Integrating Genetics Technology into a Health Care System

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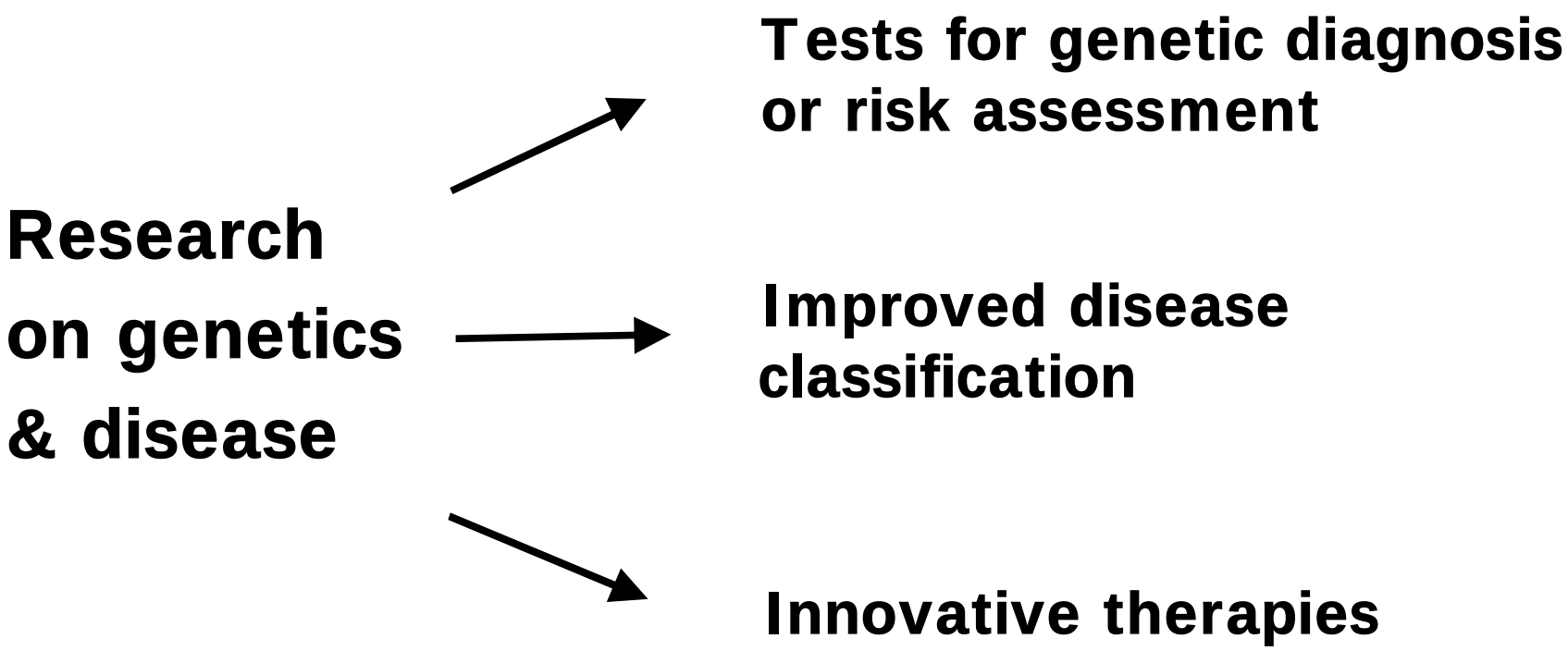
Trends

Medical genetics/ specialty à specialty/ primary care

Information as end point à reduction in morbidity/mortality

Limited information à lots of information

Pathways from genetic research to clinical benefit



Tests for genetic diagnosis and risk assessment

Penetrance of genotype	*Measures to improve disease course*	
	No	**Yes**
High	**Huntington Disease** **Prenatal diagnosis**	**Newborn screening** **Inherited risk of colorectal CA**
Low	**ApoE genotyping**	**Most pharmacogenetics/ genetic susceptibility testing**

Based on Burke et al. Am J Med Genet 2001; 106;233

Medical genetics standard: Non-directive counseling

"An attempt to help the individual or family to … choose the course of action which seems to them appropriate in view of their risk, their family goals, and their ethical and religious standards, and to act in accordance with that decision."

