Cancer Risk Prediction Models Workshop

Division of Cancer Control & Population Sciences

Current Population Resources for the Development and Validation of Cancer Risk and Susceptibility Prediction Models

Daniela Seminara, PhD, MPH

Epidemiology and Genetics Research Program

Role of Extramural NCI

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- Assessing needs
- Providing resources (NCI Bypass budget 2005)
- Facilitating and expediting research implementation and translational process
- Coordinating availability and knowledge dissemination

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Cancer Risk Prediction and Susceptibility Models: Goals (I)

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1. Extension/refinement of models currently in use to better define at-risk populations by incorporating data on

- multiple genes
- low penetrance polymorphisms
- precursor lesions (i.e. polyps,DCIS)
- genetic/bio markers (i.e. MSI)
- pathology information(i.e.ER)
- treatment/preventive intervention

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Cancer Risk Prediction and Susceptibility Models: Goals (II)

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2. Development of new models
   - more precise/accurate models for common cancers
   - "de novo" models for rare cancers or familial syndromes

3. Validation of existing models
   - Compare prediction of same model in different populations
   - Compare predictions from various models in the same data set

4. Applications
   - Benefit to patients
   - Rapid dissemination of new knowledge to clinicians, scientists and policy makers

Some Limitations of Current Data Sets

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- Limited data on racial/ethnic groups
- Lack of prospective data on environmental risk factor
- Missing data on risk factors
- Incomplete genetic profile
- Accuracy of FH
- Sensitivity of mutation detection methods

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Research Projects Supported

- DCCPS
  - 872 active grants
  - $374,000,000
    - EGRP
      - 410 active projects
      - $199,000,000

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EGRP- Supported Epidemiology Consortia

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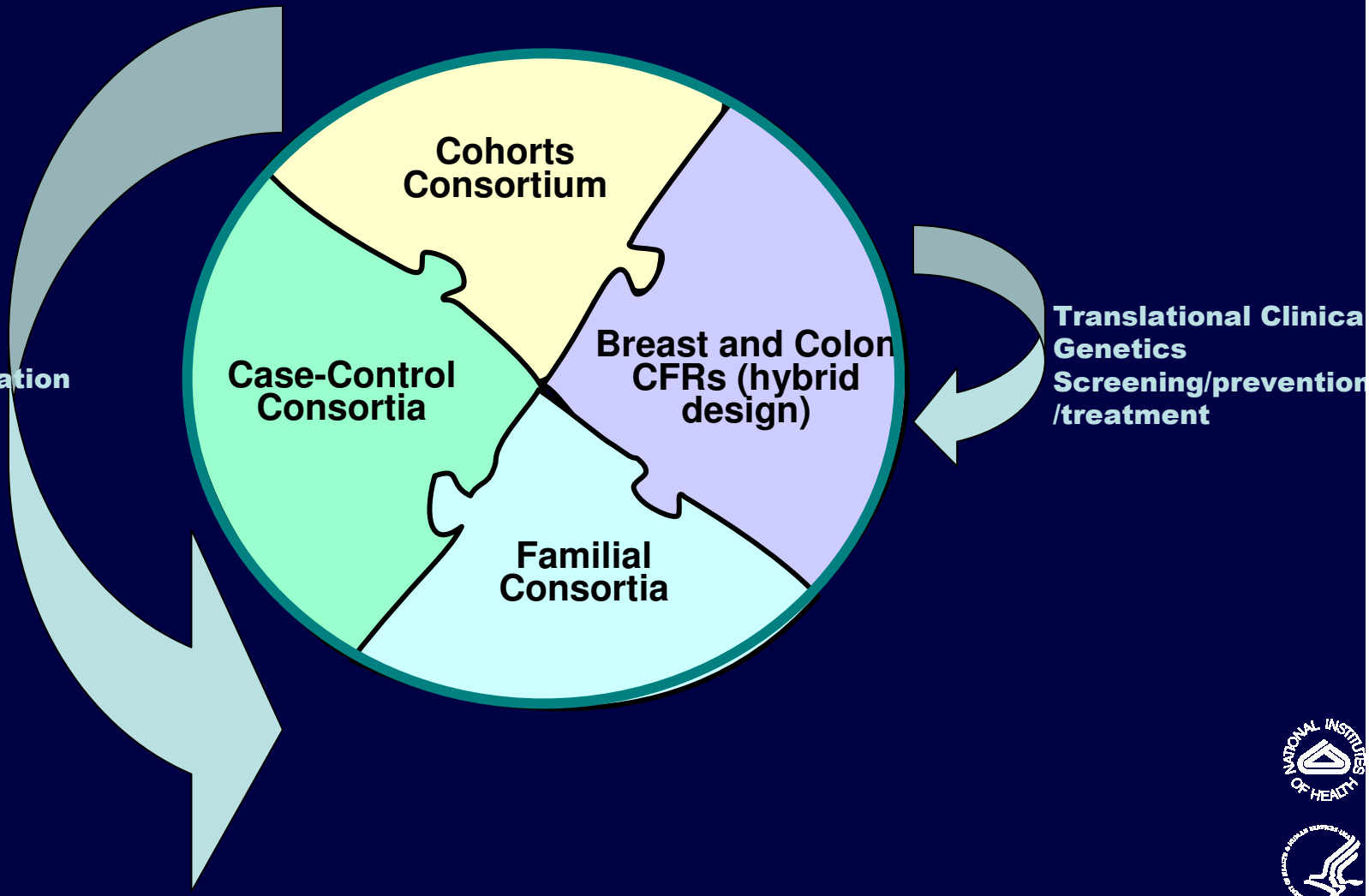

