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Genomic and Precision Medicine for the Hospitalist

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Learning Objectives

- Overview of inherited contribution to disease
  - Complex (multifactorial)
  - Single gene (Mendelian)
    - In life nothing is so neatly compartmentalized
  - Family History and Ethnicity are important
    - The more we hope to “individualize” medicine, the more we need to pay attention to the very things that make us each unique.
- Genomic applications
- Insight into when to consult a specialist
  - Simple aide memoires ‘3,2,1 Rule’

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Hospital Medicine Definition
Society of Hospital Medicine 2016

- Prompt and complete attention to all patient care needs including diagnosis, treatment and the performance of medical procedures.
  - Understand new technologies affecting diagnostics and treatments in our scope of practice
- Collaboration, communication and coordination with all physicians and healthcare personnel caring for hospitalized patients.
  - Need to have insight into our subspecialty colleagues' recommendations based on genetic technology
- Lynchpin of the hospital

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Traditional Roles of a Medical Geneticist

- **Confirm diagnosis** – “not environmental”
- **Predict prognosis**
- **Determine management**
- **Recurrence risk**
- **Investigate at-risk relatives** (and pregnancies)

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Why is this happening?

The synergy of technologies

- Next-gen sequencing
- Biologic drugs
- Gene editing

Public interest

- Ancestry
  - As more are tested, the interpretation improves
  - The public is familiarized with genetic NON-determinism
- Info-tainment
  - What friends best suit you?
  - Why type of ear wax do you have?
- Healthcare

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CRISPR/Cas9 is a Nanomachine

https://www.nature.com/articles/s41467-017-01466-8#Sec17

Supplementary Movie 5

- Bacterial immunity against viruses/plasmids
- Similar to mammalian interfering RNA
  - Cleaves a specific genetic target
- Very customizable guide RNA
  - Can also be used for gene regulation without cutting
  - Reducing antimicrobial resistance
  - A direct antiviral
  - Regenerative tissue without MHCII

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Nature Communications **8**, Article number: 1430 (2017)

Jargon

- Genetics relates to heredity and typically how single genes transmit characteristics between generations.
  - Think Mendel, linkage, Sanger sequencing
- Genomics is focused on the totality of the genetic material and how genes interact with each other and the environment
  - Think all 23,000 genes in 6 billion bp
- Misused; CRISPR/Cas9 edits genes, not genomes

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Jargon

- Somatic (acquired) mutations
  - Do not pass to offspring
- Germline (constitutional) mutations
  - Inherited and will pass to future generations

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Germline Gene Editing
ASHG Position Statement 2017

(1) At this time, given the nature and number of unanswered scientific, ethical, and policy questions, it is inappropriate to perform germline gene editing that culminates in human pregnancy.

(2) Currently, there is no reason to prohibit in vitro germline genome editing on human embryos and gametes, with appropriate oversight and consent from donors, to facilitate research on the possible future clinical applications of gene editing. There should be no prohibition on making public funds available to support this research.

(3) Future clinical application of human germline genome editing should not proceed unless, at a minimum, there is

(a) a compelling medical rationale,

(b) an evidence base that supports its clinical use,

(c) an ethical justification, and

(d) a transparent public process to solicit and incorporate stakeholder input.

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Gene Therapy

- Ex-vivo
  - (Allograft) bone marrow transplant
    - Minority have a donor match
  - Using viral vectors for autologous bone marrow tx
    - Adenosine Deaminase Deficiency (ADA-SCID)
    - Sickle Cell Disease
- In-vivo gene editing
  - Hunter Syndrome (Mucopolysaccharidosis IH)

  https://www.youtube.com/watch?v=ObzAHob9qEM#action=share
- siRNA
  - Porphyria

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Other Applications
Microbiology

- Genetics
  - viral loads, C. diff PCR etc.
- Genomics
  - Consider TAT of PCR and ability to stop/avoid antimicrobials and reduce resistance
  - Microbiome

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Other Applications
Cancer

- Genetics
  - Companion drug testing e.g. TKI for t(9;22)
- Genomics
  - Liquid biopsy (ctDNA, RNA, proteins, cells) for population screening, diagnosis, drug selection, and monitoring response

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Other Applications

- Pharmaco-genetics
  - TPMT for azathioprine, G-6-PD for rasburicase
- Pharmaco-genomics
  - All possible prescriptions and interactions (at point-of-care)

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Precision Medicine Definition
NIH 2016

- “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person.”
- “will allow doctors and researchers to predict more accurately which treatment and prevention strategies for a particular disease will work in which groups of people.”