Am J Hum Genet 1975; 27: 240

Growing presence of genetics in routine obstetrics

Screening for trisomy 21

Carrier screening

- **Tay-Sachs à Jewish panel**
- **Hemoglobinopathies**
- **Cystic fibrosis**

Use of genomic technologies to expand testing?

Newborn screening

Identify infants with phenylketonuria

↓

Institute low phenylalanine diet

↓

Prevent mental retardation

Inherited colorectal cancer risk

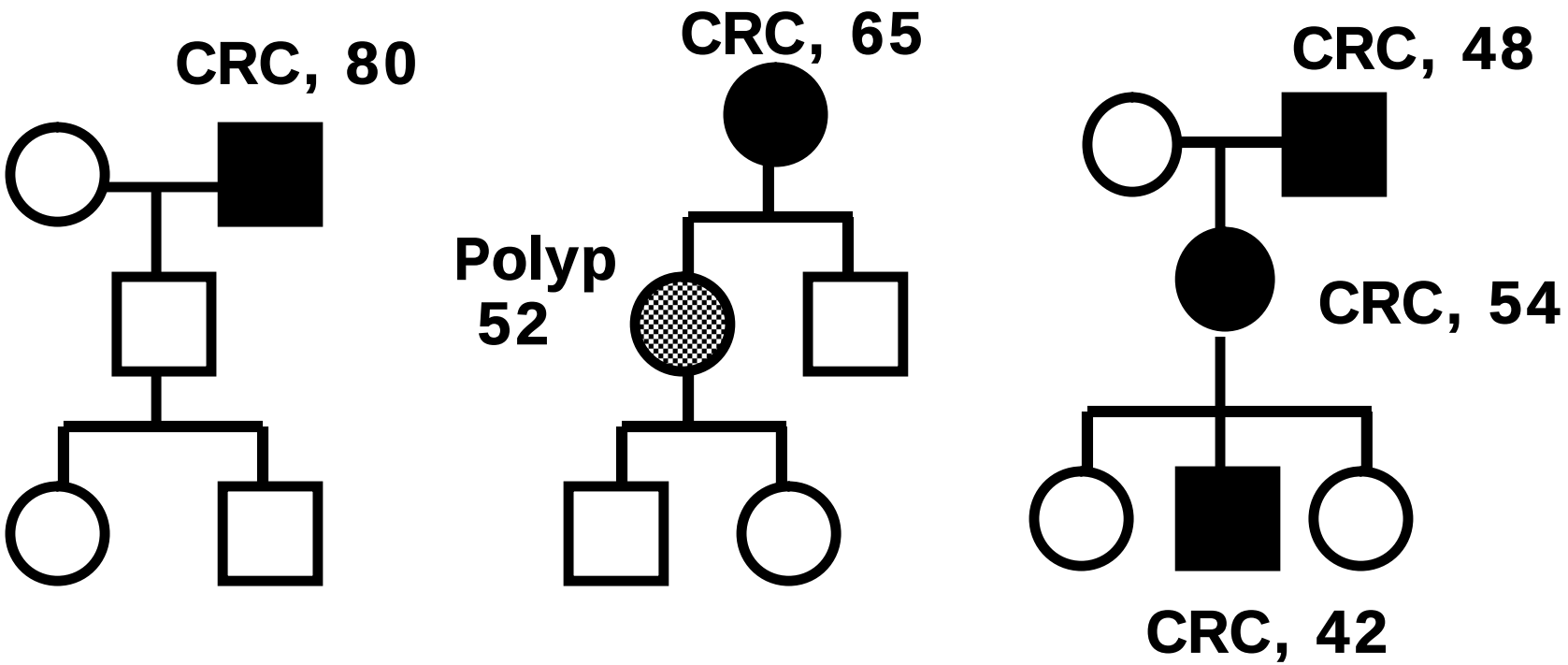
Hereditary nonpolyposis colorectal cancer (HNPCC) - Prevalence ~ 1/500

