Existing Genetic Technologies and Their Integration into Health Care and Public Health

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Two pathways from genetics to health care benefit

- Genetic testing to identify people with specific needs

(*Tailor care to person*)

- Develop new treatments based on genetic knowledge

(*Tailor care to disease*)

Spectrum of genetic contribution to disease

Newborn screening
Phenylketonuria (PKU)

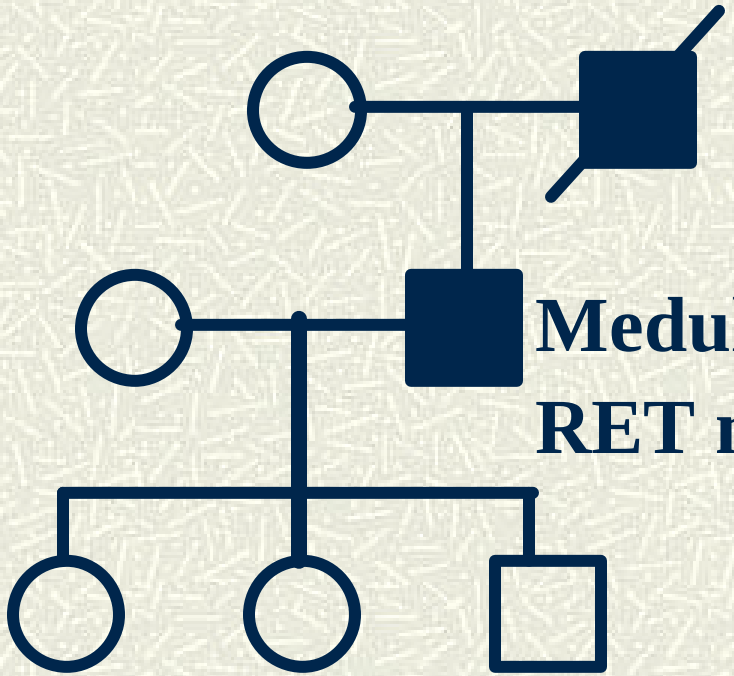
Screen newborns for PKU

Provide phenylalanine-poor diet

Prevent mental retardation

Medullary thyroid cancer & *RET* mutation testing:

Multiple Endocrine Neoplasia 2 (MEN2)

