Personal Genomics: Review of Current Practices

Kenneth Offit, MD, MPH
Chief, Clinical Genetics Service
Memorial Sloan Kettering Cancer Center

"As if we didn't already know too much about ourselves, we're having our DNA done."

Genomics in Personalized Medicine

- "The integration of genomic technologies that are capable of tailoring treatment and prevention strategies to each patient's unique genetic characteristics and individual needs into general health care…. The Initiative recognizes that the accuracy, clinical validity, and clinical utility of genetic tests are central to the realization of personalized health care."

Department of Health and Human Services Web site: "Personalized Health Care: Goals." See http://www.hhs.gov/myhealthcare/goals/index.html#Goal3. (March, 2007)

SPECIAL ARTICLE

Statement of the American Society of Clinical Oncology: Genetic Testing for Cancer Susceptibility

Adopted on February 20, 1996 by the American Society of Clinical Oncology*

As the lead
with cancer
(ASCO) reco
formed of th
cancer risk.

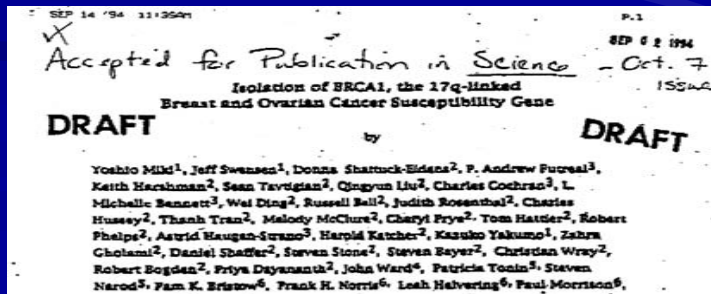
ASCO SPECIAL ARTICLE

American Society of Clinical Oncology Policy Statement Update: Genetic Testing for Cancer Susceptibility

Adopted on March 1, 2003, by the American Society of Clinical Oncology

- Genetic discrimination
- Physician education
- Reimbursement and access
- Ethical and legal Issues
- Efficacy of interventions
  - (clinical utility)
- Regulation to ensure
  - analytic validity

• ***Protection From Insurance and Employment Discrimination:*** **ASCO supports establishing a federal law to prohibit discrimination by health insurance providers and employers**



Accepted for Publication in Science - Oct. 7

Isolation of BRCA1, the 17q-linked Breast and Ovarian Cancer Susceptibility Gene

DRAFT DRAFT

by

Yoshio Miki[1], Jeff Swensen[1], Donna Shattuck-Eidens[2], P. Andrew Futreal[3], Keith Harshman[2], Sean Tavtigian[2], Qingyun Liu[2], Charles Cochran[3], L. Michelle Bennett[3], Wei Ding[2], Russell Bell[2], Judith Rosenthal[2], Charles Hussey[2], Thanh Tran[2], Melody McClure[2], Cheryl Frye[2], Tom Hattier[2], Robert Phelps[2], Astrid Haugen-Strano[3], Harold Katcher[2], Kazuko Yakumo[1], Zahra Gholami[2], Daniel Shaffer[2], Steven Stone[2], Steven Bayer[2], Christian Wray[2], Robert Bogden[2], Priya Dayananth[2], John Ward[4], Patricia Tonin[5], Steven Narod[5], Pam K. Brierley[6], Frank H. Norris[6], Leah Helvering[6], Paul Morrison[6],

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Management of an Inherited Predisposition to Breast Cancer

Mark Robson, M.D., and Kenneth Offit, M.D., M.P.H.

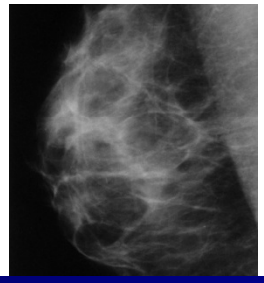
Positive *BRCA1* or *BRCA2* test result

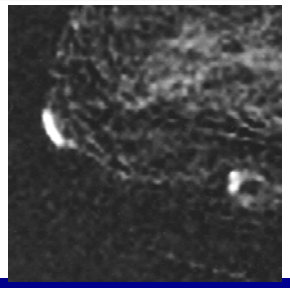
Identify at-risk adult relatives; offer genetic counseling/testing

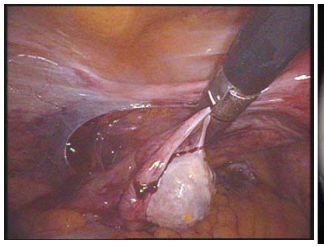
Increased surveillance

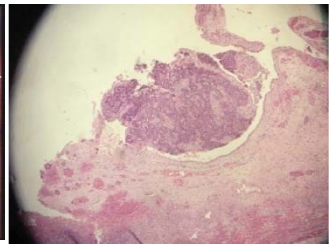
Chemo-prevention

Prophylactic surgery









Factors Impacting Translation of Cancer Genetic Testing in U.S.

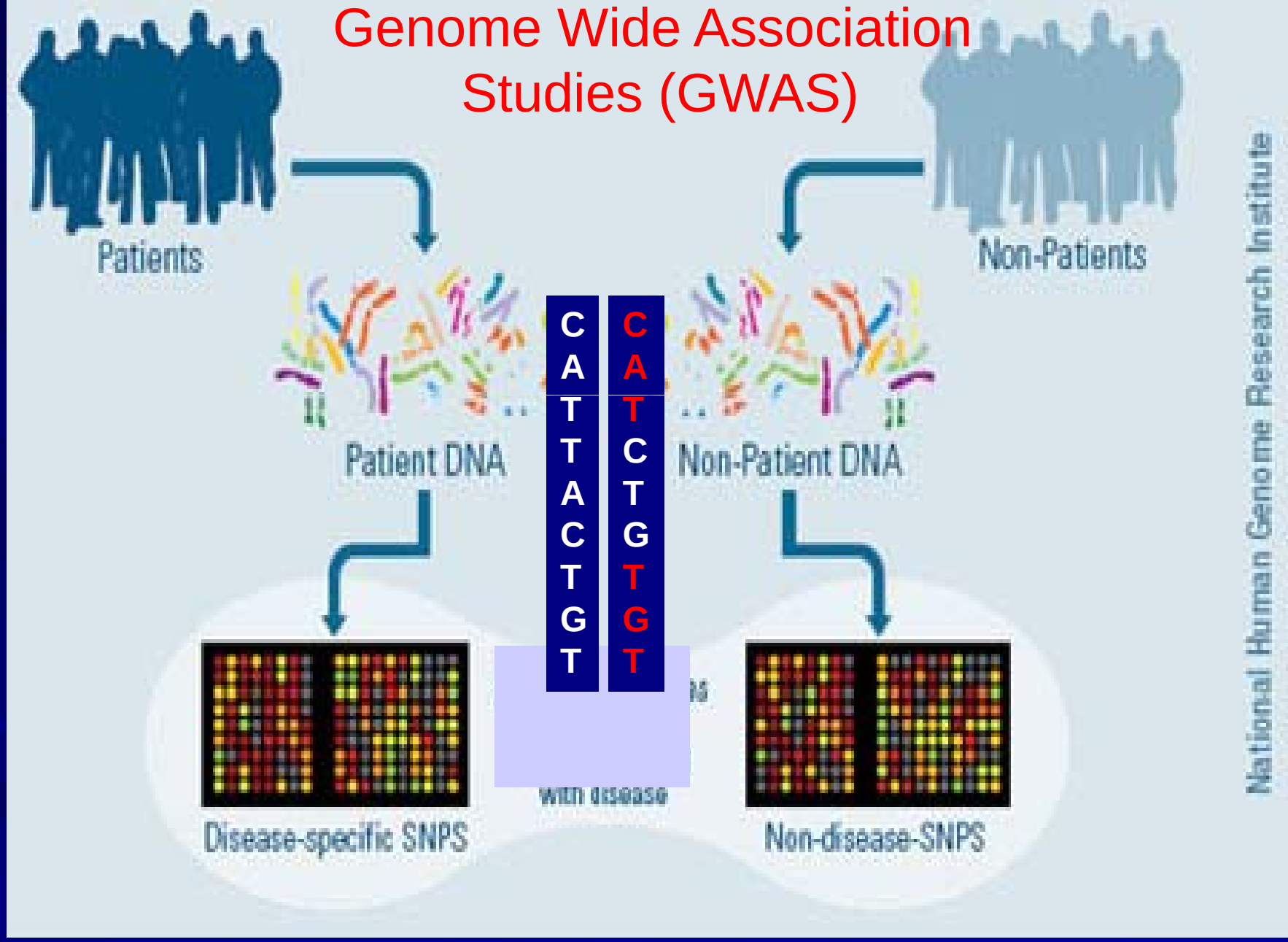
- NIH Leadership: NCI, NHGRI
  - ELSI RFA (NHGRI)
  - Cancer genetics WG
    - CFR (Cooperative Registries)
    - CGN (Cancer Genetics Network)

- Professional leadership: ASCO
  - "Train the trainer"; syllabus; Genetics WG
- Advocacy leadership: DOD grants, other
- Laboratory quality: one reference lab

