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Clinical Perspectives of a Genetic Counselor

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Interprofessional Clinical Pharmacogenomics Certificate Program

Conflict of Interest Disclosure

- I have no conflicts of interest to disclose.

I. Genetic Counseling

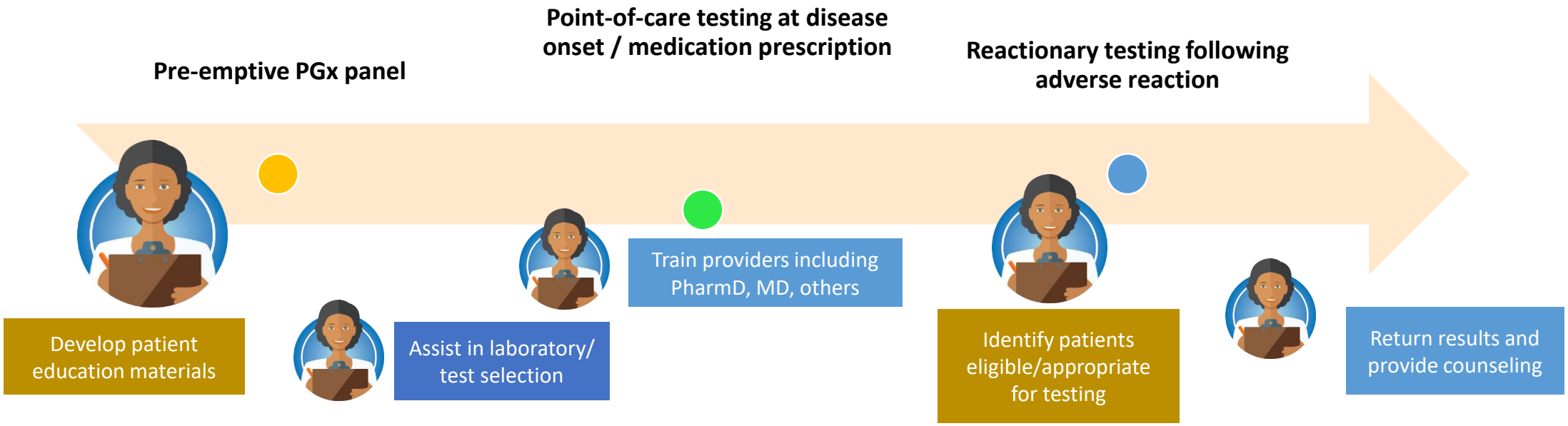
Who is a genetic counselor?

- Genetic counselors have advanced training in medical genetics and counseling to interpret genetic test results, and to guide and support patients seeking information.
- Bachelor's degree
- Master's degree in genetic counseling
  - Two-year program, includes academic classes and clinical fieldwork rotations
  - 54+ accredited programs in US
- Licensure & Certification
  - Certification board examination, Licensure in some states

What do genetic counselors do?

- Genetic counselors:
  - Explain and help process complex and sensitive genetic information
  - Counsel patients to help them work through their feelings about testing/diagnosis
  - Facilitate informed decision-making process
  - Coordinate and order genetic testing, help interpret results
  - Provide referrals, resources, and support

What is a Genetic Counselor's Role in PGx?



- Educational
- Translation of literature for patients and providers
- Facilitate decision making
- Evidence-based result disclosure

- Coordination of care with team (PCP, PharmD, etc)
- Expert resource for community
- Secondary findings/special cases

GCs and Access to Genetic Services

- 5,000+ certified genetic counselors in workforce
  - Profession has doubled over the last 10 years, predicted to double again

Problem: Not enough genetics specialists to meet patient needs

- Currently ~1,500 board-certified medical geneticists in the US

Solutions:

1. Support non-genetics HCPs in providing genetics-based clinical care
2. Provide more genetics education & training to primary care physicians
3. Increase patient access to GCs

Access to Genetic Counselor Services Act

- The “Access to Genetic Counselor Services Act” bill was introduced in the U.S. House of Representatives (H.R. 2144) and the U.S. Senate (S. 1450) in 2021
- If passed, CMS would recognize genetic counselors as independent healthcare providers
  - Provide reimbursement to GCs at 85% of MD amount

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II. Genetic Counseling Across Medicine

Genetic Counseling: Clinical Components

- **Contracting**: set expectations, review patient and provider goals, establish mutually agreed agenda for appointment
- **Counseling**: provide genetics education, psychosocial support, facilitate informed decision making
- **Family History**: obtain detailed three-generation pedigree
  - Comprehensive risk assessment
  - Identify any red flags or additional indications for work-up
    - Unrelated genetic testing, specialty referrals, etc.

Family History Essentials

- Focused questions can inform risk and have significant impact on clinical care

- <u>Red flags for genetic disease / indication for genetic testing:</u>
  - Known genetic disorders
  - Multiple individuals with rare medical problems
  - Recurrent miscarriage (>3), third trimester miscarriage, infant death
  - Congenital birth differences, intellectual disability

  - **Sudden death before age 50**
    - Early aneurysm, dissection, cardiac death without known history of cardiac problems
    - Unexplained cause, “accidents”- motor vehicle accident, drowning, etc.

  - **Concerning cancer history**

    - Cancer diagnosed before age 50
    - Multiple individuals with cancer in each generation
    - Multiple cases of the same types of cancer or rare cancers
    - Ashkenazi Jewish ancestry

