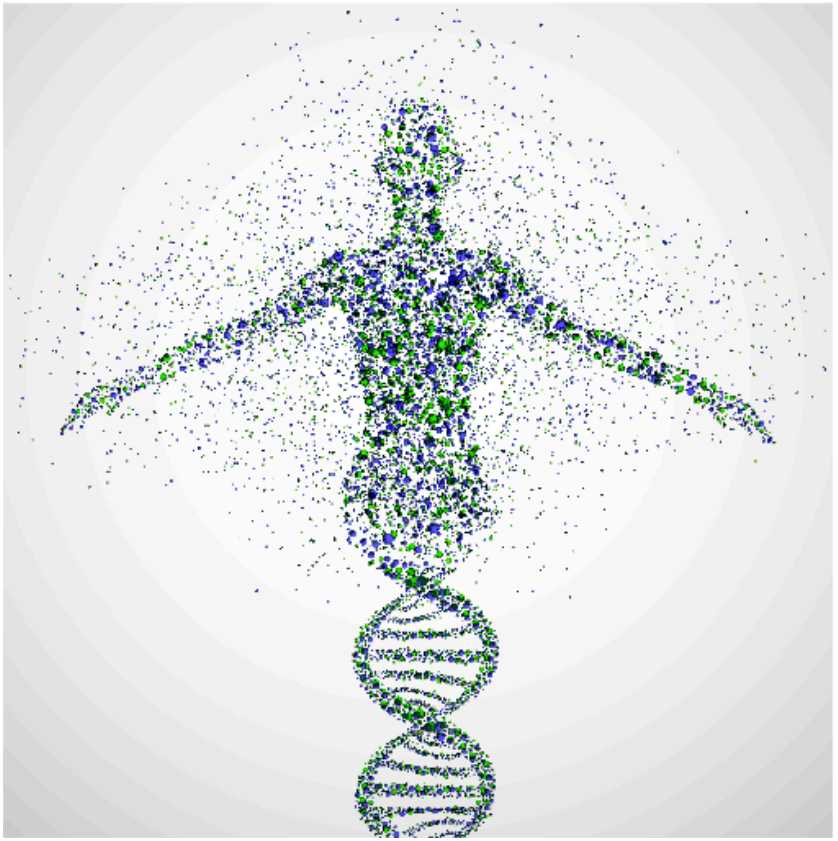
Real Life


Breast ca 60s
73
Bilat breast ca 40s
OvaNext panel:
NEGATIVE
Breast ca 48
OvaNext panel:
PALB2+