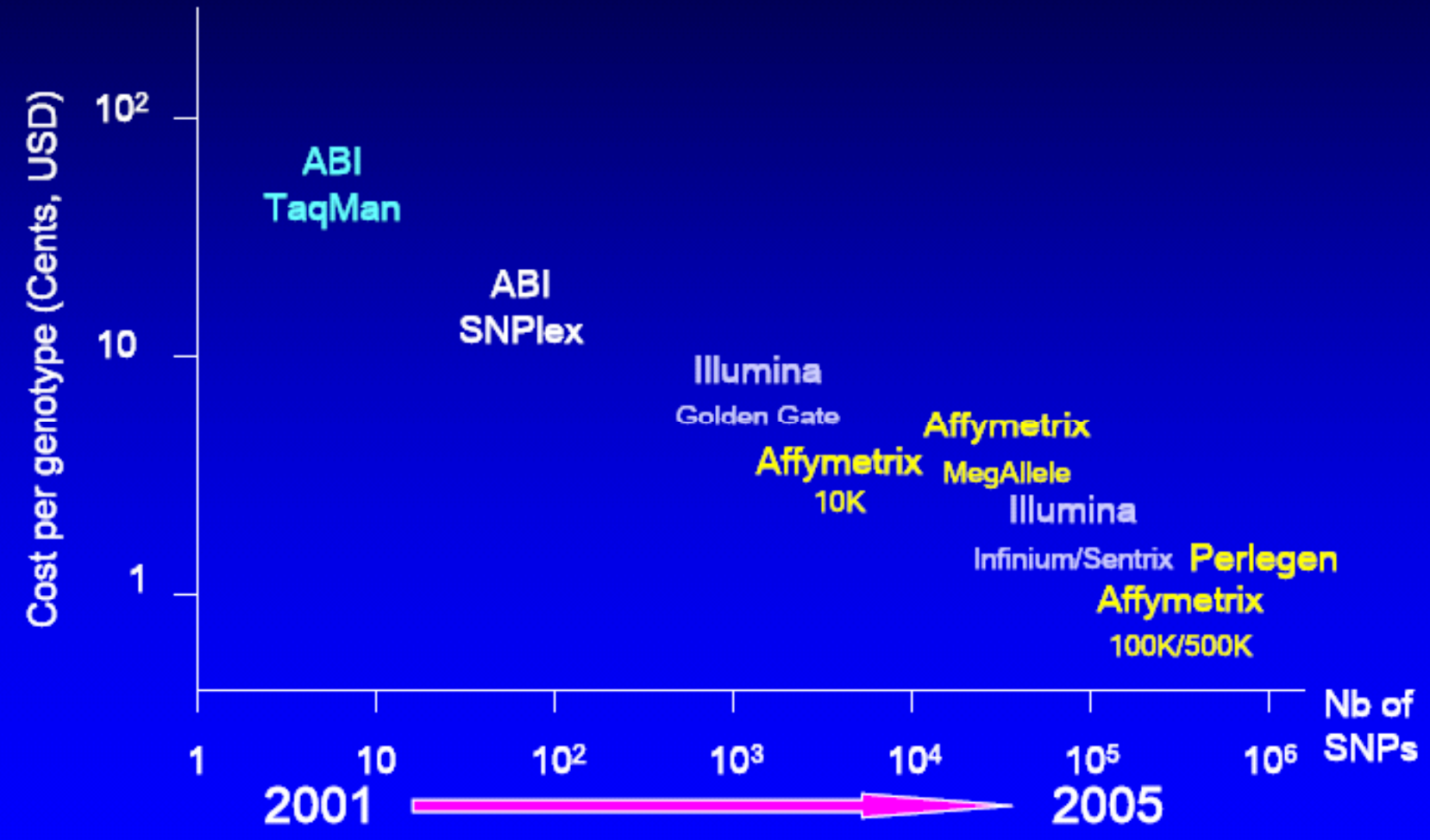
Interventions for hereditary cancer risk

Gene	Intervention
KIT	STI 571
RET	Thyroidectomy, adrenal screening;
MET	Renal screening
CDK4/CDKN2	Skin screening
APC	Colectomy, GI screening, CP
VHL	Renal, adrenal screening
RB	Eye screening
MSH2/MLH1	GI screening, colectomy
BRCA1/2	Breast/ovarian screening, CP, mastectomy,oophorectomy

Genome Wide Association Studies (GWAS)