Mendelian Disease Patterns of Inheritance

- Autosomal Dominant
- Autosomal Recessive
- X-linked

Two copies of every gene

One copy is inherited from each parent

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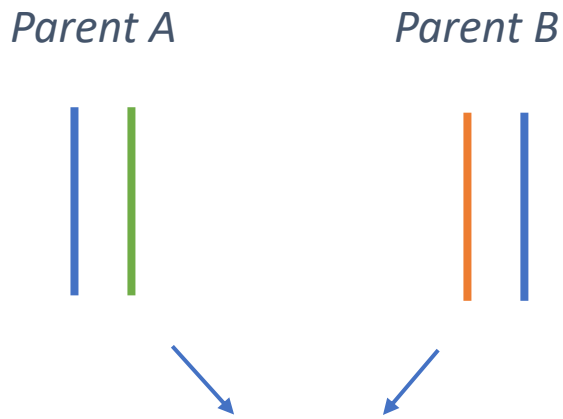
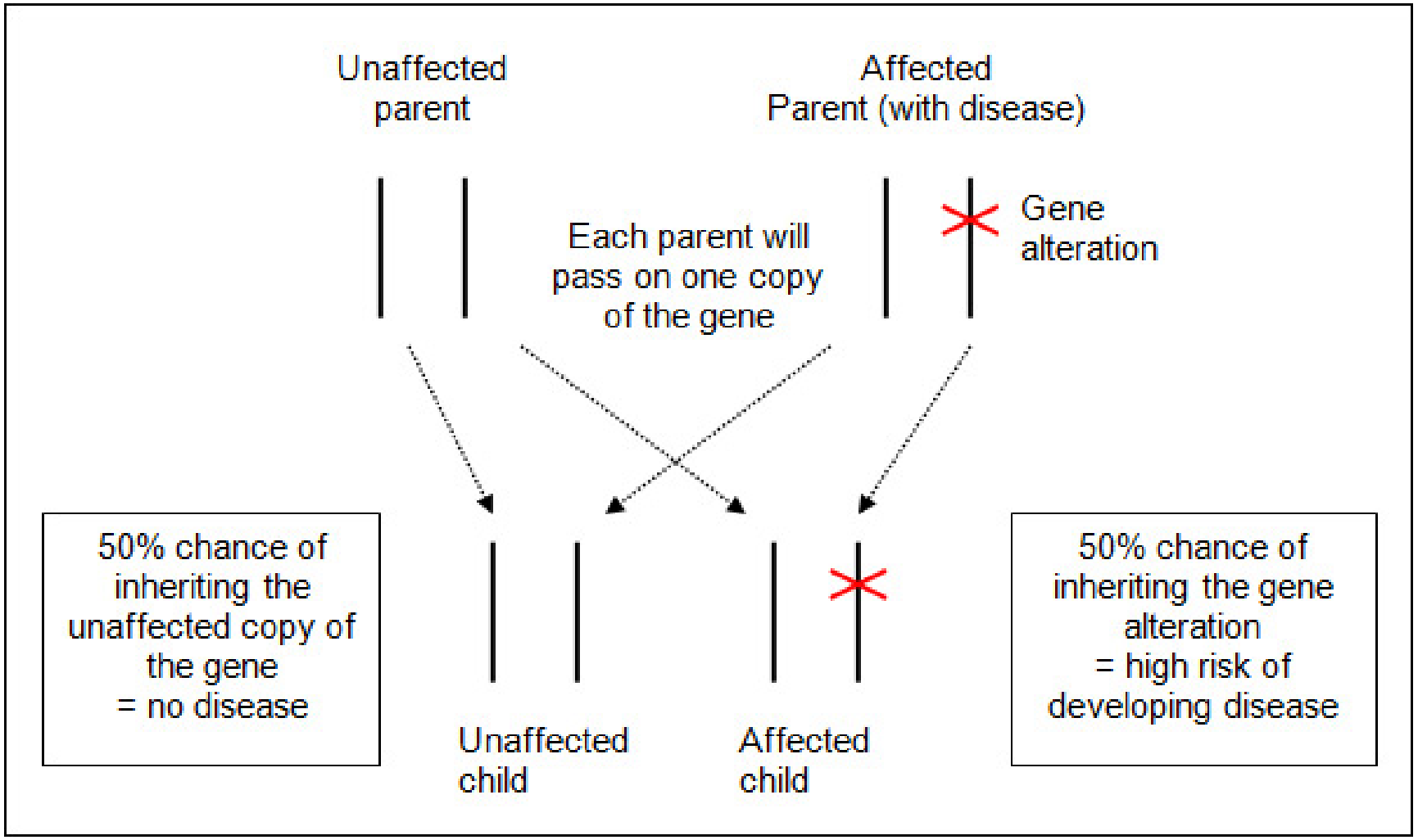
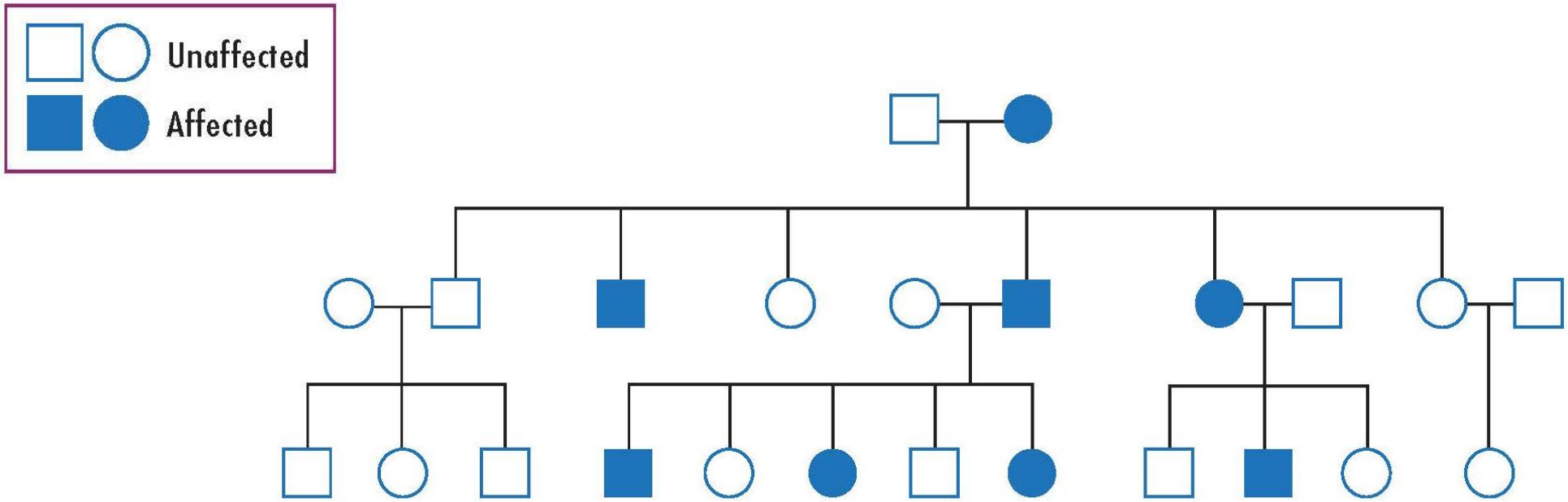


Autosomal Dominant



"Genetic Inheritance and Testing." *Australian Genetic Heart Disease Registry*, National Genetic Heart Disease Registry, https://www.heartregistry.org.au/patients-families/testing-for-genetic-heart-disease/genetic-inheritance-and-testing/.