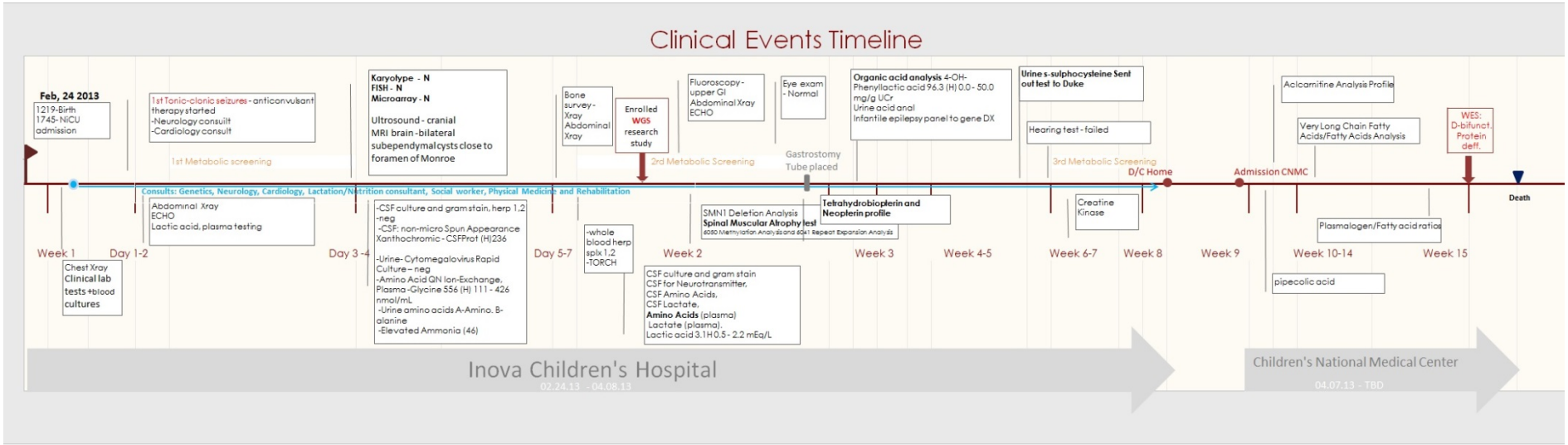
Real Life


Breast ca,
age unknown
70s
Breast ca 60s
Ovarian ca 70s
ATM+
Ovarian ca 68
BRCA1/2 -
OvaNext panel:
RAD51D+
Ovarian ca 50s
Breast ca 37
OvaNext panel:
ATM+

B. Congenital Examples



Current Practice



Khromykh et al. *Molec Syndromol* 2015

ASHG Position Statement (Botkin, AJHG 2015)

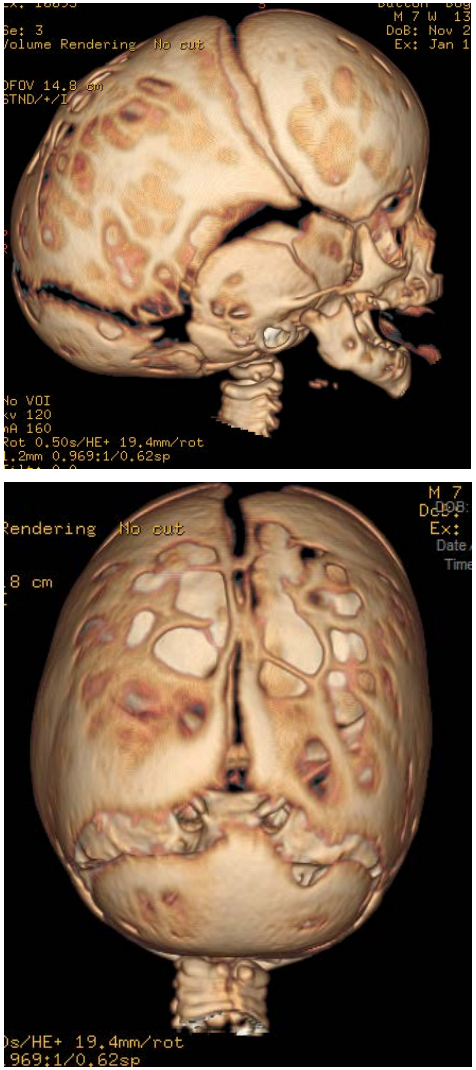
- When clinically indicated, the scope of genetic testing should be limited to single-gene analysis or targeted gene panels based on the clinical presentation of the patient.
- Targeted testing using genome-scale sequencing, but restricting analysis to a limited set of genes relevant to the clinical indication, is an acceptable alternative to a single-gene analysis or targeted gene panel in certain circumstances. When genome-scale sequencing is performed but the analysis is restricted to a limited set of targeted genes, ASHG finds it ethically acceptable for the laboratory to limit the analysis to the genes of clinical interest.
- ASHG recommends that, in the context of diagnostic testing for a child with a most likely genetic disorder, genome-scale sequencing is appropriate when prior, more limited genetic testing failed to identify a causative mutation. Depending on the clinical presentation and on the quality and availability of appropriate targeted testing, comprehensive testing such as genome-scale sequencing might also be indicated in certain circumstances, even in the absence of prior, more limited genetic testing.