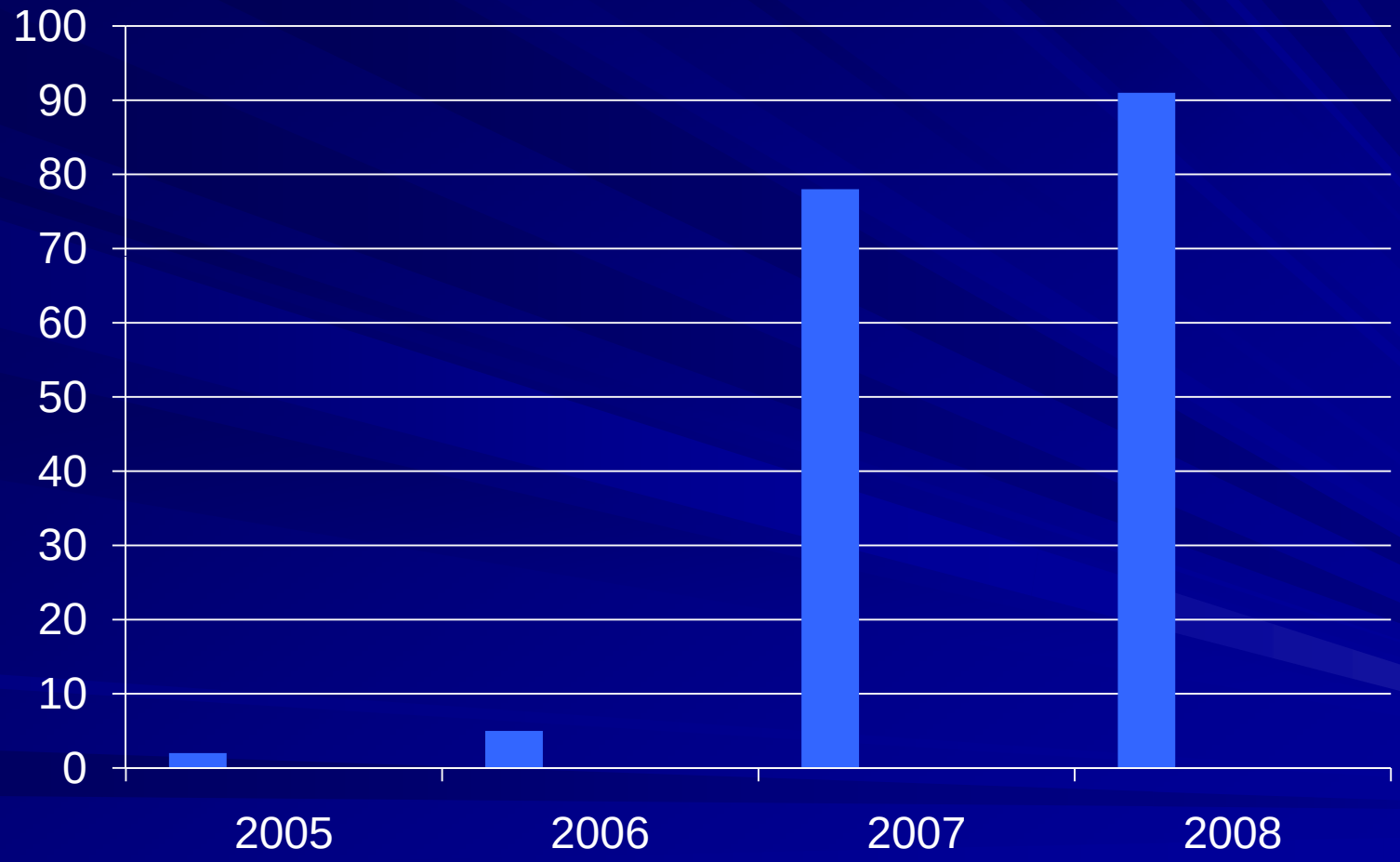
Progress in Genotyping Technology



Courtesy S. Chanock, NCI

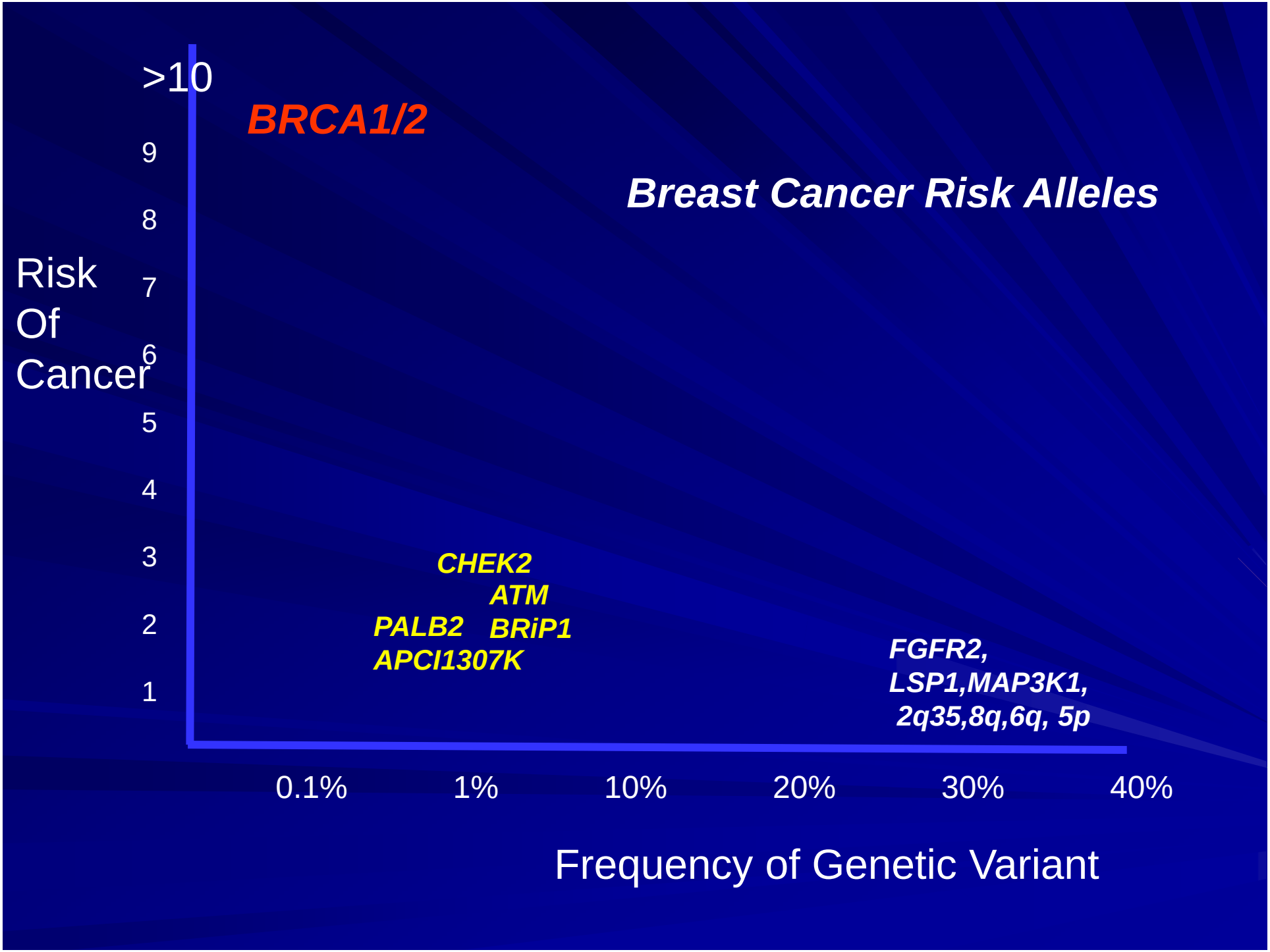
GWAS studies in NHGRI Catalogue

http://www.genome.gov/gwastudies/#top



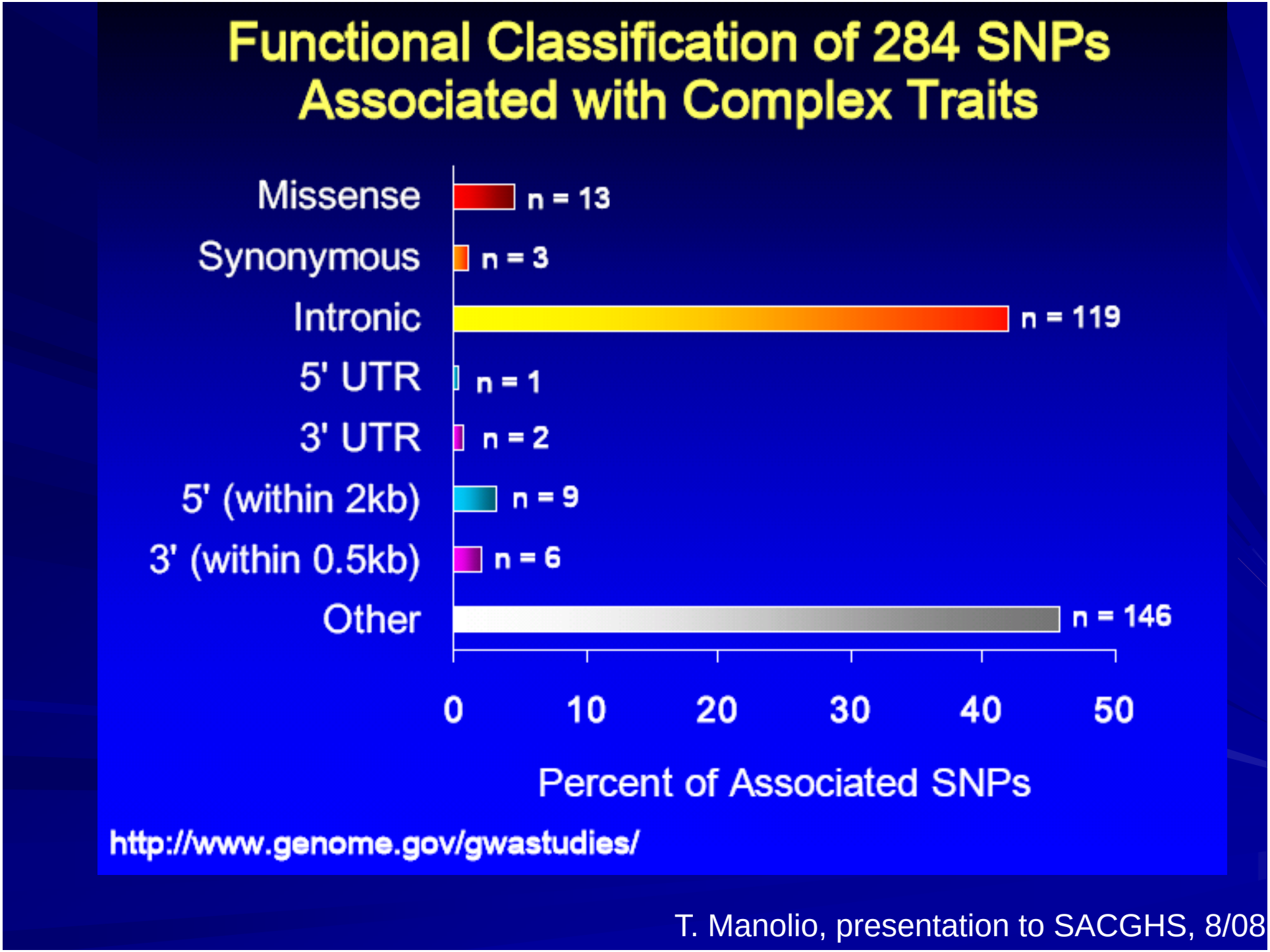
Breast Cancer
Whole Genome Association Studies

BCAC	~400 fam'l cases/controls	Perlegen 266K	***Nat Genet*** *2007*
	4,000 cases/controls	Illumina	*39:870*
	25,000 cases/controls	TaqMan/Sequenom	
MSKCC	250 fam'l cases/cont(AJ)	Affy500K	***PNAS*** *2008*
	2,000 cases/controls	Illumina	*105:4340*
	4,000 cases/controls	TaqMan	
Iceland	1,600 cases/11,563 controls	Illumina 300K	***Nat Genet 2007*** *9: 865*
CGEMS	1,142 cases/1,142 controls	Illumina 500K	***Nature*** 2007 447:1087

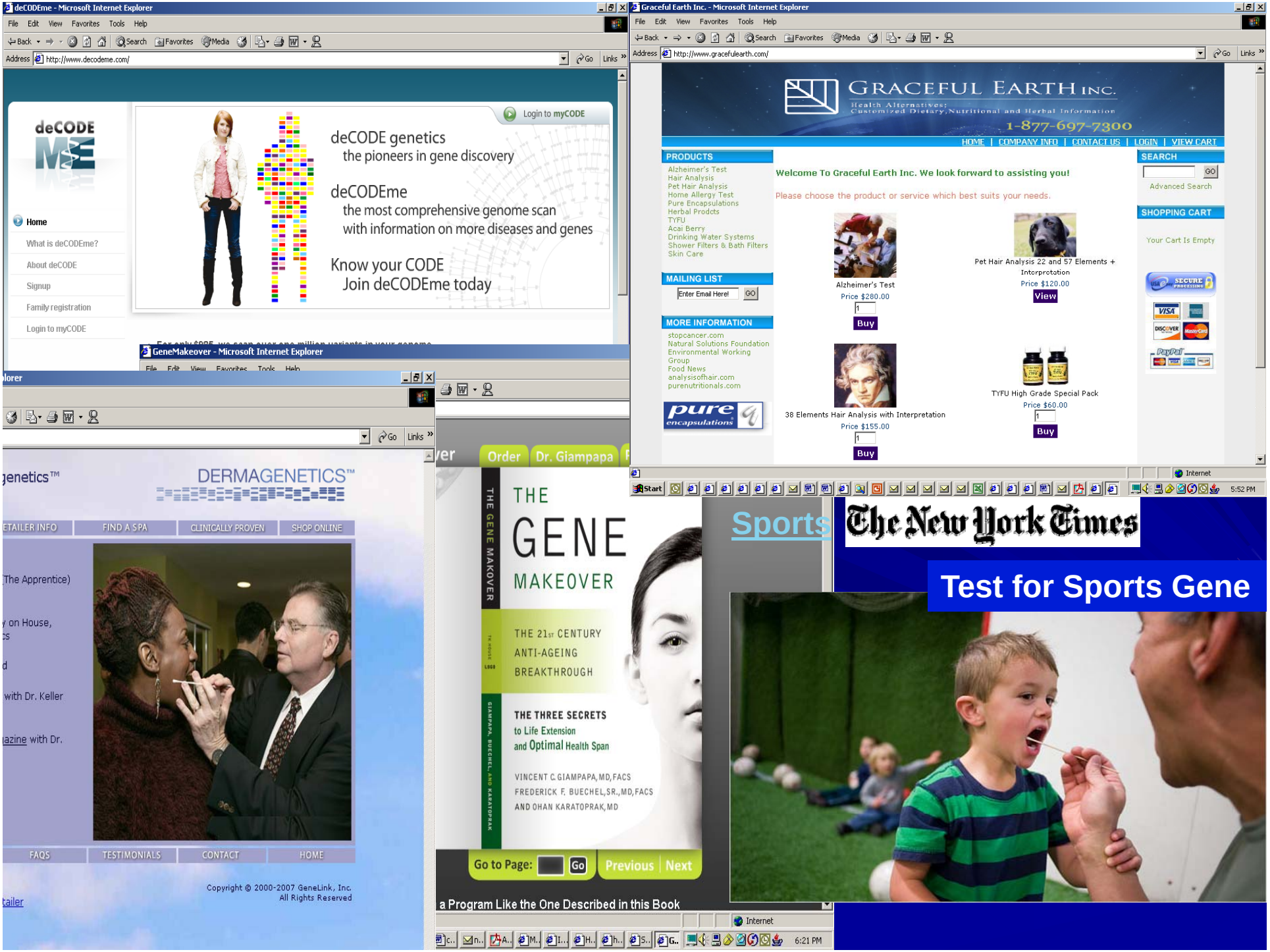

Breast Cancer Risk Alleles
Risk Of Cancer
>10
9
8
7
6
5
4
3
2
1
BRCA1/2
CHEK2
ATM
PALB2
BRiP1
APCI1307K
FGFR2,
LSP1,MAP3K1,
2q35,8q,6q, 5p
0.1%
1%
10%
20%
30%
40%
Frequency of Genetic Variant

Gene Associations with 6 common diseases

Disease	No. of studies	Cases / controls	Gene(s)	Odds ratios (95% CI)
Age-related macular degeneration	10	>5k/>3.4k	*8 genes*	Range 1.6-8.6 / or 0.36 protective
Diabetes II	11	~50k / >100k	*8 loci*	Range 1.09-2.50
Myocardial infarction	2	8.9k / 33.2/k	*CDKN2B*	Range 1.64-1.90
Schizophrenia	6	11.8k / 22.6k	*7 loci*	Range 1.12-6.01
Breast cancer	6	36.7k / 47.5k	*9 loci*	Range 1.07-1.41
Prostate cancer	8	>30k / >66k	*8q24 and other loci*	Range 1.10-1.36



T. Manolio, presentation to SACGHS, 8/08


deCODEme - Microsoft Internet Explorer
http://www.decodeme.com/
deCODE genetics
the pioneers in gene discovery
deCODEme
the most comprehensive genome scan
with information on more diseases and genes
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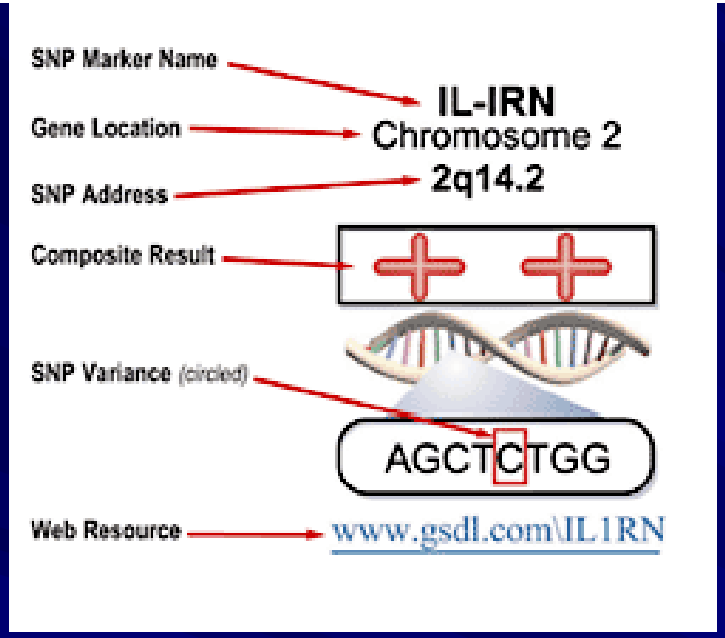
a Program Like the One Described in this Book
Sports
The New York Times
Test for Sports Gene