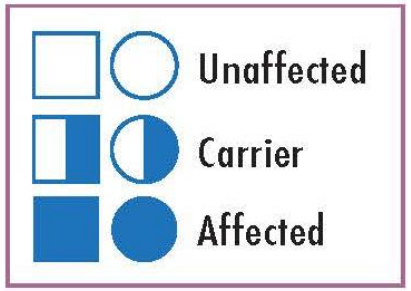
Autosomal Dominant

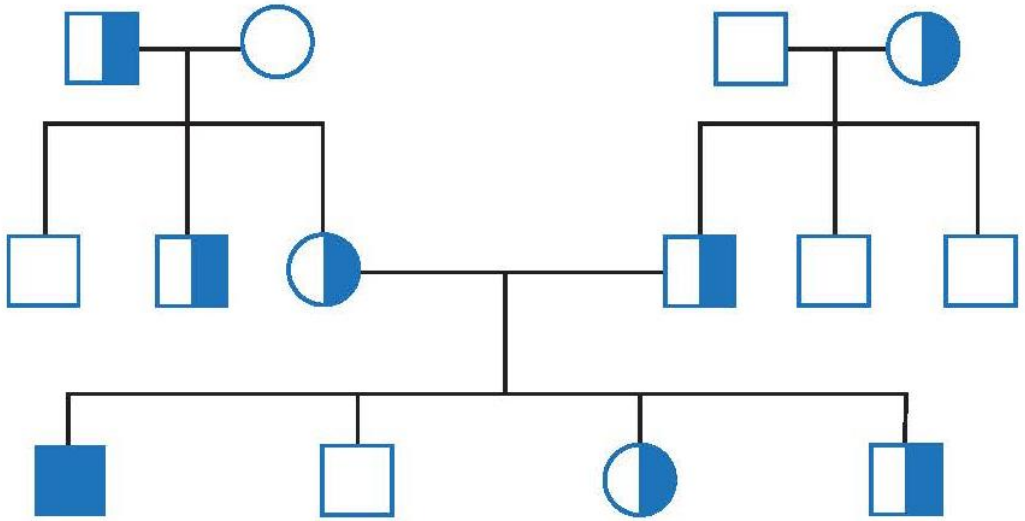


Characteristics of Autosomal Dominant Inheritance

- Multiple generations are affected.
- Males and females are equally likely to be affected.
- Male to male transmission occurs.
- Each offspring of an affected parent has a 50% chance of being affected and a 50% chance of being unaffected.