- ~ 80% lifetime risk of CRC
- Start screening early 20s
- Other risks include endometrial CA, ovarian CA

Familial adenomatous polyposis (FAP) - Prevalence $\leq$ 1/8000

- ~ 100% lifetime risk of CRC
- Prophylactic subtotal colectomy recommended

Continuum of family history of CRC:
Need for oncology, GI & primary care assessment

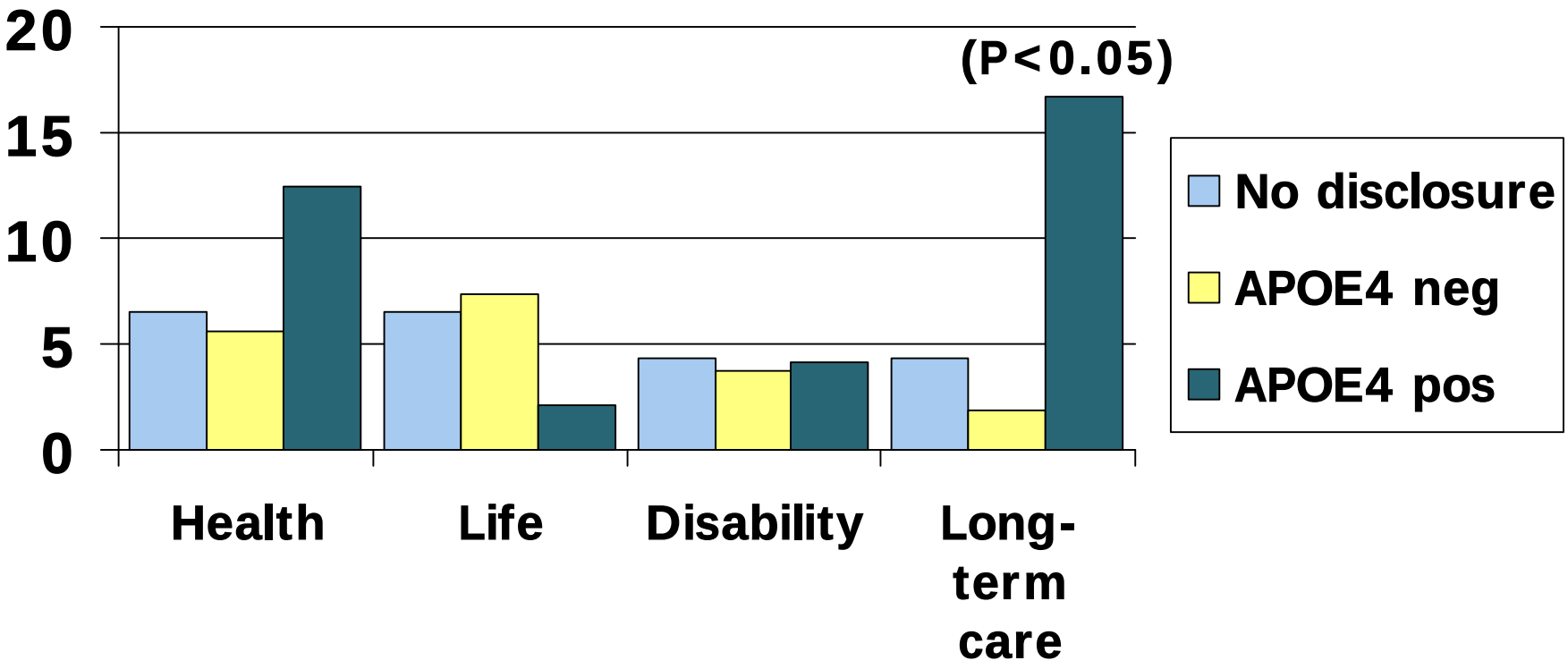