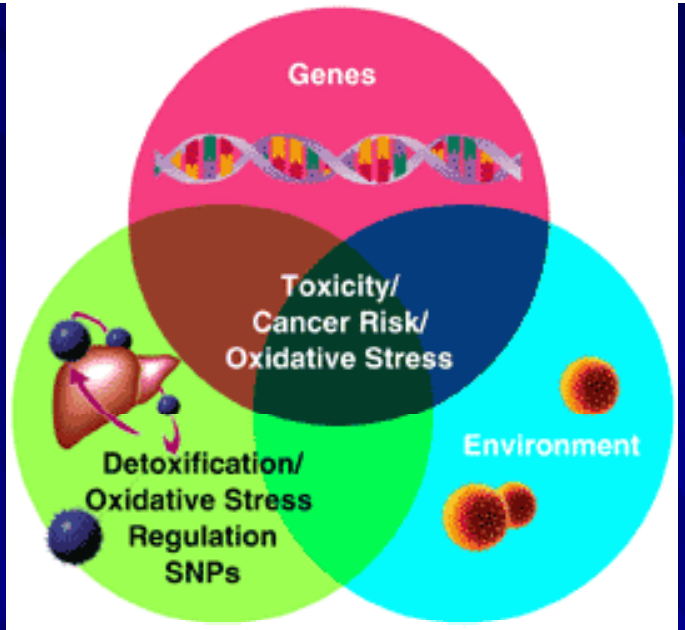
Genetics & Public Policy CENTER

Direct-to-Consumer Genetic Testing Companies

Genetic Testing Company	Personal Genome Service	Addiction	Alzheimer	Amyotrophic Lateral Sclerosis	Arthritis	Ashkenazi Jewish Screening	Asthma	Athletic Performance	Bipolar / Depression	Cancer	Cardiovascular Disease	Celiac Disease	Cystic Fibrosis	Drug Response	Eye / Hair Color	Fetal Gender	Fragile X Syndrome	Gastrointestinal Disease	Gaucher Disease	General Nutrition	Glaucoma / AMD	Graves' Disease	Hair Loss	Height	Hemochromatosis	HIV Resistance	Lupus	Infertility	Metabolic Health	Multipe Sclerosis	Narcolepsy	Neural Tube / Trisomies	OCD/ADHD	Osteoporosis / Bone Health	Parkinson's	Periodontal Disease	Psoriasis / Eczema	Recurrent Pregnancy Loss	Restless Legs Syndrome	Schizophrenia	Sickle Cell Disease	Skin Profile	Spinal Muscular Atrophy	Tay-Sachs Disease	Thrombosis	Type 1 / 2 Diabetes, Obesity
23andMe	X	X		X	X			X	X	X	X	X		X	X			X			X		X	X		X	X	X		X			X				X	X	X	X	X			X	X
Acu-gen Biolabs																X																														
BioMarker Pharmaceuticals	X	X	X		X		X	X	X	X	X	X			X			X			X	X		X			X			X				X	X	X			X						X
Consumer Genetics														X		X																														
CyGene Direct								X			X										X							X					X										X		
DeCODE	X		X		X		X			X	X	X						X			X		X		X				X					X			X		X				X	X
DNA Dimensions			X													X							X																						
DNA Direct	X					X				X			X	X					X						X			X									X					X	X	X
DNA Traits						X							X				X		X																					X		X	X	X	
Enterolab												X																																		
G-nostics		X																																											
Genelex											X	X		X						X					X						X			X		X								
GeneLink Biosciences											X									X														X							X				
Gene Partner																											X											X							
Graceful Earth			X																																										
Health Check USA												X													X																			X	
Holistic Health Consultants																				X																								
iGenix - Q Trait		X					X	X			X	X		X											X											X							X
Inneova								X		X	X			X																				X							X			X
Knome	X																																												
MediChecks						X				X			X				X		X						X															X		X	X	X	
My Genome			X								X			X																				X					X				X	
Navigenics	X		X		X					X	X	X						X			X	X							X							X		X					X
New Hope Medical			X		X		X		X	X	X							X		X								X					X		X				X		X	X	X
Niagen																X															X													
Proactive Genomics										X																																				
Psynomics									X																																					
Quixtar - Interleukin Genetics											X									X																									
Salugen		X																		X																									
Scientific Match																																						X								
Sciona								X			X																	X					X											
SeqWright	X		X	X	X					X	X							X			X								X									X					X
Smart Genetics			X																						X																			
Suracell											X																																		

- Genome Wide Association Studies
- "Personalized Medicine" hype
- Direct to Consumer Advertising
- Direct to Consumer Marketing/Home Tests
- Venture capital
- Internet
- Well intentioned basic geneticists





HEALTH IMPLICATIONS: Interleukin-1 receptor agonist (IL-1RA) is a naturally occurring competitive inhibitor of IL-1a and IL-1b-induced pro-inflammatory activity. A defect in the IL-1RA gene can contribute to a more prolonged and severe inflammatory response and has been associated with increased risk for chronic inflammatory conditions like atherosclerosis, osteoporosis, rheumatoid arthritis, lupus, colitis, and Crohn's disease. However, the IL-1RA SNP also confers benefit when fighting infections or cancer through amplified immune vigilance.

MINIMIZING RISKS: Eat a diet rich in anti-oxidants (colorful fruits and vegetables). Increase consumption of cold-water fish, like salmon, and reduce intake of vegetable oil and fatty meat.

Fish oil supplementation, silymarin (milk thistle) directly inhibit IL-1 production. Niacinamide and other anti-inflammatory botanicals like boswellia (frankincense), glycyrrhiza (licorice), and curcumin (tumeric) may mediate the pro-inflammatory effects of increased IL-1. Compounds in cannabis have also been shown to suppress IL-1 levels.

Corticosteroids and cyclosporin A inhibit IL-1 production but with significant immune suppression and numerous other side-

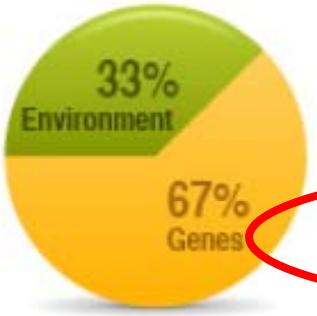
"I like to think I am pretty smart, but I am confused by this report"

-HHMxxxxxxSG, patient is a biostatistician and smoker, said after we told him to quit smoking…..

Summary

Macular degeneration

You: **3.4%**
Avg: **3.1%**



Your genetic markers

Gene or location	Risk marker	Your markers	Odds ratio	Source
LOC387715-S69A [1]	T	G G	1.0	American Journal of Human Genetics, 2005 [4]
CFH-intron [2]	A	A A	9.99	Nature Genetics, 2007 [5]
CFB [3]	T	T T	6.98	Nature Genetics, 2006 [6]

Gene or location: The place we looked on your genome.

Courtesy of Steven Murphy, MD

" Wow! My report said I was at low risk"
-HHxxxxxxES after reviewing her family history

Summary

Colon cancer

You: **4.3%**
Avg: **5%**

Causes: colon cancer

Your genetic markers

Gene or location	Risk marker	Your markers	Odds ratio	Source
8q24_R3 [1]	G	G T	1.04	Nature Genetics, 2007 [3]
SMAD7 [2]	A	G G	1.0	Nature Genetics, 2007 [4]

Gene or location: The place we looked on your genome.

Your estimated risk

We took the average risk for women and used your genetic markers to estimate your lifetime risk for colon cancer: 4.3 percent, or 43 out of 1,000.

Courtesy of Steven Murphy, MD

might be considered.

Colon cancer: Pending evaluation and a detailed family history, it may be appropriate to consider early colon screening. Also note, our panel does not cover certain important monogenic familial colon cancer syndromes such as HNPCC or FAP. We tell our members that they may be at greater risk than we have reported and should consult a Genetic Counselor if they answer "yes" to any of these questions:

- Have you or anyone in your family had colon cancer before the age of 50, or multiple colon polyps?
- Have two or more close relatives on the same side of your family (maternal or paternal) had colon, uterine or ovarian cancer, or has one relative had more than one of these cancers?
- Do you have Ashkenazi (Eastern European) Jewish ancestry and at least one family member with colon cancer at any age?
- Do you have any relatives with an identified genetic mutation that increases their risk for cancer?

•Have you or anyone in your family had colon cancer before the age of 50, or multiple colon polyps?

•Have two or more close relatives on the same side of your family (maternal or paternal) had colon, uterine or ovarian cancer, or has one relative had more than one of these cancers?

•Do you have Ashkenazi (Eastern European) Jewish ancestry and at least one family member with colon cancer at any age?

•Do you have any relatives with an identified genetic mutation that increases their risk for cancer?

Courtesy of Steven Murphy, MD

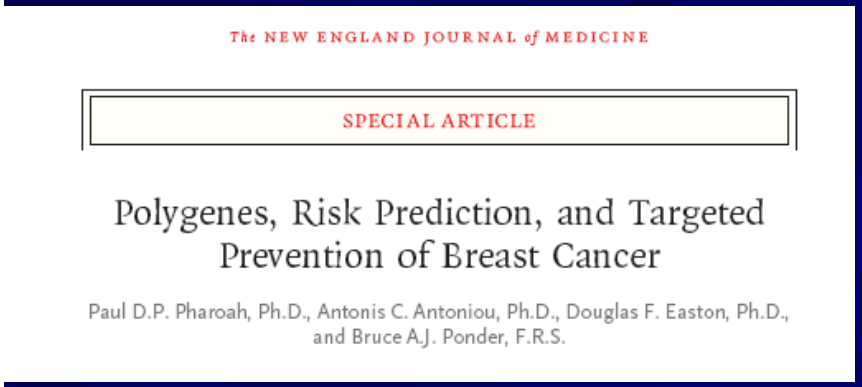
Brother with Colon Cancer at 54, Uncle with Sebaceomas died of a heart attack at 50, Father who died at 45 in a car crash.

MSH2 mutation carrier

Courtesy of Steven Murphy, MD

A 50 year old woman with an FGFR2 mutation comes for counseling….