Autosomal Recessive

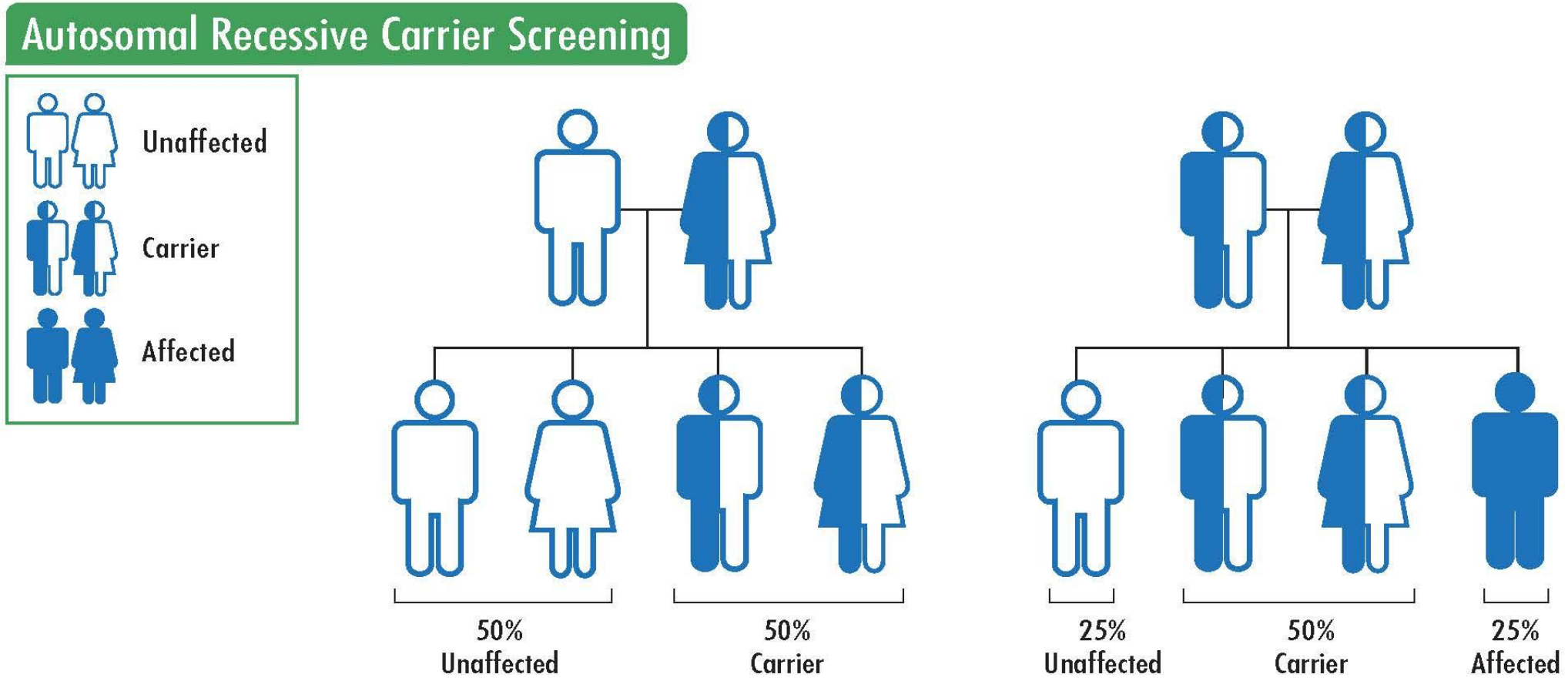




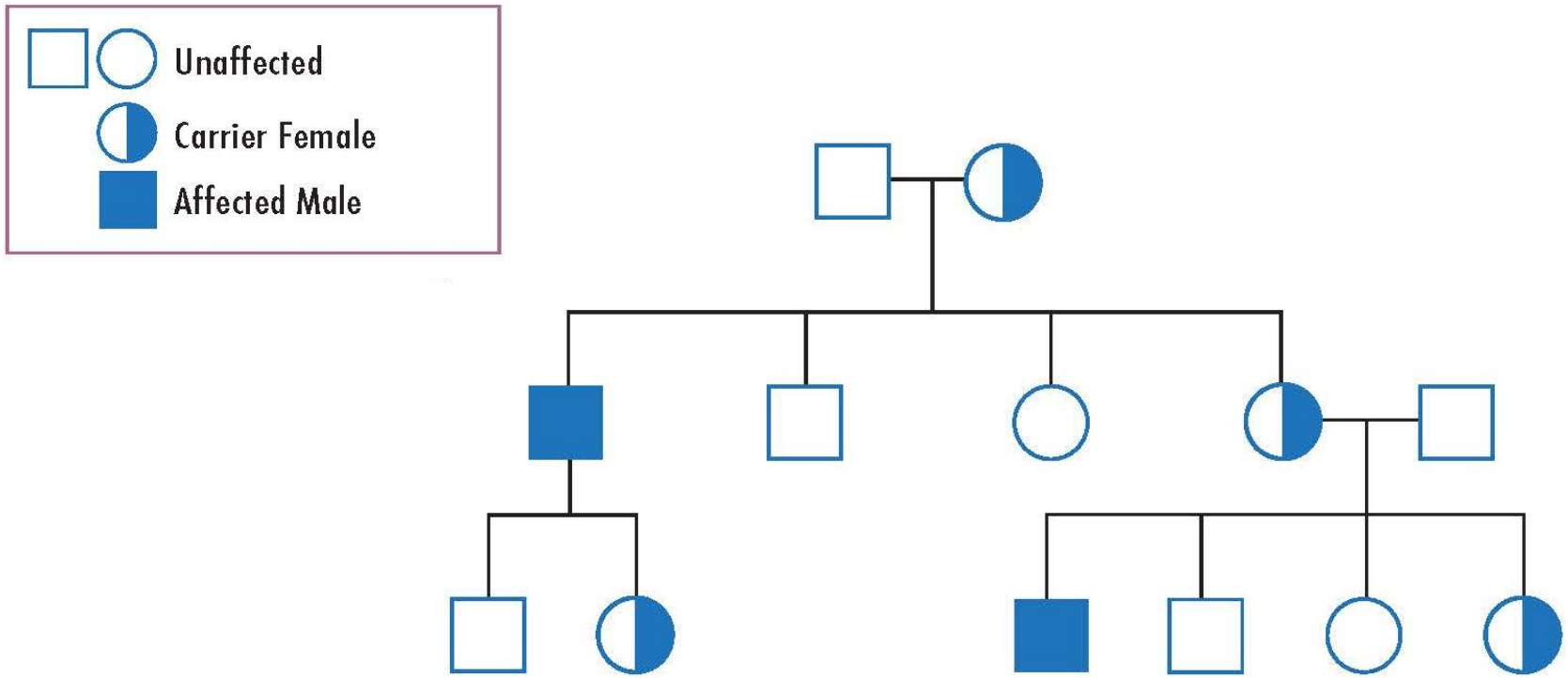
Characteristics of Autosomal Recessive Inheritance

- Greatest recurrence risk is among siblings of affected individuals.
- Males and females are equally likely to be affected.
- If parents are both carriers of mutations in the same recessive gene, each pregnancy has a 25% chance of inheriting both normal genes, a 50% chance of being a carrier, and a 25% chance of inheriting both gene mutations and being affected.
- Ethnic background and consanguinity may influence the likelihood of a specific recessive disease.