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Research Infrastructures Hybrid Design

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- The Breast and Colon Cancer Family Registries*

http://epi.grants.cancer.gov/CFR/

Contact: Daniela Seminara, seminard@mail.nih.gov

- The Cancer Genetics Network (All cancer sites)**

http://epi.grants.cancer.gov/CGN/

Contact: Carol Kasten-Sportes, kastenca@mail.nih.gov

*Family, case-control and hybrid designs

** Screening, clinical trials

Case-Control Consortia

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- Interlymph (lymphomas)
- Molecular Epidemiology of Colorectal Cancer (MECC)
- International Lung Cancer Consortium ★
- Head and Neck Cancer Consortium ★
- International Melanoma Consortium (case-control component)
- Brain Tumors Consortium ★
- Genetic Epidemiology of Melanoma (GEM)
- Breast Cancer, Radiation Exposure and Cancer Susceptibility Genes (WE CARE)

★ Newly formed

Information: http://epi.grants.cancer.gov/Consortia/casecontrol.html

Familial Consortia (Clinics)

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- Genetic Epidemiology of Lung Cancer (GELC)
- International Melanoma Consortium (familial component)
- International Consortium on Prostate Cancer Genetics (ICPCG)
- Pancreatic Cancer Genetic Epidemiology Network (PACGEN)
- Chronic Lymphocytic Leukemia Familial Consortium
- Multiple Myeloma Familial Consortium ★
- Lymphoprolypherative Cancers Familial Consortium ★

★ Newly formed

Contact: Daniela Seminara, seminard@mail.nih.gov

Large Cohorts Supported by EGRP (I)

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Black Women's Cohort: A Follow-up Study for Causes of Illness in Black Women
Lynn Rosenberg, Sc.D., Boston University

Breast Cancer Prognostic Factors/Pathobiology
Kathleen Malone, Ph.D.
Fred Hutchinson Cancer Research Center

California Teachers Study: Breast and Other Cancers in the California Teachers' Cohort
Ronald Ross, M.D., University of Southern California/Norris Comprehensive Cancer Center

Cancer in American Natives: A Prospective Study of Alaska Natives and American Indians
Martha Slattery, Ph.D., University of Utah
Anne Lanier, M.D., M.P.H., Alaska Native Tribal Health Consortium
Jeffrey Henderson, M.D., M.P.H., Black Hills Center for American Indian Health