Any Clinical Role For Breast SNPS?s

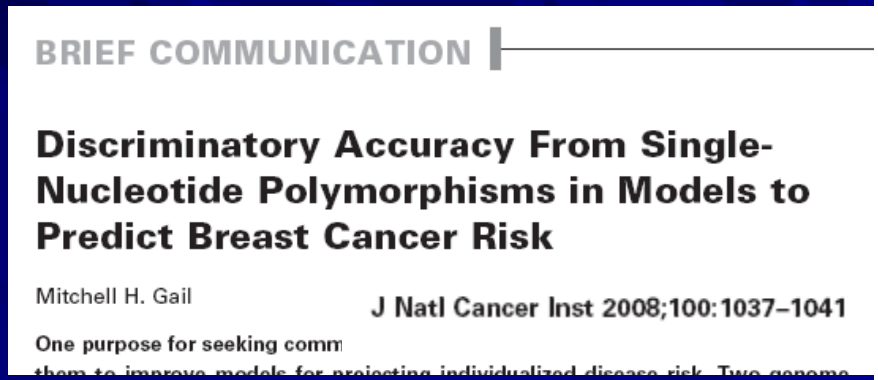


The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

Polygenes, Risk Prediction, and Targeted Prevention of Breast Cancer

Paul D.P. Pharoah, Ph.D., Antonis C. Antoniou, Ph.D., Douglas F. Easton, Ph.D., and Bruce A.J. Ponder, F.R.S.



BRIEF COMMUNICATION

Discriminatory Accuracy From Single-Nucleotide Polymorphisms in Models to Predict Breast Cancer Risk

Mitchell H. Gail

J Natl Cancer Inst 2008;100:1037–1041

One purpose for seeking comm

- MRI screening recommended in those with at hi risk (8% risk ages 40-50)
- With 7 loci, none hi risk, another 7 loci,
  3.5% population mod risk, none hi risk
- All possible loci: 2% population at hi risk
- With 7 loci , or 14 loci less discriminatory accuracy than clinical model (Gail2)
- Add 7 SNPs increase AUC by only 0.025

ARMD / adapted from David Ewing Duncan, 2008 http://oba.od.nih.gov/oba/SACGHS/meetings/july2008/Duncan.pdf

Trait	Gene	Marker	Risk	Source	Life Risk DED Ave
A	*PLEKHA1/ ARMS2*	rs932275	0.68	deCODEme	1.1%
R	*CFH*	rs1329428	0.20	deCODEme	8.0%
M	*CFH*	rs10737680	1.0	Navigenics	0.36% / 3.1%
D	*CFH*	rs1061147	0.34	23andMe	1.2%
	CFB	rs541862	6.98	Navigenics	?
	LOC387715	rs10490924	1.0	Navigenics	?
	LOC387715	rs3750847	0.46	23andMe	0.19%

sues/2008/nov-dec/cover-story-keeping-score-of-your-sequence.html?terms=davies

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Rival genetic tests leave buy... | Bio-IT World

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Keeping Score of Your Sequence

Twelve months after the debut of the first personal genomics services, Kevin Davies expectorates and explores the pros, cons and controversies of "23 et al."

By Kevin Davies

Nov. 12, 2008 | One year ago, Iceland's deCODE Genetics kicked off a new era in personalized genetics with the launch of a direct-to-consumer service dubbed deCODEme. A few days later, California's 23andMe debuted its own service with the slogan: "Genetics just got personal. Don't worry. We're here to help."

For less than $1000, deCODE and 23andMe offered customers the exciting opportunity to gander their unique genetic quirks and glitches, as revealed by the identities of more than 500,000 DNA markers (single nucleotide polymorphisms, or SNPs). Such services would have been unthinkable just two years ago, before the explosion of genome-wide association studies (GWAS) began pinpointing susceptibility genes for common, complex diseases such as cancer, heart disease, diabetes, and mental illness.

Some of the attraction of these web-based services is undoubtedly recreational—what's my haplogr
Do I have fast-twitch muscles? Am I a fast or slow caffeine metabolizer? Some people may be curiou

Internet | 100%

...at
...offer aggregate likelihood risks were in close agreement, but
...there were some intriguing disagreements. These could
...arise for a number of reasons, including different platforms
...and SNPs), statistical programs and criteria. For example:

- 23andMe reports a 50% increased risk for age-related macular degeneration based on three SNPs, but Navigenics and deCODEme indicate a lower than average risk.
- Navigenics reports a reduced risk of rheumatoid arthritis, contrary to deCODE and 23andMe.
- There is a wide discrepancy between the reported lifetime risks of abdominal aneurysm between deCODEme (17%) and Navigenics (3.1%).

...e publicity surrounding character traits earned 23andMe a "fri
...d Wojcicki reject. "We really applaud the fact that people are
...her than just their health," says Avey. "The ancestry work we d

...September 2008, 23andMe slashed the price of its service
...om $999 to a mere $399, using a second-generation Illumina

"There's a play' is bar dangerous

From The Sunday Times

September 7, 2008

Rival genetic tests leave buyers confused

Firms that offer to predict your risk of disease give worryingly varied results

Nic Fleming

Leading genetic testing companies are providing clients with widely divergent and inaccurate predictions of their chances of developing serious diseases. That is the finding from tests conducted by different firms on the same person.

Using my own DNA, I approached three firms who between them provide the majority of genetic tests for common diseases in the UK. They gave contradictory assessments of the risk I faced of developing illnesses, including Alzheimer's and glaucoma, and a confused verdict on my risk of suffering heart problems.

The findings reveal that those paying up to £825 for the tests may be receiving either misleading assurances that they face low heath risks or are being caused needless anxiety by warnings of high risks.

Lord Taverne, a member of a Lords select committee investigating genetic testing, said: "This [investigation] confirms that some of

MY PROFILE | SHOP

MOST READ | MOST COMME

TODAY

- Foreigners targeted in co-
- Europe's 20 best Christm
- Nicole Kidman drifts abou
- Pirate 'mothership' was re

TIMES RECOMMENDS

- Spike Milligan has the last laugh
- Pubs told to bring an end to happy hours
- Pianist's bequeathed skull stars in Hamlet

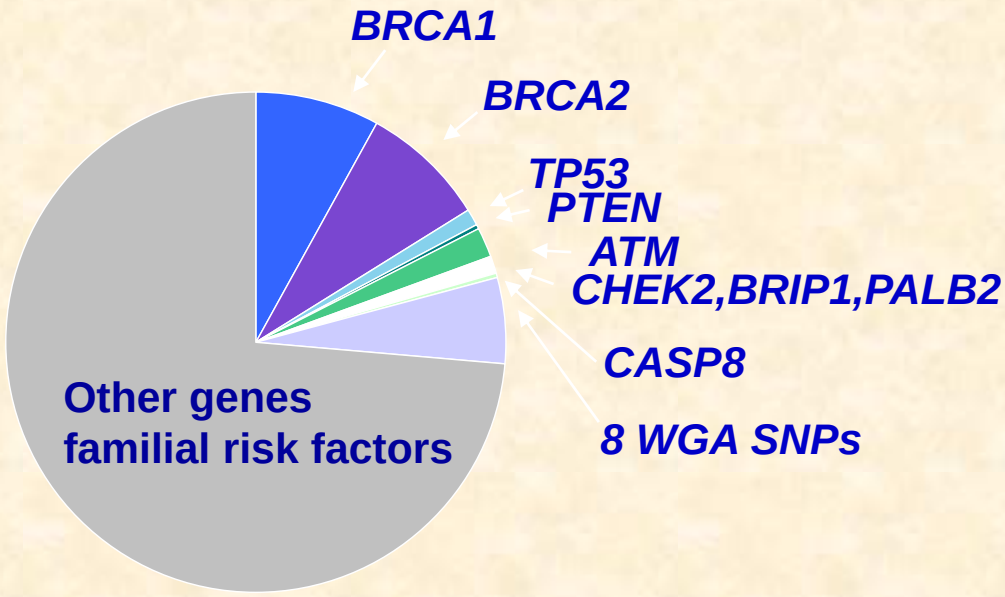
PARENT POWER

Barriers to Translation to Practice

- Underlying clinical research questions
  - Genetic heterogeneity
  - Variable penetrance;
  - Epistasis
  - Population heterogeneity
  - poor models
- Clinical Misinterpretation, Error and Injury
- Risk of Loss of Trust, Added Expense

Solutions?