- Not new e.g. blood transfusion

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NIH Precision Medicine Initiative is called ‘All of Us’
A new architecture for biotech

- New partnerships across wide range of specialties, patient advocacy, universities, pharma, payers, etc.
- New tools for building, analyzing, and sharing large sets of medical data
- Improvement of FDA oversight of tests, drugs, and other technologies to support innovation while ensuring products are safe and effective
- Opportunity for millions of people to contribute to the advancement of scientific research

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NIH 2017

- Big data
- Team science
- Not a subset of medicine but simply how science and practice are evolving

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Measures of Success

- Better understanding of the underlying mechanisms by which various diseases occur.
- Improved approaches to preventing, diagnosing, and treating a wide range of diseases.
- Better integration of electronic health records (EHRs) in patient care, which will allow doctors and researchers to access medical data more easily.
  - Right drug, Right dose, Right time
  - 1; 100; 0.
    - ie. Drug tailored to 1 individual. Effective 100%. 0% adverse effects

      Ezekiel Emmanuel, MD
- Study *all* ethnicities
- Multiple environments and lifestyles
  - To account for those confounders to the coding nucleic acid sequence

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- Basic science
- Translation
- Application

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Barriers

Cost

- Sequencing and storage costs are decreasing quickly but that stimulates deeper interrogation

SNP array → exome → genome + epigenome/transcriptome/spliceome/proteome/….

metabolome/microbiome….. even the epitranscriptome!

- Targeted drugs are likely to be expensive
- Reimbursement from third-party payers may become an issue
- Protection from Genetic Discrimination

Healthcare providers

- Will need to know more about molecular genetics and biochemistry
- Will need to do basic test interpretation and convey this knowledge to patients
- Collect Family History and basic understanding of pedigree analysis
- Navigate the associated ethical issues

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Hierarchy of Evidence Concept Needs to Adapt

JAMA 2017;318(17): 1649

FDA May 2017

"Alternative Approach based on Precision Medicine"

- Mechanistic information instead of population-derived knowledge
- Expanded the indication for Ivacaftor for Cystic Fibrosis to 23 mutations based on functional assay alone
  - Working on approval for splice site mutations
- Granted accelerated approval for Pembrolizumab for any progressive metastatic MSI-H or dMMR solid tumor; regardless of tumor origin or location
  - Now added PD-L1 expression (Sep 2017)

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Choosing Wisely in Medical Genetics

1. Do not order a duplicate genetic test for an inherited condition unless there is uncertainty about the validity of the existing test result.

2. Do not order *APOE* genetic testing as a predictive test for Alzheimer disease.

3. Do not order *MTHFR* genetic testing for the risk assessment of hereditary thrombophilia.

4. Do not order *HFE* genetic testing for a patient without iron overload or a family history of *HFE*-associated hereditary hemochromatosis.

5. Do not order exome or genome sequencing before obtaining informed consent that includes the possibility of secondary findings.

(Inherited Thrombophilias?)

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ACMG 2015

Precision Genomics at Population Level

- 1-3.5 % of everyone has a well-defined actionable mutation
- Most ‘actionable’ genetic variation is from rare/unique variants
  - Would not be found without unbiased NGS
- Each person has
  - 200 protein-coding family-specific variants from recent ancestors *not* present in databases- typical V.U.S.
  - 50 *de novo* mutations not present in either parent
    - Most do not change protein function

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JAMA 2017;317(17): 1904

Precision Genomics in Rare Disease

- Several series (NIH, Baylor, Mayo) put the likelihood of diagnosis 25-30 % for those who have already been highly investigated
- End the diagnostic odyssey
- Supports the idea of moving unbiased genomic testing to earlier in the workup
  - Especially as costs decrease, turnaround times improve, risks of indeterminate results decrease, and off-target results are becoming better received and routinely manageable

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Precision Genomics in Cancer

- Mayo study
  - 92/141 (65 %) with actionable mutations
  - 29/92 (32 %) received targeted therapy
  - 13/29 (45 %) responded
  - Only 9 % by intention to treat
- Barriers
  - 8 weeks result turnaround time
    - Revert to standard therapy or hospice
  - Targeted drug not available
  - Pharma willingness
  - Insurance coverage

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Oncotarget. 2017; 8:27145-27154.