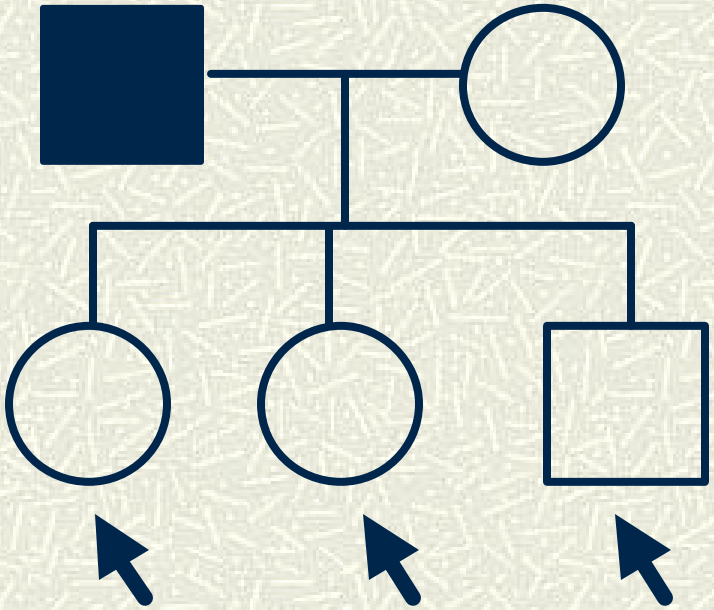


Medullary thyroid cancer

Medullary thyroid cancer, RET mutation +

If RET +, offer prophylactic thyroidectomy

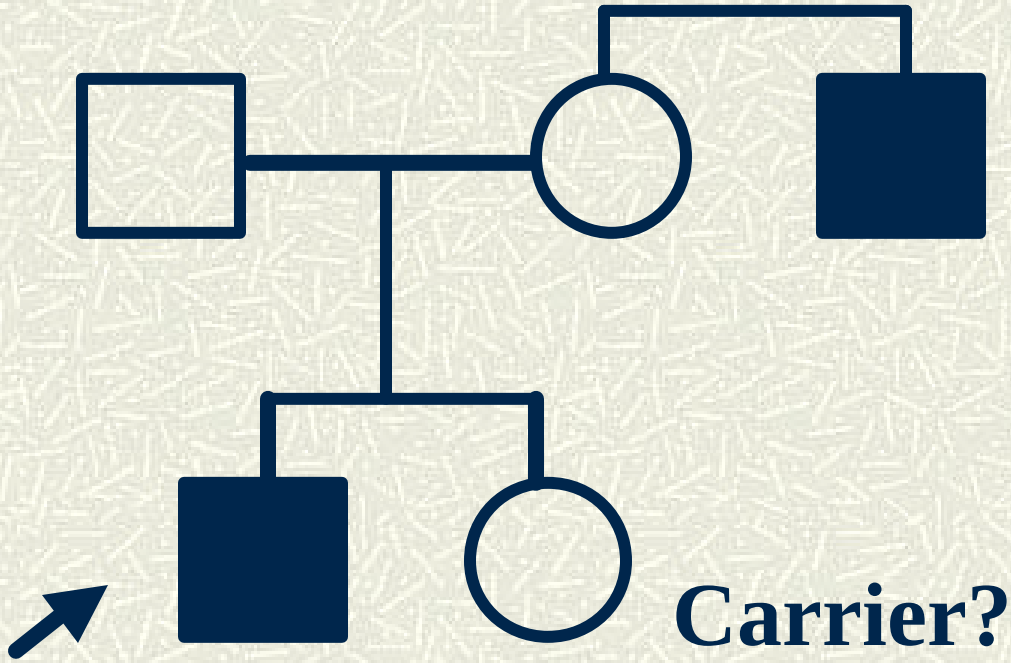
Huntington Disease



= Huntington disease

50% chance of having inherited HD

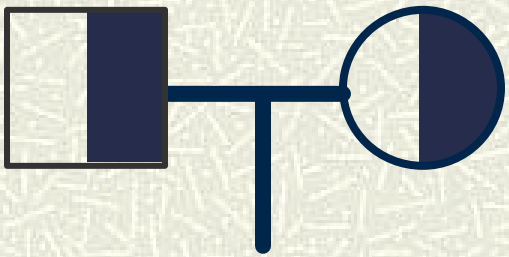
Child with Duchenne Muscular Dystrophy



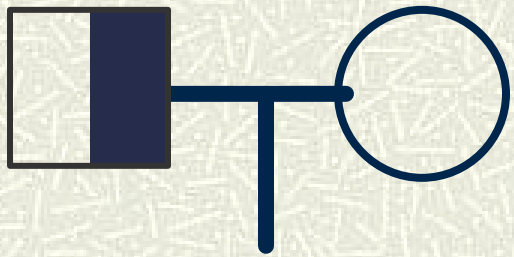
Carrier?