The majority of familial risk for breast cancer is not yet accounted for



Doug Easton

Common and rare variants in multifactorial susceptibility to common diseases

Walter Bodmer & Carolina Bonilla

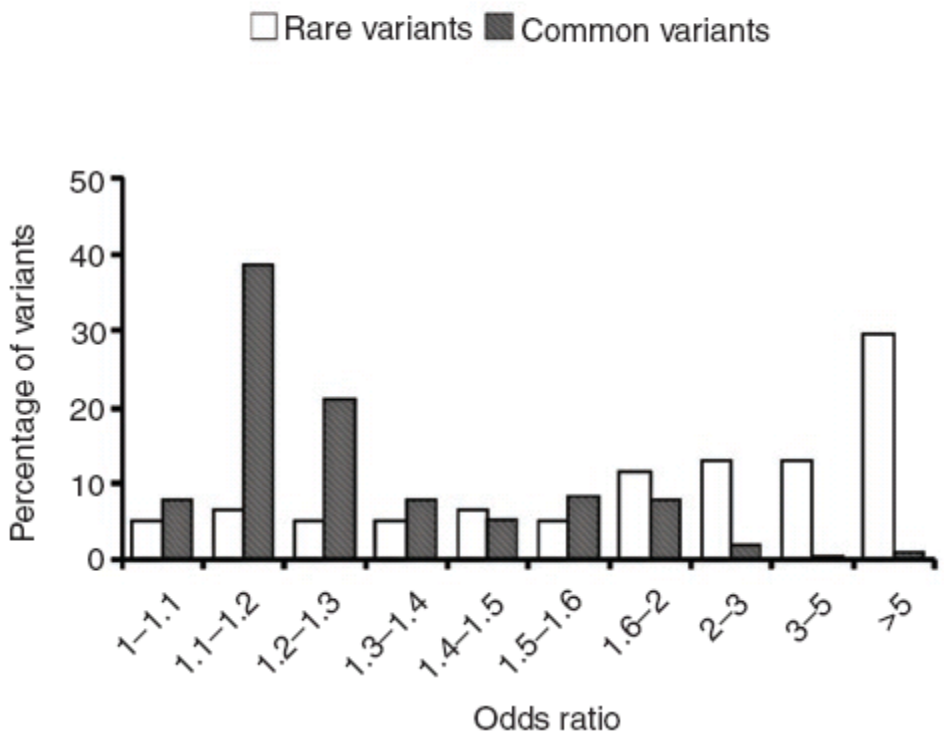
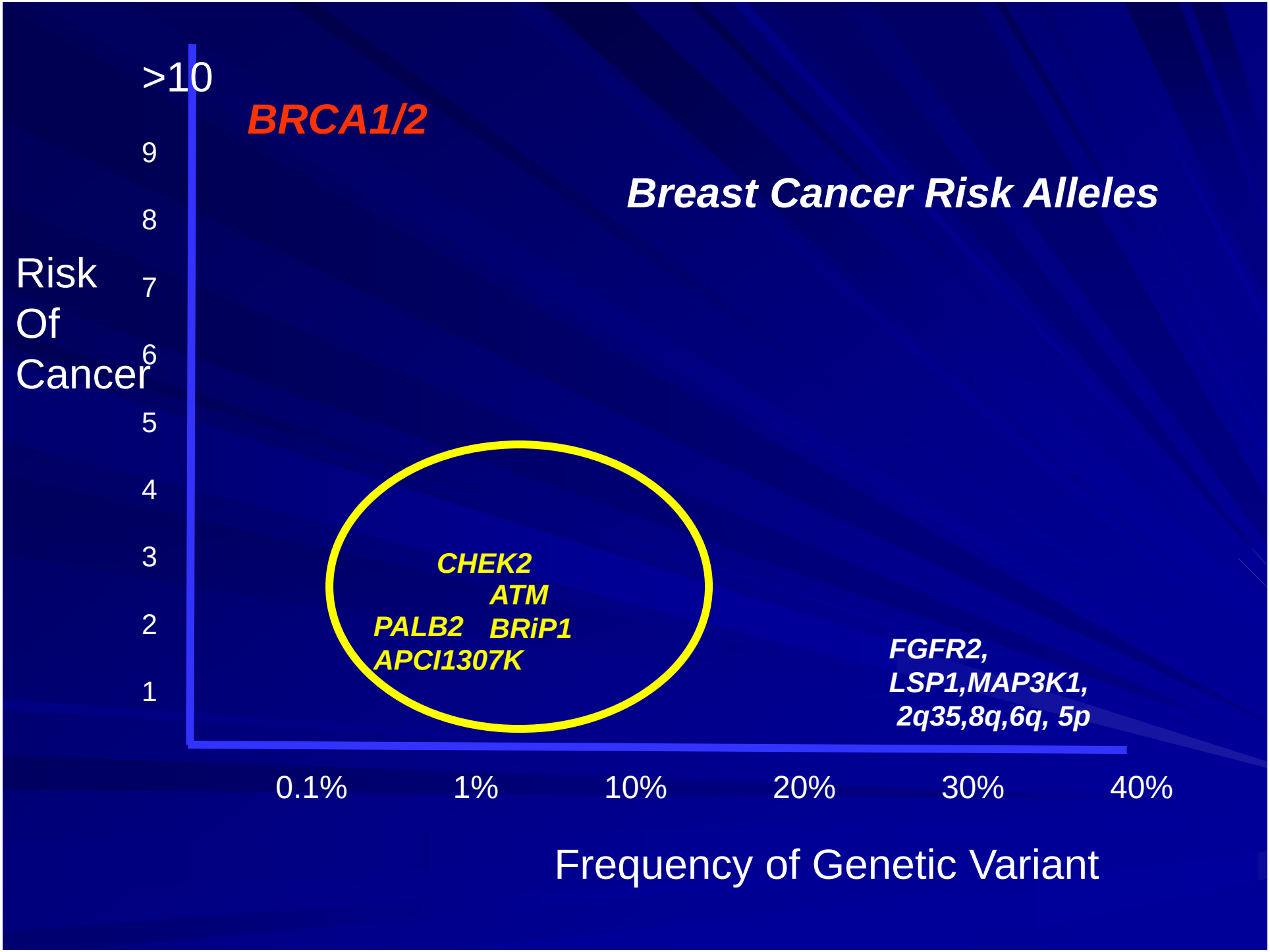


Figure 2 Distribution of odds ratios for common and rare variants. Odds ratios were obtained from the literature (**Supplementary Note**). We included 61 rare variants and 217 common variants in this analysis.


>10
9
8
7
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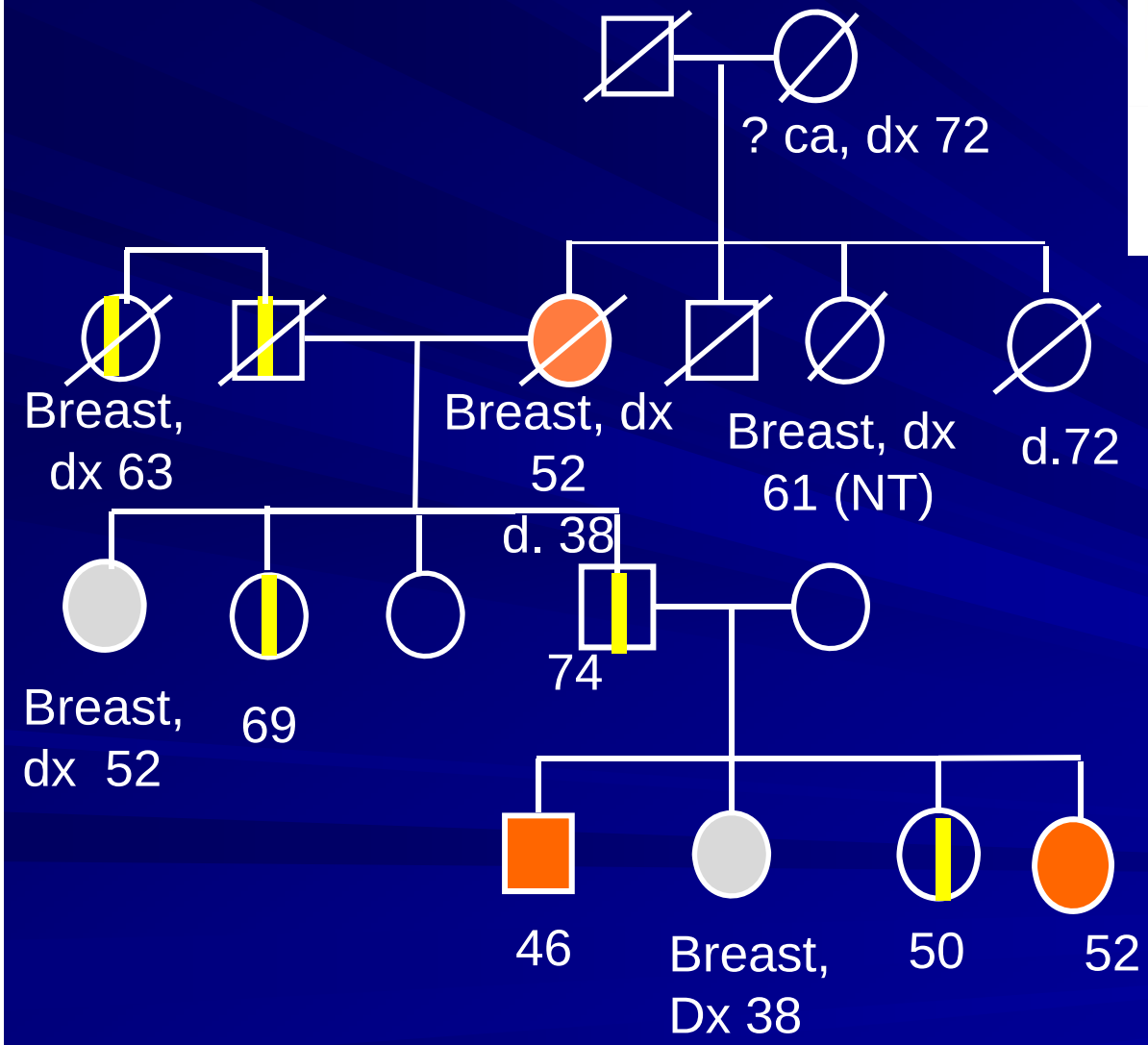
2
1
Risk Of Cancer
BRCA1/2
Breast Cancer Risk Alleles
CHEK2
ATM
PALB2
BRiP1
APCI1307K
FGFR2,
LSP1,MAP3K1,
2q35,8q,6q, 5p
0.1%
1%
10%
20%
30%
40%
Frequency of Genetic Variant