Pharmacogenomics

- Live on point-of-care EMR alerts for 9 drugs
  - Abacavir
  - Carbamazepine
  - Clopidogrel
  - Codeine
  - Simvastatin
  - Tamoxifen
  - Thiopurines
  - Tramadol
  - Warfarin
- 99% have atypical metabolism of at least 1

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Legal Pre-requisite

- Protection from genetic discrimination for pre-symptomatic diagnoses

- GINA (2008) in US protects against health insurance and employer discrimination
  - Includes protections for family history
  - Some significant exemptions eg. Military
  - Life and disability insurance are not covered

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Familial Hypercholesterolemia

- 1 in 250
- 2.5-10x increased risk of ASCVD
- But when diagnosed and treated early, risk is reduced ≈ 80 %
- <15 % of the at least 120,000 people with FH in the UK are currently diagnosed (BHF)
  - Model for Cascade screening

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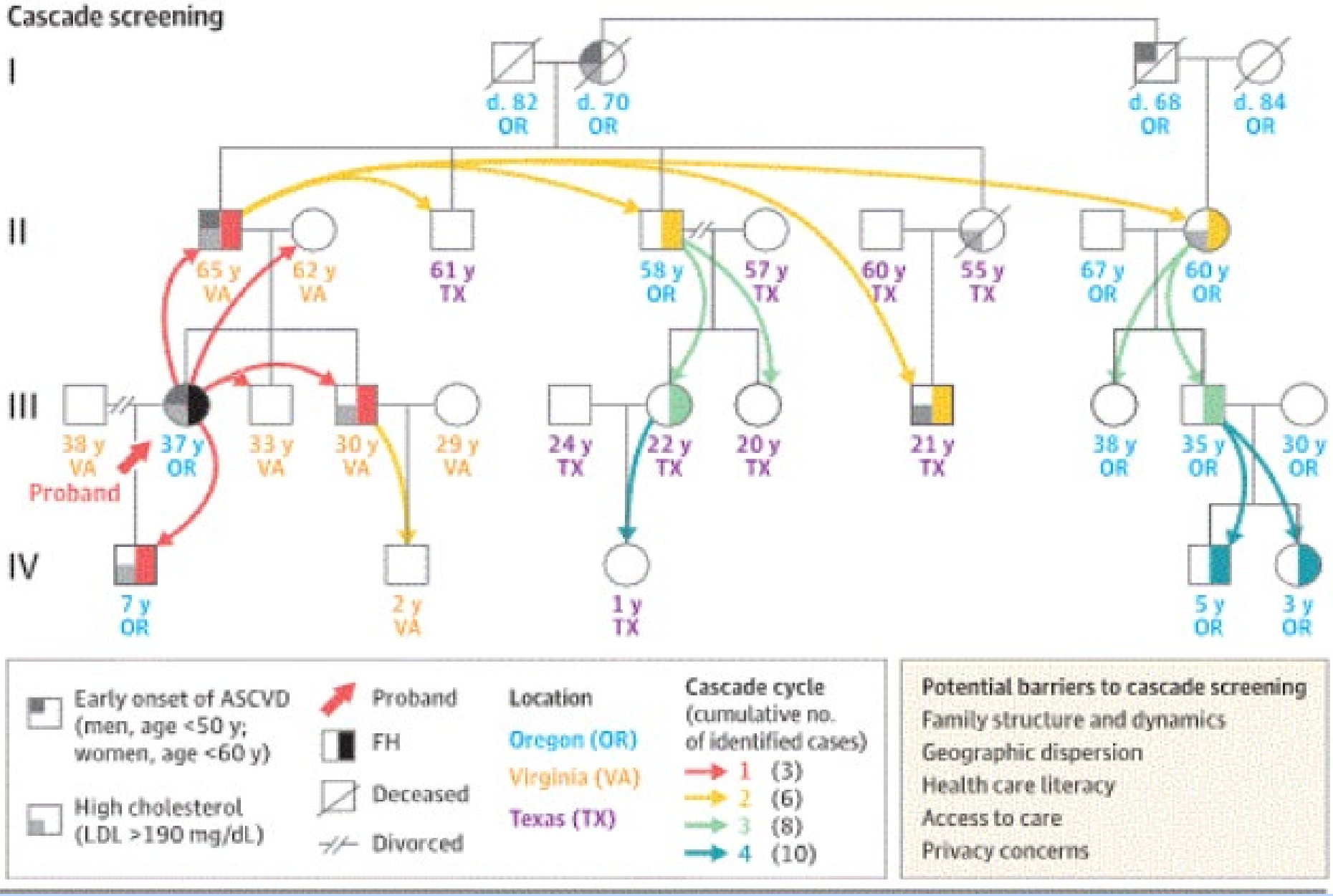
JAMA. 2017;318(4):381-382.