Autosomal Recessive



X-linked Recessive

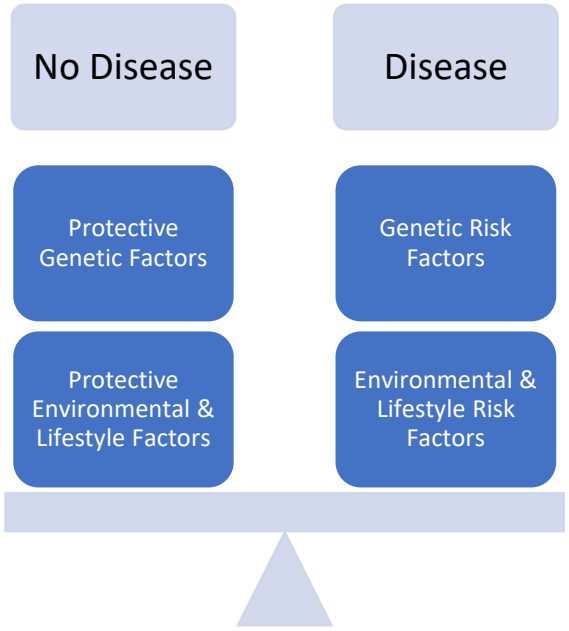


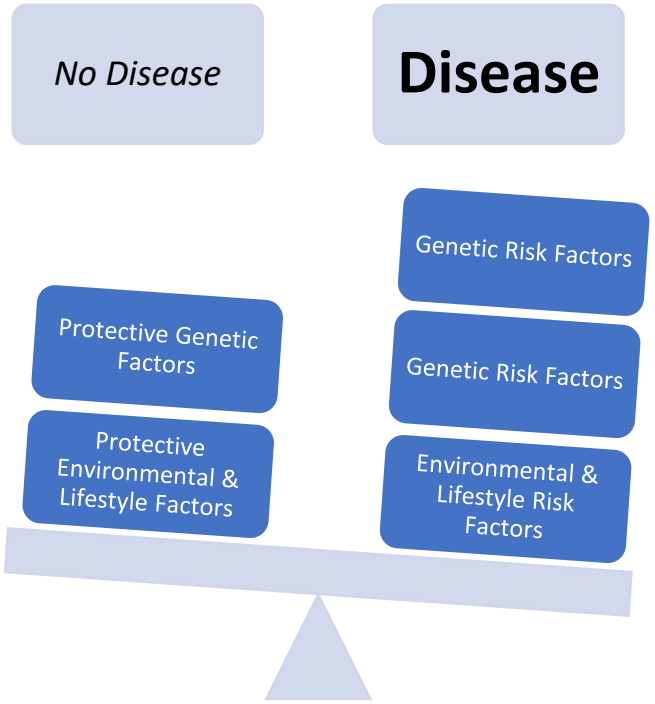
Characteristics of X-Linked Recessive Inheritance

- The incidence of the condition is much higher in males than females.
- All daughters of affected males will be carriers.
- The condition is never transmitted directly from father to son.
- Sons of carrier females have a 50% chance of being affected and a 50% chance of being unaffected.
- Daughters of carrier females have a 50% chance of being a carrier and a 50% chance of inheriting the normal copy of the gene.

Additional Disease Models in Genetics

- De Novo
- Polygenic Risk Scores (PRS)
- Genome Wide Association Studies (GWAS)
- Multifactorial Disorders





Review: Genetic Disease Inheritance Models

Autosomal Dominant

- 1 heterozygous variant = affected

Autosomal Recessive

- 2 variants (homozygous or compound heterozygous) = affected
- 1 variant = carrier

X-linked Recessive

- 1 heterozygous variant in male = affected
- 1 heterozygous variant in female = carrier
- 2 variants (homozygous or compound heterozygous) in female = affected

Heterozygous: two different gene alleles, one with a variant present and one without

Homozygous: two identical gene alleles with the same variant present

Compound heterozygous: two different gene alleles, both with a different variant present

III. Pharmacogenomics Clinic at Brigham & Women's Hospital

Pharmacogenomic Clinical Programs

- Brigham and Women's Hospital
- Boston Children's Hospital
- Stanford
- Cleveland Clinic
- Children's Minnesota
- Northshore University Health System (Chicago)
- University of Florida Health System
- Mission Hospital (NC)
- Mayo Clinic
- Others

Broader Implementation: Mayo, Vanderbilt, St. Jude, U. Pittsburgh, Mt. Sinai

- St. Jude and UF established American Society for Health System Pharmacist's Accredited residency in clinical pharmacogenomics

Brigham & Women's Hospital Pharmacogenomics Clinic

Clinical Team

- Primary Care Physician **previously Medical Geneticist
- Genetic Counselor
- Clinical Pharmacist (PharmD, BCPS)
  - Pharmacy Practice residency and specialty residency in Clinical Pharmacogenetics
  - Board certified pharmacotherapy specialist (BCPS)
  - Assistant Professor of Pharmacy Practice at MCPHS University

Brigham & Women's Hospital Pharmacogenomics Clinic

- **Patient Population & Referral Reasons**
  - History of problems with past medication responses
    - Prior therapeutic failure or adverse effects
    - Patient concerns about adverse effects
  - Interest in using pharmacogenomics to guide current or future medications
    - Initiating therapy for a drug with PGx implications
    - Choosing between therapeutic equals
  - Pharmacogenomic testing done previously
    - Patient presents for results review and interpretation