The Hazards of Using Low-Penetrance Variants



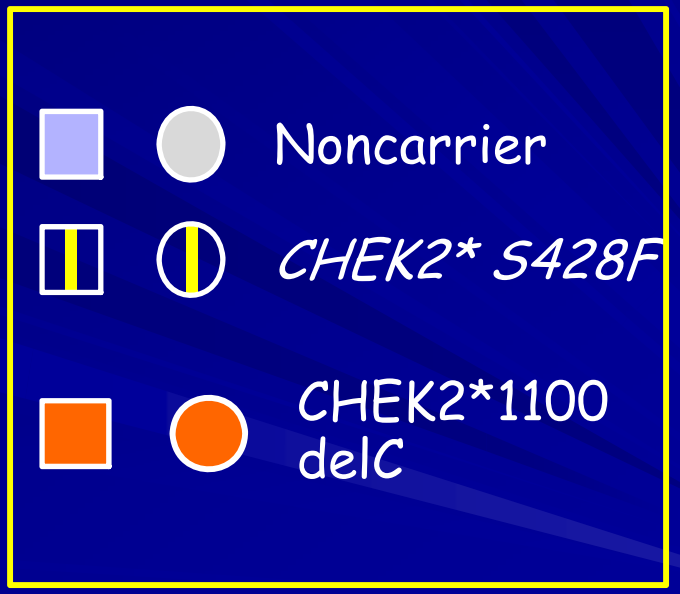

VOLUME 26 · NUMBER 4 · FEBRUARY 1 2008

JOURNAL OF CLINICAL ONCOLOGY | EDITORIAL

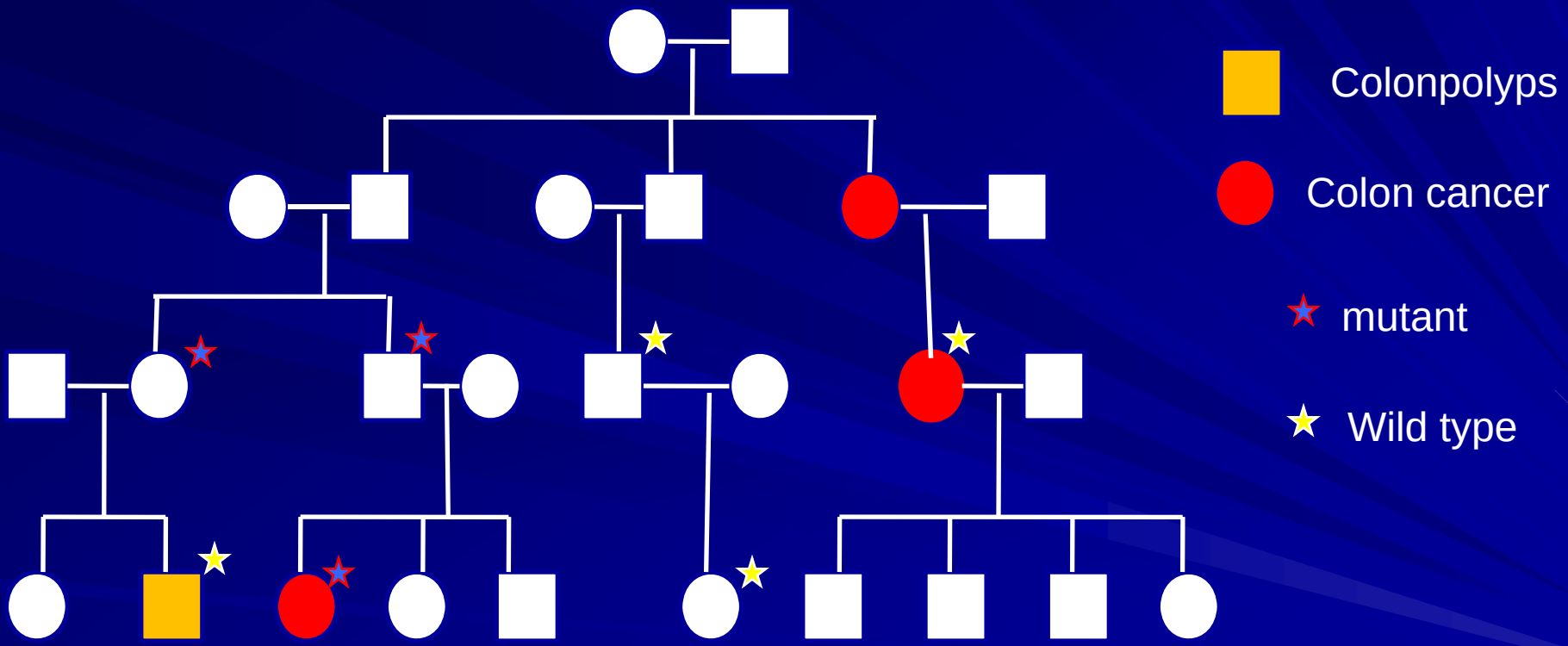
Time to Check *CHEK2* in Families With Breast Cancer?

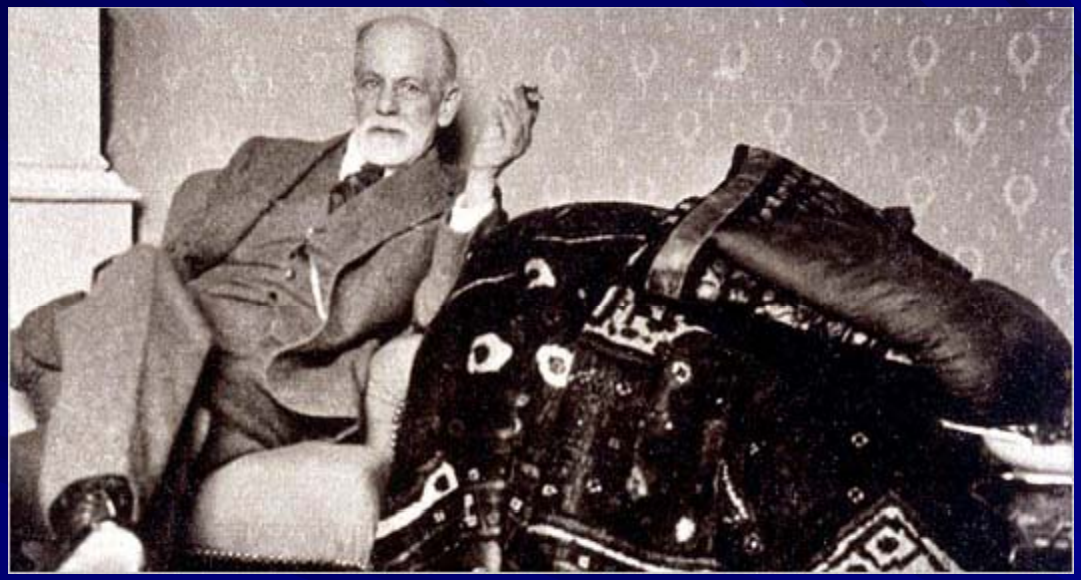
Kenneth Offit, *Memorial Sloan-Kettering Cancer Center, New York, NY*
Judy Ellen Garber, *Dana Farber Cancer Institute, Boston, MA*

CHEK2 (cell cycle checkpoint kinase 2) is an important player in cer in men and in colorectal and prostate cancers, but these have not



APC*I1307K (RR ~2) is not useful in clinical counseling





The absence of the regulating effect offered by the payment of a fee… makes itself very painfully felt….the patient s deprived of a strong motive…

Freud "On Beginning the Treatment"
1913

Barriers to Translation to Practice

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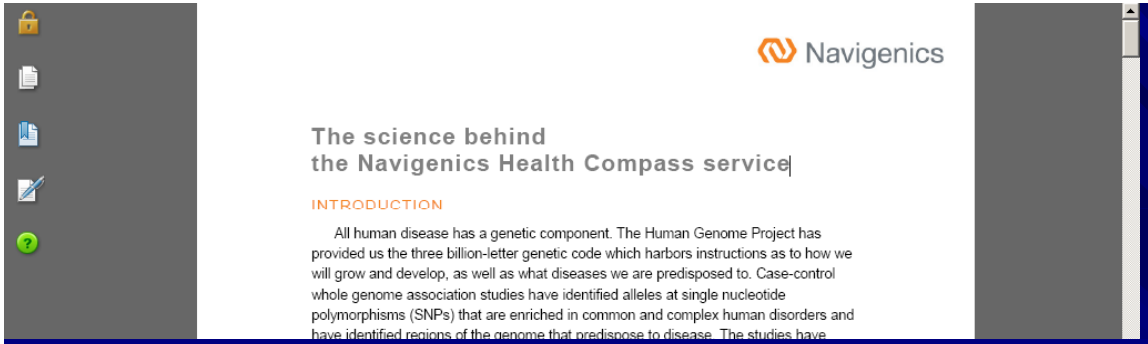
Solutions?



The Models

- Average population risk (SEER for cancer, ?? other acute or chronic diseases)
- Adjust risk up or down depending on the individual's constellation of risk factors
- Need relative risks, can use large, well designed case-control study, assume risk factors act multiplicatively (i.e. independently)
- Mathematical energy spent converting OR to RR unnecessary
- Distinguish controls who will get the disease from those who won't? All controls at risk of the disease; appropriate incidence density sampling takes all this into account.
- Real validity threats:

  underlying population average risks difficult to ascertain (except for cancer)

  quality aspects: (e.g. how the subjects were ascertained, how controls were selected, participation rates, publication bias etc. etc.) of any case-control data they might use.

Technical method for obtaining risk is less crucial than the analytic biases that may intrude due to selectivity of published studies, multiple comparisons, poor quality study design, etc.

Barriers to Translation to Practice

- Underlying clinical research questions
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Solutions?

Table 3 Type and frequency of laboratory errors

Test phase	Error	Percent of directors that reported detecting this type of error during the past two years	"Which was the most common type of error over the past 2 years?"
Pre-analytic errors	Referrer ordered incorrect test	74	27
	Referrer labeled specimen incorrectly	68	10
	Contamination before receipt by laboratory	19	4
	Transcription error at specimen receipt	32	2
	Sample switch at specimen receipt	16	2
	Error in written protocol	7	1
	Patient's transfusion not reported by referrer	13	0
	Total pre-analytic		45
Analytic errors	Faulty reagent	52	13
	Equipment failure	52	11
	Human error in data analysis	44	3
	Contamination during specimen testing	18	2
	Sample switch during specimen testing	27	1
	Total analytic		30
Post-analytic errors	Typographical error on test report	55	17
	Data transcription error	42	5
	Misinterpretation of data	19	1
	Wrong results reported to patient/provider	20	1
	Software error in data analysis	8	0
	Total post-analytic		24
Other	Other	4	1

Analytic Validity

190 Genetic testing labs surveyed in 2006

	23andMe					deCODEme					Navi-xgenics				
	Odds	Gene	SNP	Geno-type	OR (Eur)	Odds	Gene	SNP	Geno-type	RR	Odds	Gene	SNP	Geno-type	OR
Age-Related Macular Degen.	11.3/100 Vs 7/100	CFH C2 ARMS2	rs1061147 rs547154 rs3750847	AC GG CT	0.97 1.07 1.63	6.4% Vs 8.0%	CFH ARMS2	rs1329428 rs932275	AG AG	0.63 1.26	3.0 Vs 3.1%	LOC387715 CFH CFB	rs10490924 rs10737680 rs541862	TG CA TT	2.72 3.16 6.98
Prostate Cancer	25.9/100 Vs 17,8/100	8q24 17q24 TCF2	rs1447295 rs6983267 rs10505483 rs1859962 rs4430796	CC GT CT GG AG	0.95 1.01 1.48 1.2 0.94	19.7% Vs 16%	MSMB POU5F1P1 TCF2 8 11 8 17 2 X	rs10993994 rs6983267 rs4430796 rs10505483 rs10896449 rs1447295 rs1859962 rs2710646 rs5945572	CC GT AG AG– AG CC GG CC G	0.83 0.99 0.99 1.59 0.98 0.91 1.21 0.95 0.93	28% Vs 17%	8q24 8q24 8q24 17q24	rs16901979 rs4242384 rs6983267 rs17765344	CA AA GT AA	1.79 1 1.26 1.45
Abdominal aneurysm	N/A		rs10757278	AG	Typi-cal	22.3% Vs 17%	CDKN2A/B	rs10116277	TT	1.31	3.1% Vs 3.1%	9p21	rs1333049	CG	1.36
Rheumatoid arthritis	5.4/100 Vs 42/100	HLA PADI4 PTPN22 MMEL1 6q23 TRAF1	rs6457617 rs11203366 rs2476601 rs3890745 rs2327832 rs3761847	TT AG GG CT AA AG	1.96 N/A 0.79 0.92 0.93 0.97	2.2% Vs 1.0%	HLADRB1 IL2 PTPN22 RA-6q23 STAT4 TRAF1-C5	rs660895 rs6822844 rs2476601 rs2327832 rs13192841 rs7574865 rs3761847	GG GT GG AA AA GG AG	5.45 0.8 0.89 0.62 0.87 1.03	1.5% Vs 1.6%	MHC PTPN22 Chr 6 Chr 6	rs6457617 rs6679677 rs13207033 rs6920220	TT CC AA GG	5.21 1 1 1

Why the Difference in AMD risk in the various Labs?