CRC = colorectal cancer

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

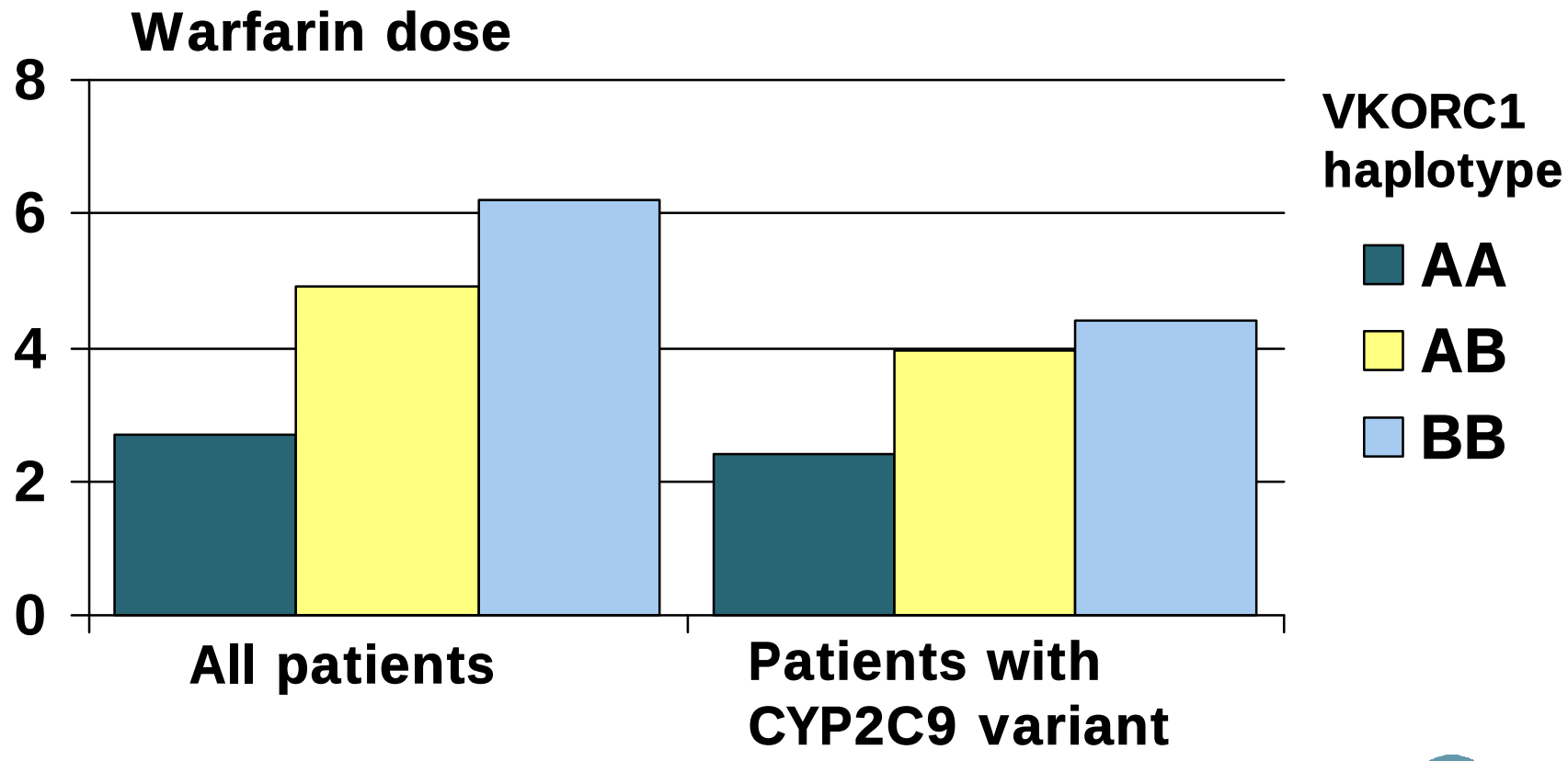
- **Apolipoprotein E, lipid carrying protein with 3 variants: APOE2, APOE3, APOE4**
- **á risk of AD with APOE4:**
  - **2 copies: 5x higher risk, onset 10 yr earlier**
  - **1 copy: 2x higher risk, onset 5 yr earlier**
- **No treatment available to reduce risk**