My Interpretation

- If a targeted test is available use it
- If a limited panel exists, use it
- It’s OK to get the limited panel from genomic sequencing
- Starting with genomic sequencing can be justified in some situations

Patient

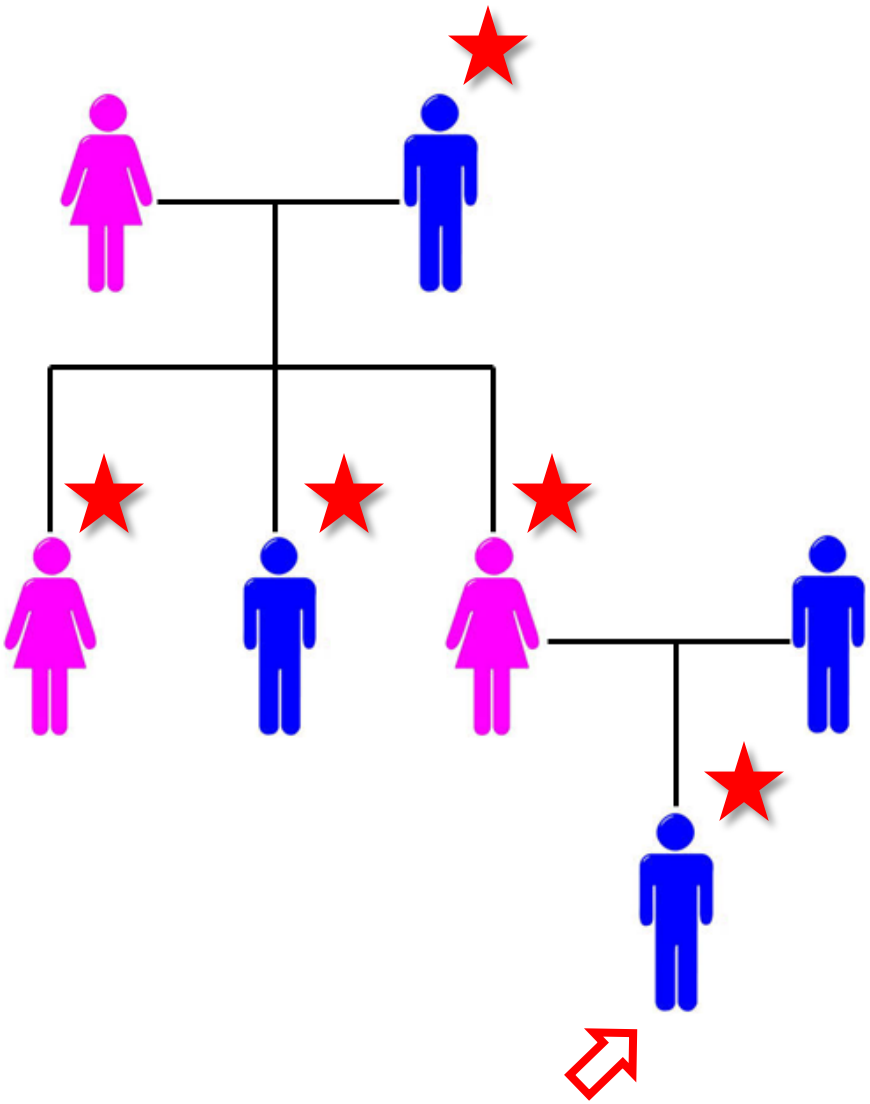
- IUGR, oligohydramnios
- Delivery at 34 3/7 weeks
- Hypoaldosteronism
- Hypercalciuria
- Sagittal craniosynostosis
- Renal U/S: Grade II hydronephrosis
- Echo: small ASD, PDA



Bodian et al. *MGGM* 2014

Testing

- Prenatal: increased risk of Down syndrome
- CVS: 46,XY
- Normal postnatal testing: microarray, 7-dehydroxycholesterol, TORCH testing, H19 methylation and uniparental disomy for chromosome 7 (Russell-Silver)



Just In Case Things Seemed Easy…

Thank You