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JAMA. 2017;318(4):381-382.

‘A Major Treatment Gap In Preventive Cardiology’

- 509 pts *under 60 yrs* admitted to CCU with symptomatic CAD
- 70 % had insufficient data for pedigree analysis
- In a subsequent cohort of 103 pts in the same unit, a NP recorded a 1st degree relative with CV disease <60y in 43 %
- 95 % of these CCU pts had phenotypic FH

→ < 30 % of these admissions, on whom you miss the FH dx.

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Bates et al. Heart Lung Circ 2008; 17: 411-3

Clues to a Genetic Etiology

- Early Onset
- Severity
- Unusual Pattern of Disease
- Frequency of Recurrences
- Family History

- Severe illness is used to justify shortcuts
  - But this group is self-selecting for pathology and high pick-up rates

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Family History and Ethnicity

- Personalized

- Captures the overall *biologic* effect of gene-gene and gene-environment interactions shared within families/communities
  - Well understood risks for Ashkenazi, French Canadian, Amish…

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Missed Inherited Cancer Syndromes

- Referrals to Genetics commonly occur when all affected relatives are deceased
- Makes testing and risk assessment more difficult
- Reduces benefit from testing and prophylactic interventions

.

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J Palliat Med. 2013 Nov;16(11):1350-5. Could triaging family history of cancer during palliative care enable earlier genetic counseling intervention? Lakhani NS et al.

3-2-1 Family History Rule

- 3 affected relatives with the same/associated cancers
- Across 2 generations
- With at least 1 affected < 50 years

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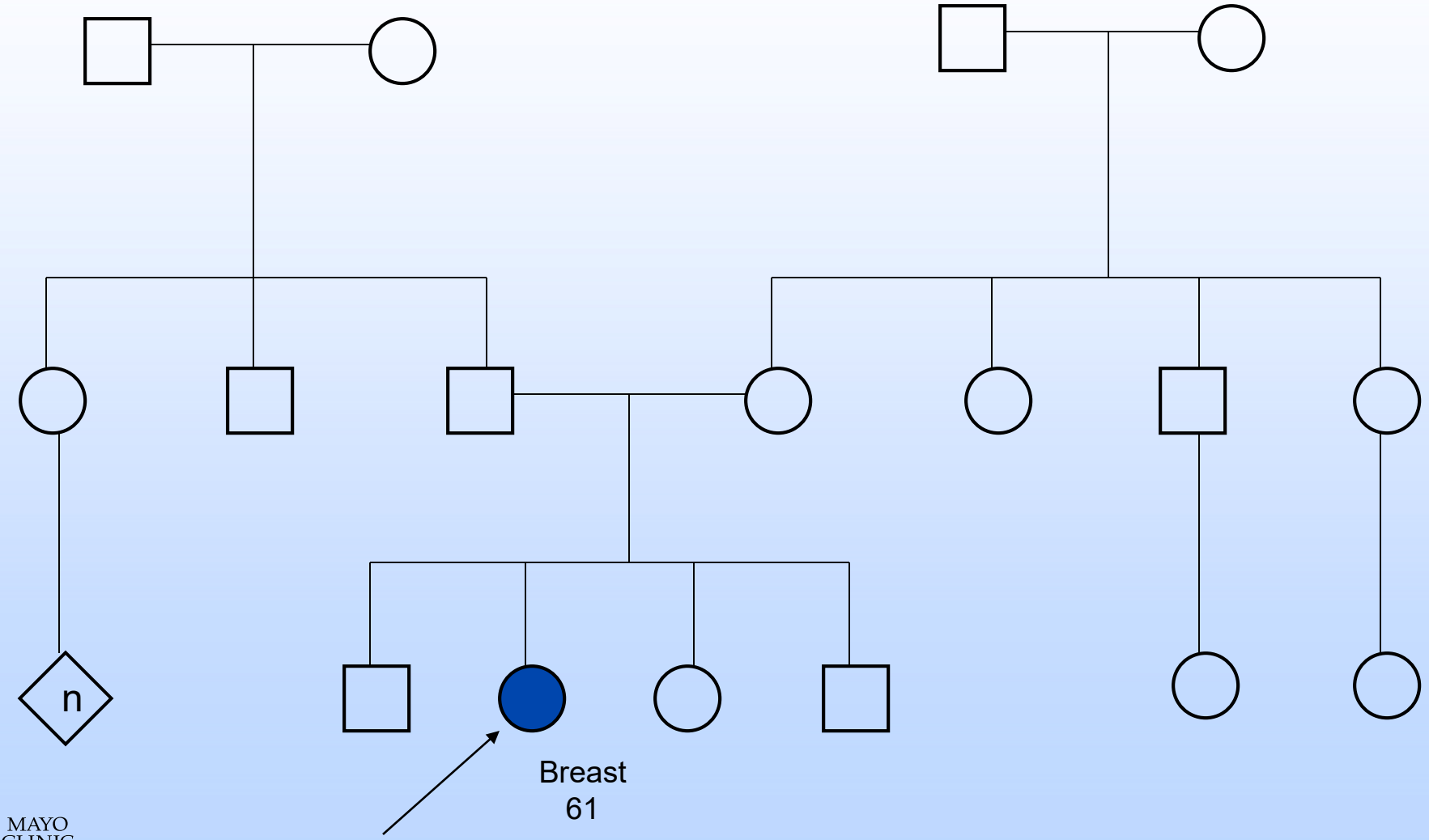
Sporadic Cancer Pattern