Effect of *APOE4* testing on insurance purchasing



REVEAL Study -Alzh Dis Assoc Dis 2003;17:86

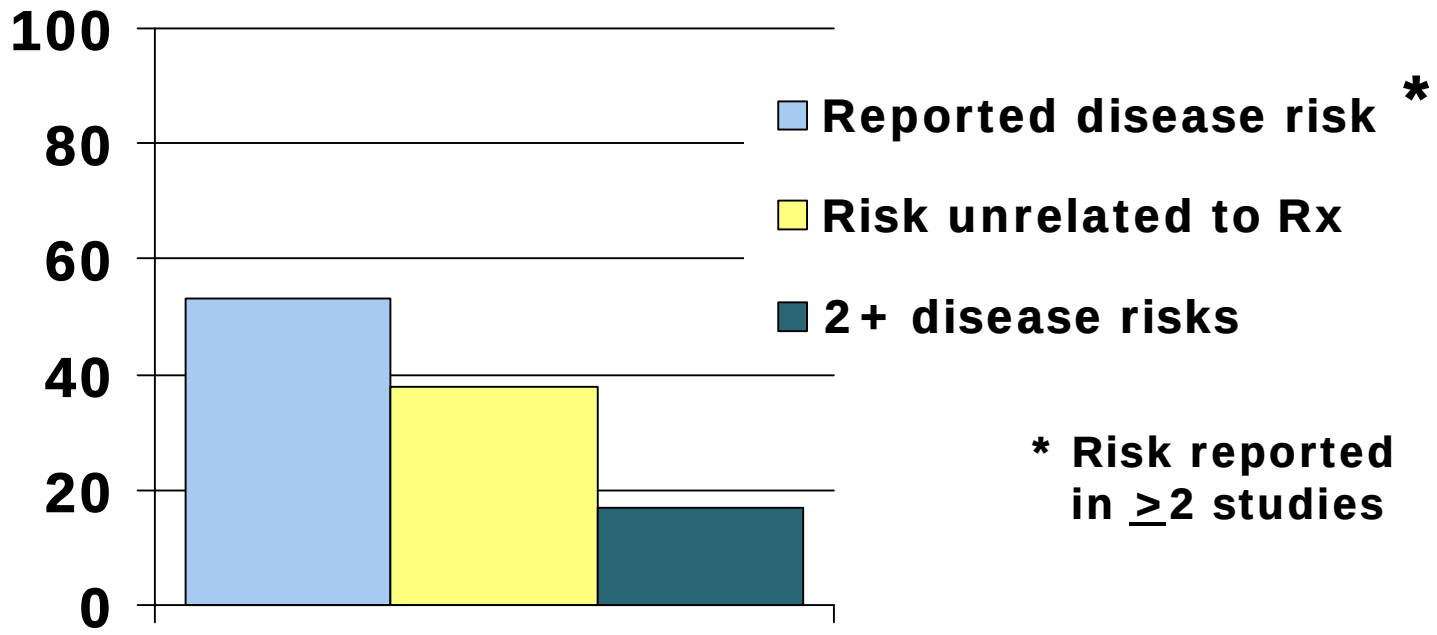
Warfarin dose:
Effect of variation in *VKORC1 & CYP2C9*