Brigham & Women's Hospital Pharmacogenomics Clinic

VISIT 1

14 Days

VISIT 2

PGx education + goals + expectations

Medication / family history

Decision for or against testing

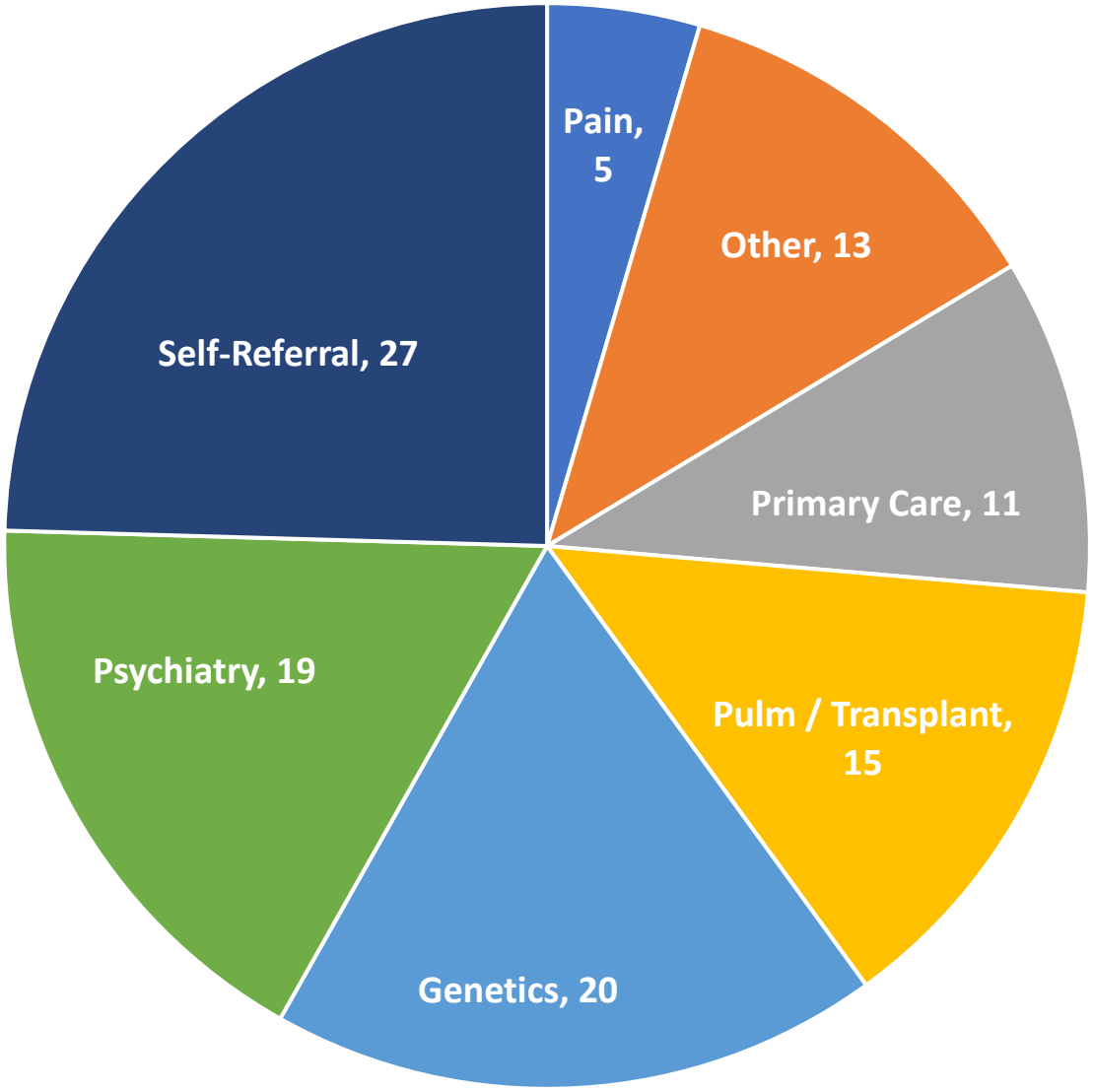
Medication history

Results interpretation + recommendations

Results shared with providers

Pharmacogenomics Clinic: Patient Metrics

- **110** patients evaluated between May 2019 - Feb 2022
- Average patient age: 45 ½ yo
- **80** patients tested
- Remaining **35** patients:
  - 8 have testing pending
  - 15 cancelled testing
  - 6 with recent PGx testing
  - 6 declined- panel would not meet needs / goals
- **100%** of patients tested had clinically actionable result



III. Benefits & Limitations of Pharmacogenomics

With pharmacogenomic testing, providers can:

Minimize adverse side effects and treatment failures

40-70% of patients experience ADR or lack of response

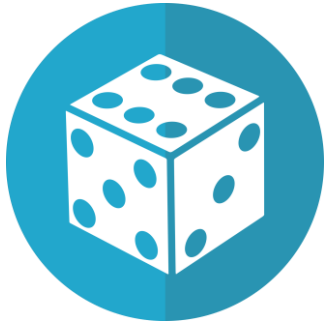
Save time and cut down healthcare costs

"Therapeutic odyssey"

Annual cost of drug-related morbidity & mortality > *$177 billion*

Improve patient-provider dynamics and care outcomes

Could build trust, improve patient compliance and adherence



Reduce trial and error process of prescribing

Predict drug response before patient receives single dose

MAXIMIZE the likelihood of optimal response	(**efficacy**)
MINIMZE the likelihood of adverse drug response	(**safety**)

Barriers & Limitations

- **Data and utility of results**
- **Lack of confidence / familiarity / experience with PGx**
- **Non-genetic factors** can impact effectiveness of PGx
  - Drug-drug interaction
  - Herbal medicine, supplements, diet, environment
- **Insurance reimbursement**
- **EMR alerts** and clinical decision support

Barriers & Limitations

- Data and utility of results
- Lack of confidence / familiarity / experience with PGx
- Non-genetic factors can impact effectiveness of PGx
  - Drug-drug interaction
  - Herbal medicine, supplements, diet, environment
- Insurance reimbursement
- EMR alerts and clinical decision support
- **Race-based medicine and health inequities**

IV. Race in Pharmacogenomics

REA: Race, Ethnicity, Ancestry

Race: *socially* defined trait often based on skin color and cultural identity

- Social construct and ideology of inequality

Ethnicity: *socially* defined trait typically based on one's cultural group

- Often linked to community, religion, language, etc.

Ancestry: refers to geographical origins and can imply genetic origins

- GWAS (genome-wide association studies) data can provide an objective measurement of ancestry but is limited by the lack of diversity in reference population data sets