- 1. Differences in SNPs genotyped, which is the baseline at which the calculations start; most important SNPs are on chr. 1, chr10, chr. 6, and chr. 19.

- 2. Differences in the choice of SNPs to analyze, which can be driven by
  - a. Decision to include or exclude a whole locus (such as complement B and ApoE in AMD, which DeCode ignores)
  - b. Decision of which SNP or SNPs should be use to tag a locus, as different studies report different SNPs and haplotypes all in LD with each other
  - c. patenting and licensing considerations??

- 3. Differences in the choice of odds ratio from the literature for a given tag SNP/haplotype, and how to convert the odds ratio into a relative risk versus the average person.

Why Different Results?

- Different SNPs/studies used
- Different methods for determining SNP risk
  - deCodeme: Relative Risk
  - 23andme and Navigenics: odds ratios
- Different methods for determining combined SNPs risk/lifetime risk
- Reliance on correlative SNPs

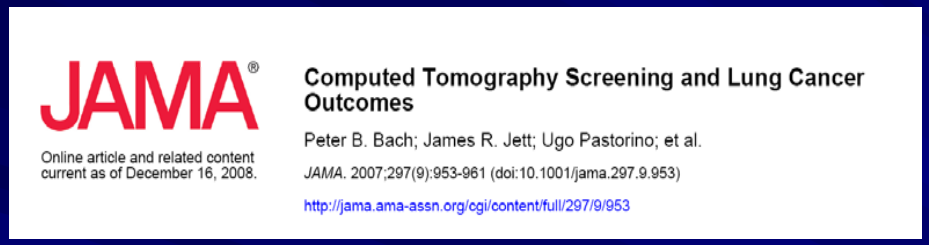
End Result: head scratching, what does it mean?

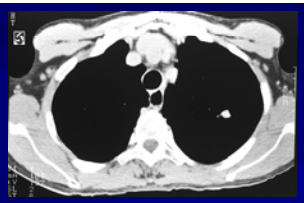
David Ewing Duncan, testimony to SACGHTS 8/08

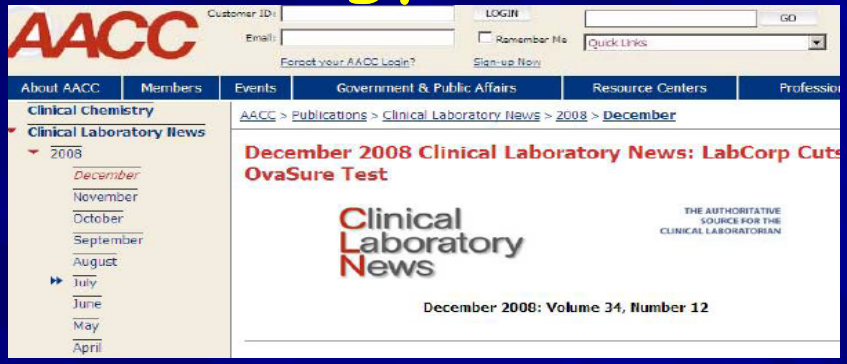
Direct to Consumer Marketing of Research Based Testing

- Can lead to :
  - Uninformed decisions
  - Inconsistent informed consent, appropriate education, or support
  - May not have appropriate result interpretation
  - Negative test does not always mean patient will be cancer free

Examples of dilemmas caused by premature translation of preventive technologies in oncology







Lung cancer screening increased diagnoses and surgeries, but had no impact on mortality

Ovasure tested 6 proteins in blood (incl CA 125) to screen for ovarian cancer In Sept. 2008 warning letter, the FDA identified OvaSure as a device under section 201(h) of the Food, Drug, and Cosmetic Act intended for diagnosing or treating disease, and therefore requiring marketing clearance or approval from the agency. "Because you do not have marketing clearance or approval from the FDA, marketing OvaSure is in violation of the law."

COMMENTARIES

JAMA

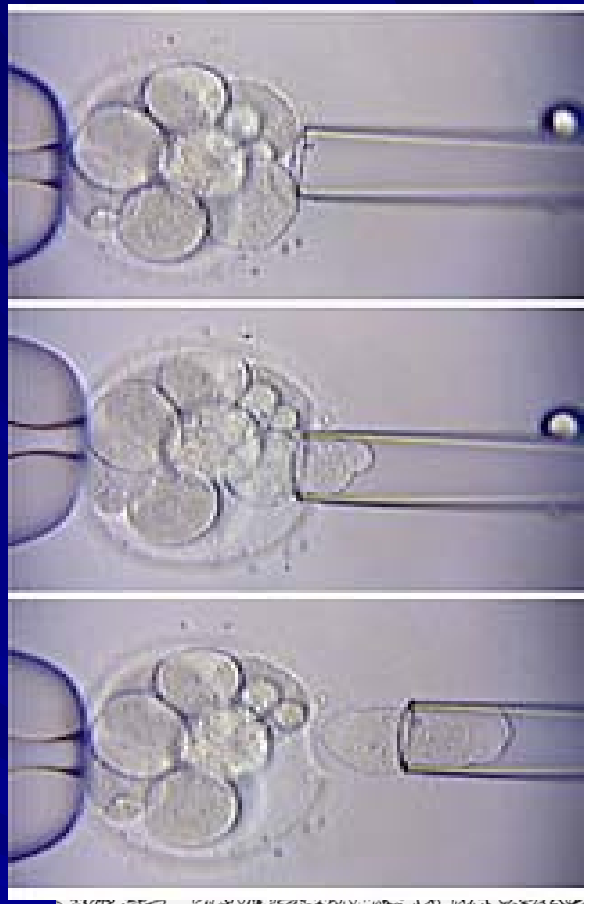
Preimplantation Genetic Diagnosis for Cancer Syndromes

A New Challenge for Preventive Medicine

Kenneth Offit, MD, MPH
Michal Sagi, PhD
Karen Hurley, PhD

with their physicians and genetic counselors the option of genetic testing to guide reproductive choices.

Types of ART



The New York Times

New Yo
warmer,
cloudy, l
high 79.
Weather

NEW YORK, SUNDAY, SEPTEMBER 3, 2006

Couples Cull Embryos to Halt Heritage of Cancer

By AMY HARMON

THE DNA AGE
Choosing Genes

As Chad Kingsbury watches his daughter playing in the sandbox behind their suburban Chicago house, the thought that has flashed through his mind a million times in her two years of life comes again: Chloe will never be sick.

Not, at least, with the inherited form of colon cancer that has devastated his family, killing his mother, her father and her two brothers, and that he too may face because of a genetic mutation that makes him unusually susceptible.

by the near certainty that diseases like cystic fibrosis and sickle cell anemia will afflict the children who carry the genetic mutation that causes them. The procedure has also been used to avoid passing on Huntington's disease, a severe neurological disease that typically does not surface until middle age but spares no one who carries the mutation that causes it.

Couples like the Kingsburys, by

rial Sloan-Kettering in New York start to suggest the possibility of P.G.D., more young patients are finding that their answer lies in trading natural conception for the degree of scientific control offered by the procedure. And if the growing interest in screening for cancer risk signals an expanded tolerance for genetic selection, geneticists and fertility experts say it may well be accompanied by the greater use of preimplantation diagnosis to select for characteristics that range from less serious diseases to purely matters of preference.

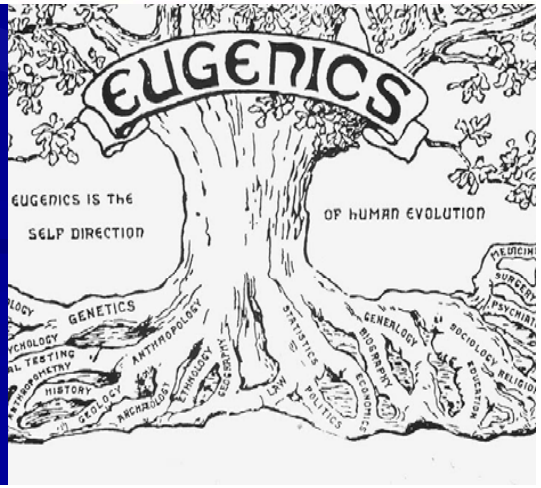
Already, it is possible to test em-

relies largely on decidedly
measures to confront th
posed by explosives at airp
ticularly at checkpoints.

Members of Congress ar
domestic security officia
poor management for stum
search, turf fights, staff tur
underfinancing. Some
have also faced opposition
airlines or been slowed b
cratic snarls. Among the tr
delayed efforts are the follo

¶The agency conducted
year that members of Con
a former Homeland Securit
ment official called "disast
"stupid" because the agenc
tested the smaller, cheaper
screening device in the way
tended to be used.

¶After spending years a
document scanner that w



JOBNAME: JAMA XML PAGE: 1 SESS: 2 OUTPUT: Mon Feb 18 12:22:44 2008
/jama/08jobs/weekly/19mar08/jco80016

COMMENTARY

Genomic Profiles for Disease Risk

Predictive or Premature?

Kenneth Offit, MD, MPH

THERE HAS BEEN A RECENT EXPLOSION OF COMMERcial availability of genomic "tests" for diseases, conditions, traits, and ancestry. Dozens of companies

files seems to have escaped the careful vetting that accompanies the introduction of new biomedical technologies. Unlike the new harvest of genomic panels, *BRCA* testing and other cancer predisposition tests have been subject to a decade of prospective study and validation, physician

How to do it better for our patients?

Regulation of DTC Genomic Testing is a vital first step but not enough….

The role of Prospective Registries/Cohorts

- Then:
  - Federally sponsored CFR's, CGN
  - High penetrance; short f/u; endpoints
- Now:
  - Private public partnerships
  - Large epidemiologic studies
  - Low penetrance; behavioral/cost endpoints
  - Appropriately powered design
  - Independent scientific leadership
  - Must involve/educate health care community!

SACGHS, April 2008

- Centers for Medicare & Medicaid Services: require proficiency testing (PT)
- FDA: address all laboratory tests, regardless of how they are produced
- HHS: fund a mandatory, publicly available, Web-based registry for lab tests.
- HHS: fund a public-private partnership to evaluate clinical utility of genetic tests
- HHS: education or training deficiencies; FDA: guidance on regulation of clinical decision support systems.

Primum non nocere

- "Outcomes of testing have not been studied. These tests may have no effect on health, or may have beneficial or harmful effects."

JAMA, December 10, 2008—Vol 300, No. 22

With gratitude to colleagues at Memorial Sloan-Kettering Cancer Center, University of Cambridge, Broad Institute, the National Cancer Institute for helpful discussions; views expressed are my own and not those of any institution, or organization with who I am affiliated including EGAPP (CDC), ASCO, and the Coriell Personalized Medicine Collaborative.