Reider et al NEJM 2005; 352:2285-93

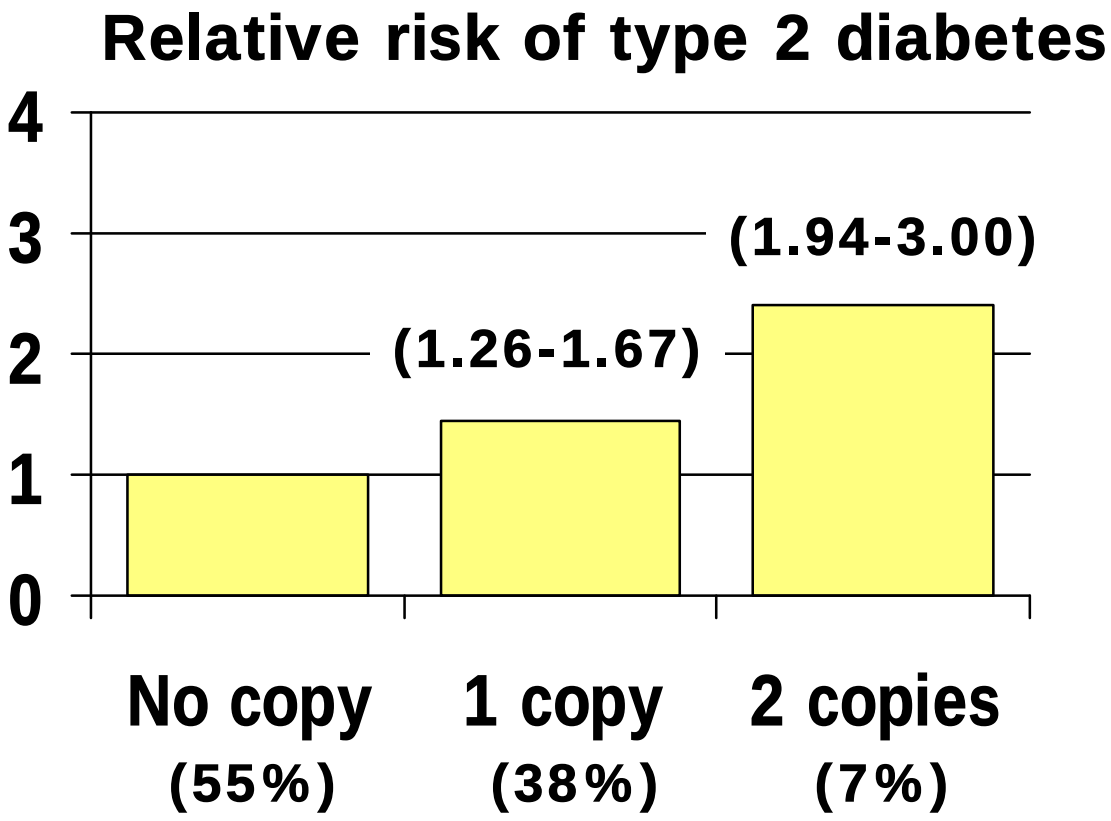
Ancillary risk information as a frequent, unintended consequence