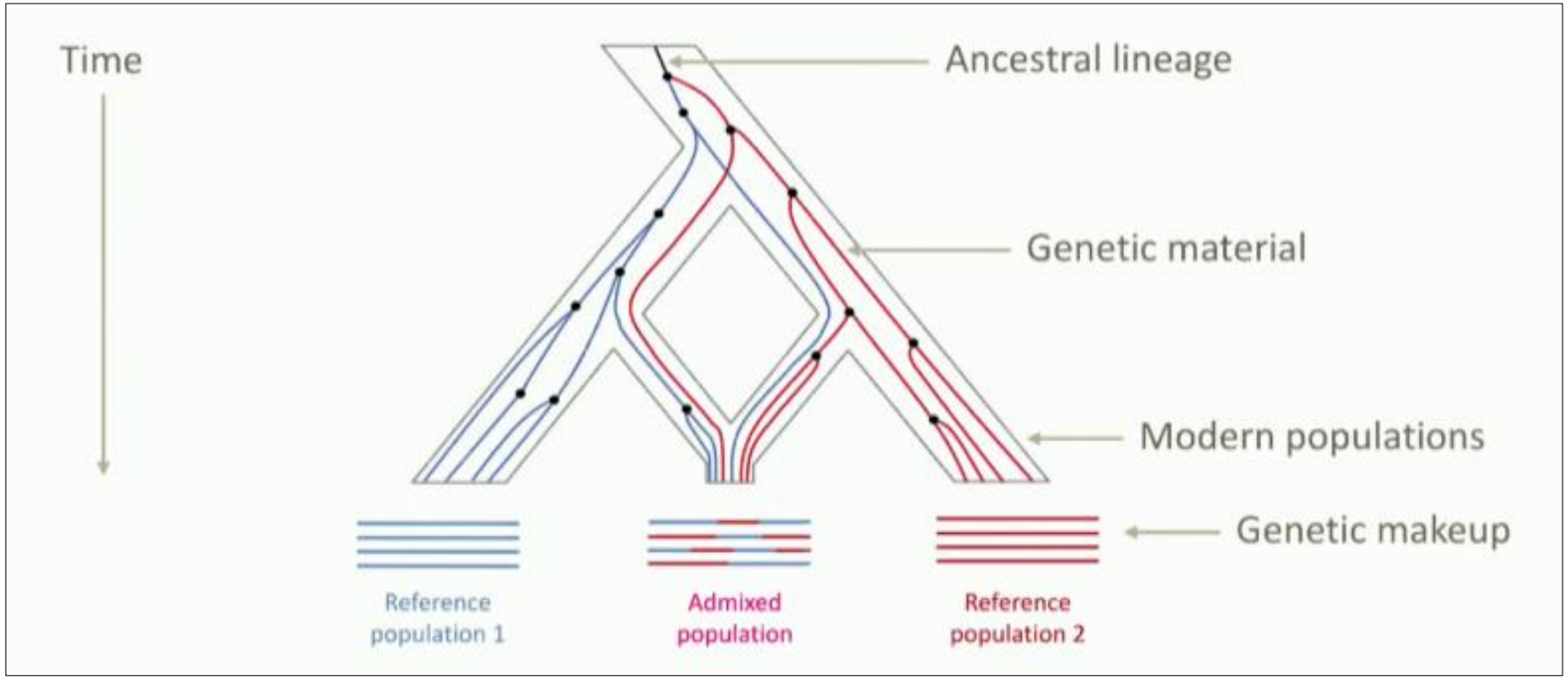
GWAS & Ancestry

- GWAS = genome-wide association studies
- Genetic ancestry is estimated from DNA
  - Reflects origin by assessing DNA inherited from biological ancestors
- Individuals with similar ancestral origins have shared **genomic signatures** due to migration of common ancestors, mutations and recombination, genetic drift, and natural selection
- Genetic ancestry is calculated by comparing an individual's genotype to the global reference populations
  - Incomplete references creates biased calculations and genomic outliers

GWAS is the only objective way to measure and calculate ancestry
GWAS is limited by the lack of diversity in reference population data sets

Ancestry Admixture

- Lineage from different biogeographical groups



Alice Popejoy, PhD- Stanford University School of Medicine. Popejoy, Alice. Genetic Ancestry Testing: What Does It All Mean?. National Human Genome Research Institute, 13 May, 2020. webinar.

It’s OK to Talk About Race

- **Racial data <u>can</u> be collected and used to study social differences**
  - Racism can cause disparate outcomes between races
- **Racial data should <u>not</u> be used to study biological differences**
  - Race is not a reliable indicator of genetics

Defining & Collecting REA Data

- Objective (but not perfect) way to measure ancestry is sequencing data (GWAS, SNP assay, etc) for patient population
  - Not a standard practice in a typical clinic setting- what are we using instead?

- **Inherent challenges in collecting REA data, but best practices include:**
  - Self-identified race/ethnicity (SIRE)
  - Use correct terms and categories, provide definitions
  - Allow participants to select multiple options

REA Categories in Pharmacogenomics

Geographical populations

American (AME): The American genetic ancestry group includes populations from both North and South America with ancestors predating European colonization, including American Indian, Alaska Native, First Nations, Inuit, and Métis in Canada, and Indigenous peoples of Central and South America.

Central/South Asian (SAS): The Central and South Asian genetic ancestry group includes populations from Pakistan, Sri Lanka, Bangladesh, India, and ranges from Afghanistan to the western border of China.

East Asian (EAS): The East Asian genetic ancestry group includes populations from Japan, Korea, and China, and stretches from mainland Southeast Asia through the islands of Southeast Asia. In addition, it includes portions of central Asia and Russia east of the Ural Mountains.

European (EUR): The European genetic ancestry group includes populations of primarily European descent, including European Americans. We define the European region as extending west from the Ural Mountains and south to the Turkish and Bulgarian border.

Near Eastern (NEA): The Near Eastern genetic ancestry group encompasses populations from northern Africa, the Middle East, and the Caucasus. It includes Turkey and African nations north of the Saharan Desert.

Oceanian (OCE): The Oceanian genetic ancestry group includes pre-colonial populations of the Pacific Islands, including Hawaii, Australia, and Papua New Guinea.

Sub-Saharan African (SSA): The Sub-Saharan African genetic ancestry group includes individuals from all regions in Sub-Saharan Africa, including Madagascar.(25)

Admixed populations

African American/Afro-Caribbean (AAC): Individuals in the African American/Afro-Caribbean genetic ancestry group reflect the extensive admixture between African, European, and Indigenous ancestries(26) and, as such, display a unique genetic profile compared to individuals from each of those lineages alone. Examples within this cluster include the Coriell Institute's African Caribbean in Barbados (ACB) population and the African Americans from the Southwest US (ASW) population, (27) and individuals from Jamaica and the US Virgin Islands.

Latino (LAT): The Latino genetic ancestry group is not defined by an exclusive geographic region, but includes individuals of Mestizo descent, individuals from Latin America, and self-identified Latino individuals in the United States. Like the African American/Afro-Caribbean group, the admixture in this population creates a unique genetic pattern compared to any of the discrete geographic regions, with individuals reflecting mixed Native and Indigenous American, European, and African ancestry.

Huddart, Rachel, et al. "Standardized biogeographic grouping system for annotating populations in pharmacogenetic research." *Clinical Pharmacology & Therapeutics* 105.5 (2019): 1256-1262.

REA Categories in Pharmacogenomics

A personal take on science and society

World view

By Alice B. Popejoy

Too many scientists still say Caucasian

Racist ideas of categories for human identity continue to warp research and medicine.