Testing for Cystic Fibrosis (CF) carrier state

= + test for CF carrier state



25% risk of child with CF for each pregnancy



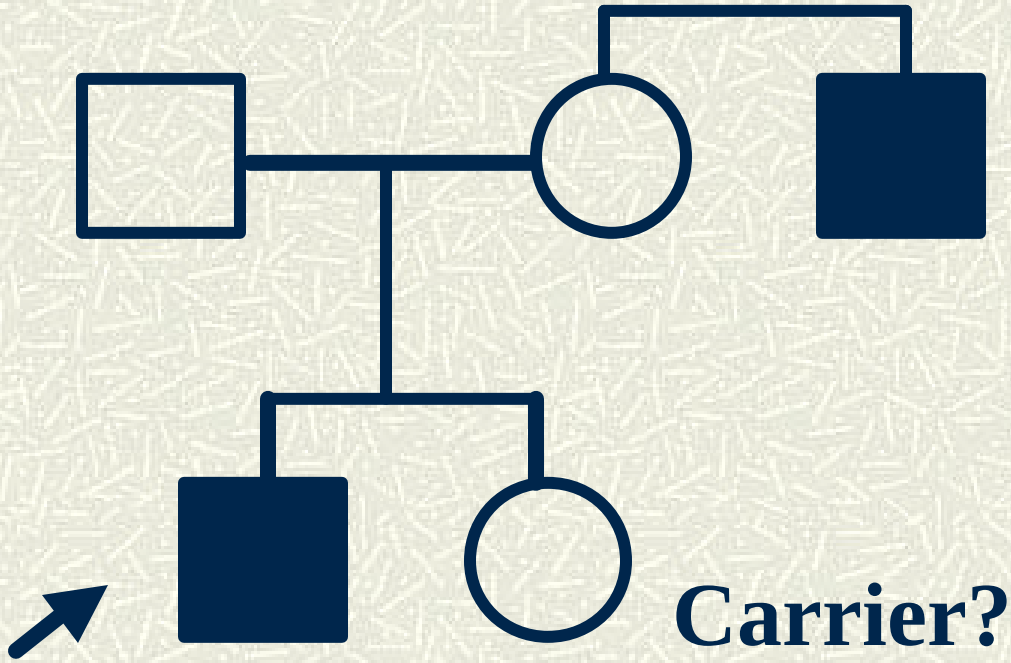
Very low risk of child with CF

CF carrier testing: Recommended testing strategy
American College of Medical Genetics

- Preconception screening whenever possible
- Pre-test education
- Screening panel of 25 mutations
  - Reflex tests: Additional tests to clarify initial + test result
- Post-test counseling if test results + for either or both in couple

(www.acmg.net)

Hemophilia



Carrier?

Understanding & treating hemophilia

1952	Differentiation of Factor VIII and Factor IX deficiencies
1950-60s	Experimentation with plasma, (as well as adrenaline, other Rx)
1965	Cryoprecipitate – concentrated clotting factor from many donors

Unintended consequences: Hemophilia and AIDS

1982	First case reported
1983-6	Most exposures occurred
1986-7	Beginning efforts to test & protect blood supply

✍

~40% of hemophiliacs infected
(80% of those with severe disease)

Contribution of genomics to current therapy

Recombinant factor VIII

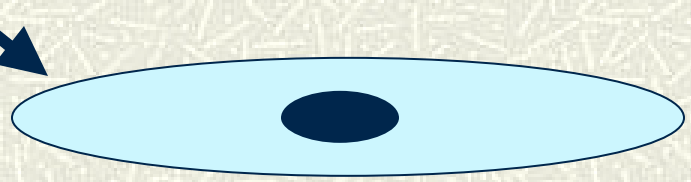
(now standard of care in US)

- Cost: $72,000 + / per year
- Not an option in most developing countries

Gene therapy for hemophilia?

(Roth et al New Engl J Med 2001;344:1735)

Introduction of Factor VIII gene into fibroblasts derived from skin biopsy



Selection and cloning of cells expressing Factor VIII

Implantation

Spectrum of genetic contribution to disease

Predictive genetic testing for common complex diseases

Venous thrombosis (blood clots)

Gene Variant	Prevalence (%)
Factor V Leiden (FVL)	1-5
Prothrombin G20210A(PT)	1-2
Protein C deficiency	0.3
Antithrombin deficiency	0.02

Potential interventions for people with increased risk of VT

Anti-coagulant treatment

- Long-term treatment after blood clot
- Episodic treatment in times of increased risk (example: pregnancy)
- Preventive treatment

Avoidance of other risk factors

- Oral contraceptives, hormone treatment

(Grody et al Genet Med 2001; 3:139)