Study of 42 pharmacogenetic variants



Henrikson et al, TPJ, epub May 2007

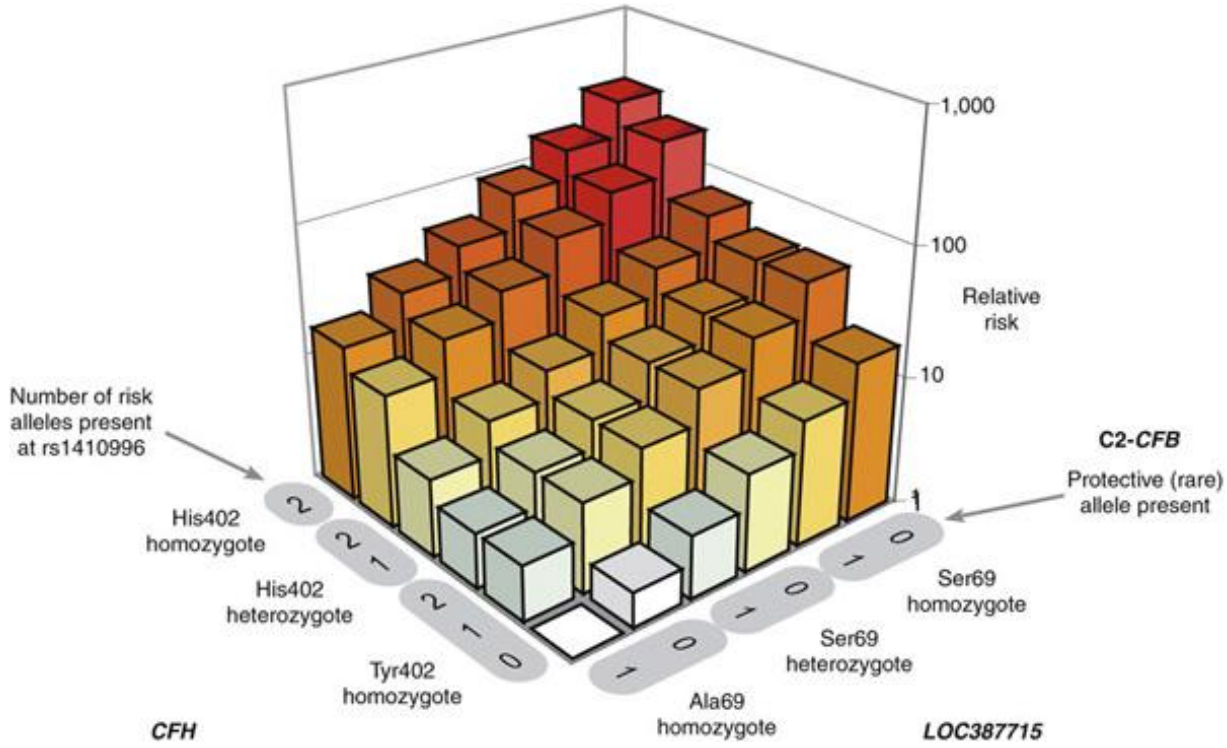
TCF7L2 variant DG10S468 and type 2 diabetes



Grant et al Nat Genet 2006; 38: 320

Effect of common variation in 3 genes on risk of age-related macular degeneration

Maller et al Nat Genet 2006;38:1055-9



Estimated lifetime risk of AMD ranges from

<1% (in 2% of population) to > 50% (in 1% of population).

However, most have risk close to population average

Acquired genetic change: Characterizing breast cancer

Her-2-neu amplification: identifying candidates for herceptin therapy

Gene expression profiling (Oncotype Dx, Mammaprint): predicting likelihood of recurrence / identifying candidates most likely to benefit from chemotherapy

Novel therapy for chronic myelogenous leukemia (CML)

Imatinib (Glivec)

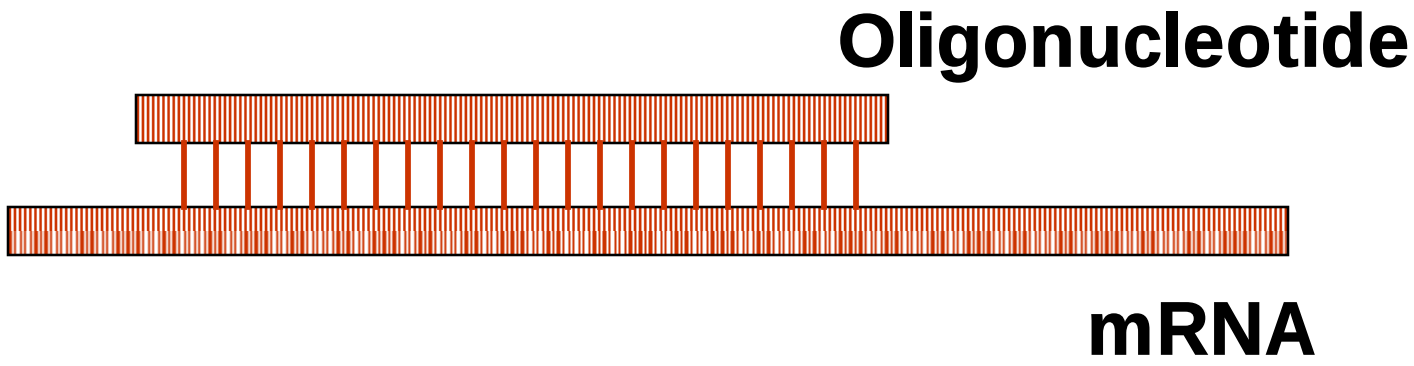
Selective inhibitor of BCR-ABL tyrosine kinase