Of the ten clinical genetics labs in the United States that share the most data with the research community, seven include 'Caucasian' as a multiple-choice category for patients' racial or ethnic identity, despite the term

> **"'Racial groups' are defined by societies, not by genetics."**

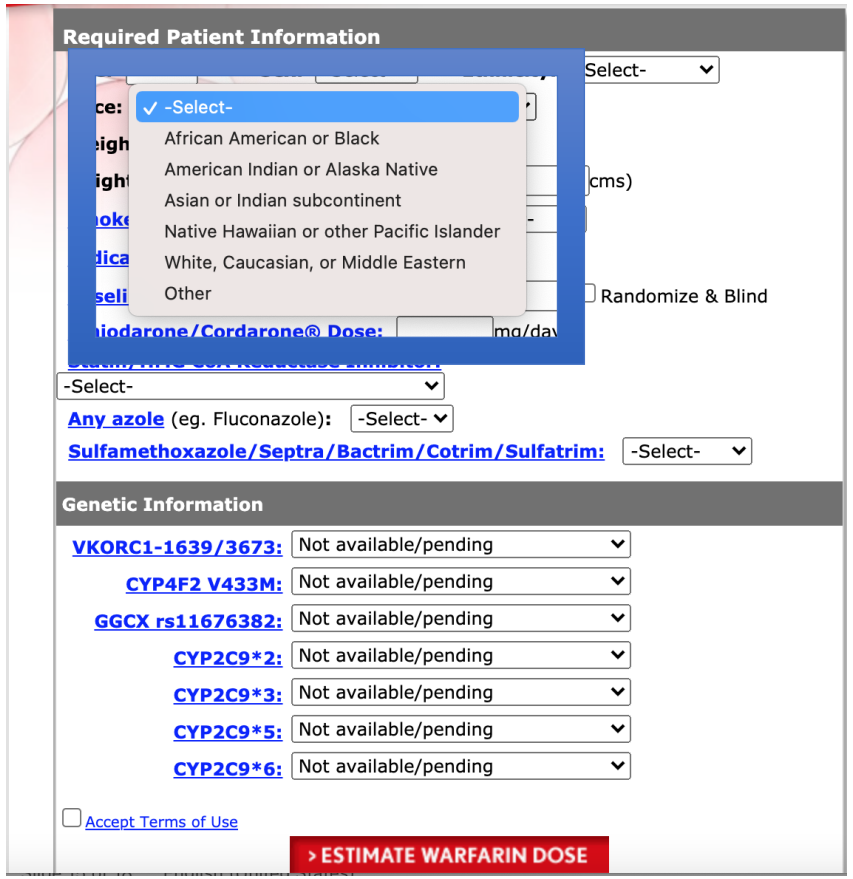
analyses, despite the fact that fewer and fewer individuals identify with a single population of origin.

One practical way forwards is to move away from having people identify themselves using only checkboxes. I am not calling for an end to the study of genetic ancestry or socio-cultural categories such as self-identified race and ethnicity. These are useful for tracking and studying equity in justice, health care, education and more. The goal is to stop conflating the two, which leads scientists and clini-

Unknown / not provided

Popejoy, Alice B. "Too many scientists still say Caucasian." *Nature* 596.7873 (2021): 463-463.

Pharmacogenomic Problems: Warfarin Calculator



WARFARINDOSING www.WarfarinDosing.org

Welcome to **WarfarinDosing.org**, a free Web site to help doctors and other clinicians begin warfarin therapy by estimating the therapeutic dose in patients new to warfarin. This site is supported by the Barnes-Jewish Hospital at Washington University Medical Center, the NIH, and donations. Estimates are based on clinical factors and (when available) genotypes of two genes: *cytochrome P450 2C9 (CYP2C9)* and *vitamin K epoxide reductase (VKORC1)*.

Recommendations on this Web site are based on data from over 1000 patients. Once information is entered onto the next page, the initial estimate of therapeutic dose explains 53% of the variability in a warfarin dose. If you return to the Web site and enter an INR value after 3 and/or 4 warfarin doses, the dose refinement is even more accurate.

Race should not be used as a proxy for genotype

Pharmacogenomic Problems: CYP2C & Warfarin

Warfarin (coumadin): most commonly used oral anticoagulant worldwide

rs12777823 SNP in *CYP2C* gene cluster was identified in West African populations via GWAS studies

"Although this variant is common in other ethnic populations, an association with warfarin dose has only been detected among African Americans, suggesting it is not the underlying cause but likely inherited with other variant(s) on a haplotype that influences warfarin dose in this population".

Interpretation of positive rs12777823 SNP result depends on the patient's ancestry

- If SNP is present in patients of African American descent, it is clinically actionable for Warfarin dosing
- If SNP is present in patients of non- African American descent, it is not clinically actionable for Warfarin dosing
- No guidelines for interpretation or clinical application of SNP in admixed populations

What is mechanism of CYP2C SNP & co-segregating variants?

How to define & measure ancestry in absence of GWAS data, or in presence of admixture?

Pharmacogenomic Problems: HLA & carbamazepine / abacavir

Carbamazepine

- Used to treat seizure disorders
- *HLA-B*15:02* - increased risk for severe cutaneous adverse reactions (SCARS)

Abacavir

- Used to prevent & treat HIV/AIDS
- *HLA-B*57:01* allele - increased risk for hypersensitivity reaction

FDA recommends *HLA-B*15:02* screening in "at-risk populations", i.e. Asian ancestry

- Nearly absent AF in South Korea and Japan

*4/12 of European patients tested positive for HLA-B*15:02 allele, changed ancestry to Asian*

FDA recommends *HLA-B*57:01* screening for all patients, regardless of race / ancestry

Why aren't there universal genetic screening recommendations for medication/genotypes with high risk ADRs?

Reducing Racism in Pharmacogenomics

The problem:

- Inequitable access to PGx testing and clinical utility of PGx results

The solution(s):

- Offer pan ethnic pharmacogenomic panel test assay to all patients
- Advocate for insurance guidelines and coverage policies that do not use REA criteria
- Include diverse populations in pharmacogenomic research
- Improve patient access to pharmacological treatment
  - *Must have access to diagnosis before can access treatment*

Many steps = many possible barriers

1. Seek out medical care after onset of symptoms
2. Undergo medical work-up and any testing / studies indicated
3. Receive appropriate and accurate diagnosis for symptoms
4. Be prescribed medication to treat symptoms

Race in Pharmacogenomics: Summary Points

- Race-based medicine remains an insidious and overlooked problem.
- Clinicians should not incorporate race, ethnicity, or ancestry into clinical decisions about ordering pharmacogenomic testing.
- Race should not be used as a proxy for genotype.

Pharmacogenomics and precision medicine have the potential to help close the gap in healthcare disparities.

Acknowledgements

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Questions?

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