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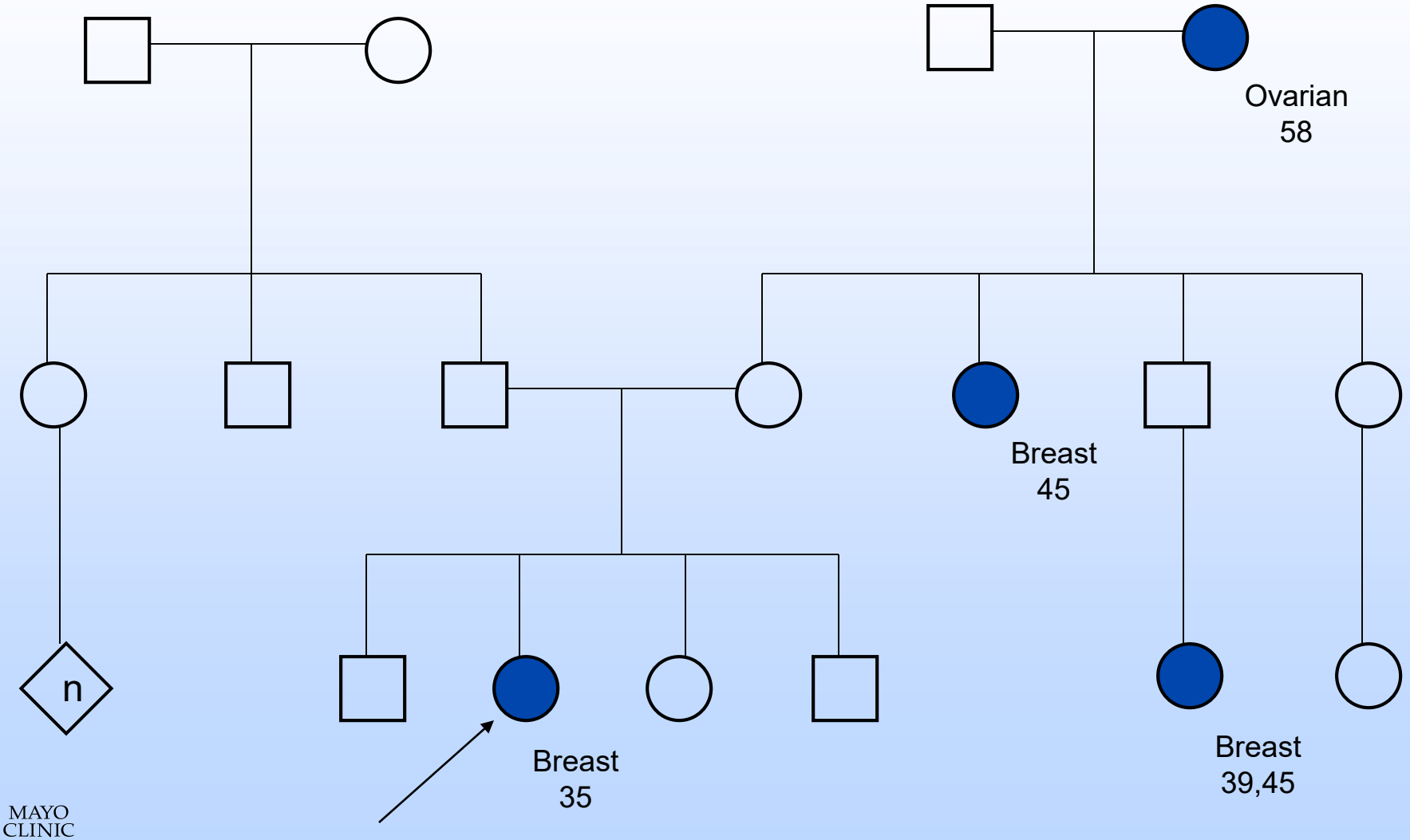
Hereditary Cancer Pattern