- **Philadelphia chromosome, found in 90% of patients with CML à BCR-ABL**
- **Mouse model demonstrated BCR-ABL necessary & sufficient à leukemia**

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

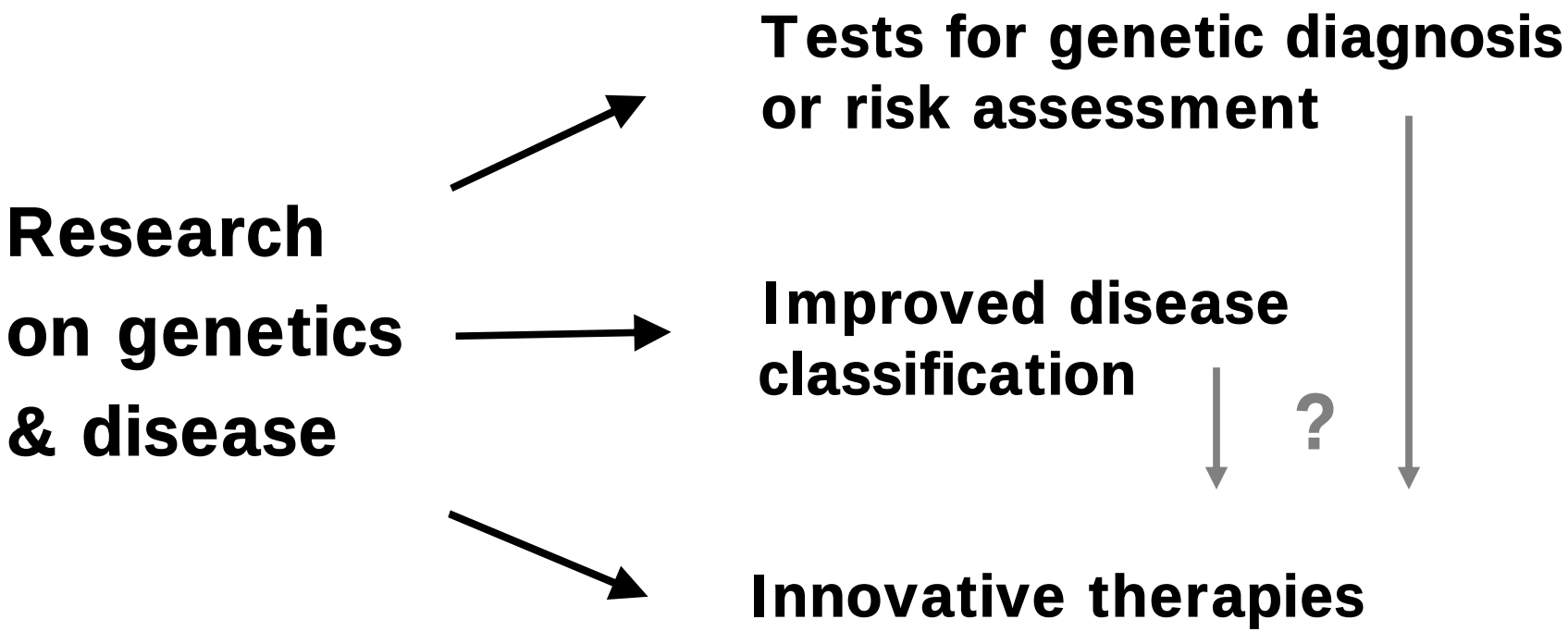
Genetic therapy for cytomegalovirus infection of eye (Fomivirsen)

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



Am J Ophthamol 2002;133:467

Pathways from genetic research to clinical benefit



Clinician needs

- Point of service information
- Billable services that improve health outcome
- Evidence-based guidelines
- High quality, cost-effective educational & counseling strategies