Risks of anti-coagulation therapy

- Rate of major bleeding events: 3% per year
- Proportion of major bleeding events that are fatal: 20%

(Hirsh & Lee, Blood 2002;99:3120)

Predictive genetic testing: Assuring benefit

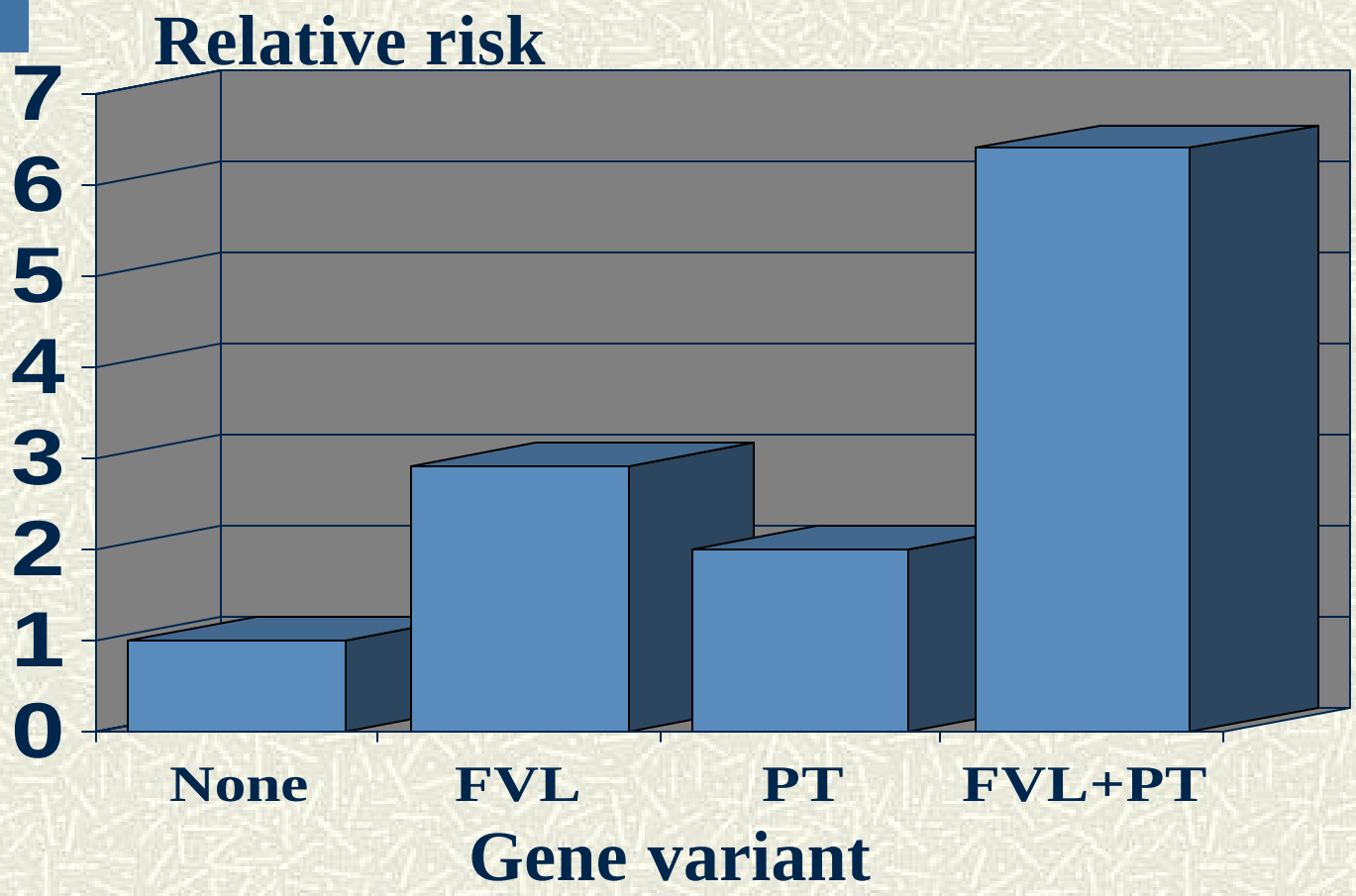
What test?