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Could referral be improved using the **3-2-1** family history rule?

- 508 random pts referred to a cancer genetics clinic
- 59% met all 3-2-1 criteria
- 23% more met 2 criteria
- 67% could have been referred earlier

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J Palliat Med. 2013 Nov;16(11):1350-5. Could triaging family history of cancer during palliative care enable earlier genetic counseling intervention? Lakhani NS et al.

3 Months in an Adult Genetics Practice

CANCER

Amsterdam I Criteria FHx Colon Ca, Personal Hx early Br Ca.
Strong FHx Breast Cancer
Breast Cancer dx 46 (PENN II=8%) with widespread metastases with neuroendocrine features
BRCA2 (Ashk 617delT) with pancreatic adenocarcinoma (dx 66),
AD early onset Prostate cancer FHx

HEMOGLOBINOPATHIES

Alpha-0 Thalassemia carrier
Likely thalassemia silent carrier- decided to not pursue testing

THROMBPHILIAS

AD Inherited Protein C Deficiency
No suggestion of a familial propensity to thrombosis +/- recurrent stroke

GI

Idiopathic (?Hereditary) Recurrent Acute Pancreatitis

NEUROLOGIC

Length dependent sensory>motor neuropathy; ?*HSN1*
AD Dementia, *PSEN1* Negative
Fronto-temporal dementia dx 64; simplex
Isolated bilateral Lisch nodules
?limb girdle muscular dystrophy or Kennedy's disease, ?X-linked neuro-myopathy

ENDOCRINPOPATHIES

Nonsecretory Adrenocortical and Hyperparathyroidism; MEN1 negative from adrenal tumors
Autoimmune Polyendocrine (Schmidt) Syndrome Type II; Multifactorial autoimmune FHx

RENAL

AD PKD
Hereditary Nephritis, likely AD Alport Syndrome > Epstein syndrome

CARDIAC

Familial Hypercholesterolemia, Definite clinical dx per Dutch criteria
MI <30y, migraines with normal lipids and likely strong FHx of MI/stroke
AD FHx of (early) vasculopathy without hypercholesterolemia ?ADCAD1

SYSTEMIC MONOGENIC DISEASE

a1AT deficiency (ZZ) with COPD, c congenital cirrhosis and HCC (age 68)
Familial Amyloidosis s/p liver and kidney tx 1996

DYSMORPHOLOGY

Sacral agenesis with symptomatic hypogonadism
ID, microephaly, cerebellar hypoplasia, fused coronal suture, upslant palpebral fissures, long ears, tall stature, hypogonadism
4q partial monosomy with ID, recurrent pelvic fluid collections

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Summary

- Overview of inherited contribution to disease
  - Nothing is perfectly compartmentalized
  - Environment and ethnicity are important
- Genomic applications are across medicine
- ‘3,2,1 Rule’
  - But specialists want to assist

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Questions & Discussion