What treatment?

At what level of risk?

Risk of venous thrombosis (VT) according to genotype

(Martinelli et al Br J Haematol 2000; 111:1223)



Factor V Leiden
Increased effect in homozygote

Genotype	Prevalence	Relative Risk
Heterozygous (1 copy of FVL)	1- 5%	3-7
Homozygous (2 copies of FVL)	≤0.08%	80

Unintended harm of genetic information

- Stigmatization
- Discrimination
- Unnecessary or unproven treatment

APOE4 Testing: A means to predict Alzheimer Disease (AD) risk

- Apolipoprotein E, lipid carrying protein with 3 variants: APOE2, APOE3, APOE4
- ↑ risk of AD with APOE4:
  - 2 copies: 5x higher risk, onset 10 yr earlier
  - 1 copy: 2x higher risk, onset 5 yr earlier
- No treatment available to reduce risk

Range of ethical concerns in predictive genetic testing

Predictive value of test	***Treatment*** Yes	No
High	Assure access	Protect autonomy
Low	Evaluate risks & benefits	Avoid harm

(Burke et al. Am J Med Genet 2001; 106;233)

Pharmacogenetic testing:
CYP2C9 variants & anticoagulation (warfarin therapy)

CYP2C9*2 & CYP2C9*3

- ↓↓ rate of excess anticoagulation
- Longer time to stable dose
- ↓↓ risk of life-threatening bleed

Test for variants before use of drug?

(Higashi et al JAMA 2002; 287:1690)

Novel therapy for chronic myelogenous leukemia (CML)

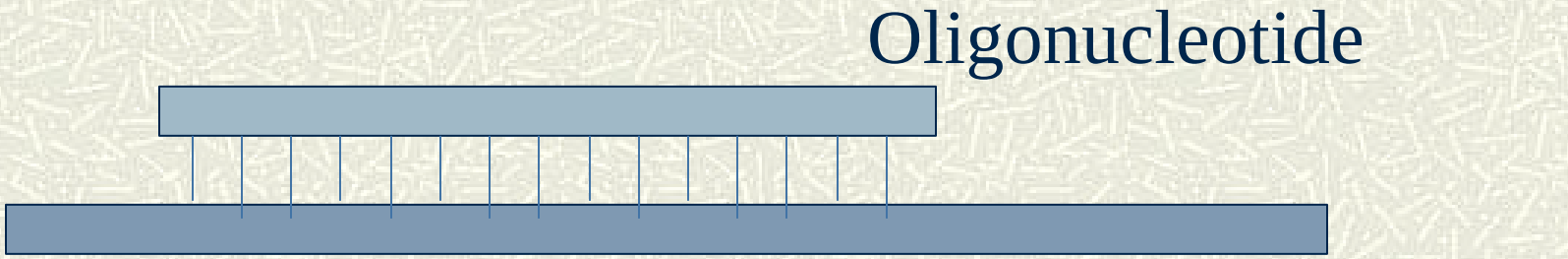
Imatinib (Glivec)

- Selective inhibitor of BCR-ABL tyrosine kinase
  - Philadelphia chromosome, found in 90% of patients with CML ✍ BCR-ABL
  - Mouse model demonstrated BCR-ABL necessary & sufficient ✍ leukemia

(O'Brien et al, NEJM 2003;348:994; Capdeville & Silberman, Semin Hematol 2003;40:15)

Novel genetic therapy for cytomegalovirus infection of eye (Fomivirsen)

Antisense oligonucleotide binds to messenger RNA✍ Inhibits expression of essential viral protein



(Am J Ophthamol 2002;133:467)

Questions in the era of genomic health care

- When does harm of a genetic label outweigh its benefit?
- Who decides when new technologies have sufficient safety & efficacy for use, and on what basis?
- How do we ensure fair access?