Health Professionals Follow-up Study: Prospective Studies of Diet and Cancer in Men and Women
Walter Willett, M.D., M.P.H., Dr.P.H., Harvard School of Public Health

Iowa Women's Health Study: Epidemiology of Cancer in a Cohort of Older Women
Aaron Folsom, M.D., M.P.H., University of Minnesota

Multiethnic/Minority
Laurence Kolonel, M.D., Ph.D., Cancer Research Center of Hawaii

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Large Cohorts Supported by EGRP (II)

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Nurses' Health Study I
Graham Colditz, Dr.P.H., M.D., Harvard School of Medicine

Nurses' Health Study II
Walter Willett, M.D.,M.P.H., Dr.P.H., Harvard School of Public Health

Prospective Study of Breast Cancer Survivorship
Lawrence Kushi, Sc.D.
Kaiser Permanente

Seventh-day Adventist Cohort Study: Cancer Epidemiology in Adventists - A Low Risk Group
Gary Fraser, M.B.Ch.B., Ph.D., M.P.H., Loma Linda University

Singapore Cohort Study of Diet and Cancer
Mimi Yu, Ph.D., University of Southern California/Norris Comprehensive Cancer Center

Southern Community Cohort Study
William Blot, Ph.D., Vanderbilt University and International Epidemiology Institute, Ltd.

VITAL Vitamins and Lifestyle Study: Cohort Study of Dietary Supplements and Cancer Risk
Emily White, Ph.D., Fred Hutchinson Cancer Research Center

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Current EGRP-Supported Cohort Studies

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http://epi.grants.cancer.gov/ResPort/cohorts.html

Contact: Sandra Melnick, melnicks@mail.nih.gov

Consortium of Cohorts (Co-Co)

http://epi.grants.cancer.gov/Consortia/cohort.html

Contact: Edward Trapido trapidoe@mail.nih.gov

or, for list of P.I.s, http://ospahome.nci.nih.gov/cohort/rosters/nov01_roster.html

Table of Cohorts Characteristics (Co-Co)

http://ospahome.nci.nih.gov/cohort/table.htm

Surveys

National Health and Nutrition Examination Surveys - CDC (NHANES)
http://archive.nlm.nih.gov/proj/dxpnet/nhanes/nhanes.php
Behavioral Risk Factors Surveillance System - CDC (BRFSS)
http://www.cdc.gov/brfss/about.htm
Physicians' Health Survey – ARP, DCCPS
http://cebp.aacrjournals.org/cgi/content/full/12/4/295#SEC2

Intervention trials supported by NCI:www.cancer.gov

The Cohort Consortium

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The Cohort Consortium was formed by NCI to address the need for large-scale collaborations for study of gene-gene and gene-environment interactions in the etiology of cancer, and more than 20 cohorts are participating.

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Cohort Consortium Membership

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Invited: general cohort studies worldwide with >10,000 subjects, blood samples (including white blood cells) and questionnaire data on important cancer risk factors.

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Cohorts Assembled for Co-Co 1

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Study	Year started	Subjects with blood samples	Breast cancer cases	Prostate cancer cases
EPIC	1992	397,256	2,050	900
ACS (CPS-II)	1998	39,000	500	1,450
ATBC	1991	20,500	-	1,180
HARVARD:				
Phys. HS I-II	1982	20,000	-	1,500
Nurses HS	1989	32,826	945	-
HealthProfS	1993	33,240	-	600
WomenH	1993	28,263	675	-
MultiEthnicC	1983	100,000	1,990	2,400
PLCO	1993	75,000	-	1,000
Total		797,085	6,160	9,030

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Proof of Principle Study

- Goals
  - To define disease-related haplotypes by resequencing DNA from known breast and prostate cancer cases, thereby oversampling for rare mutations;
  - To assess relations with plasma steroid hormone and IGF levels; and
  - To examine interactions with known lifestyle and environmental factors.

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Proof of Principle Study

- Candidate genes were selected because of their role in disease-related pathways.
  - They include androgens, estrogens, gonadotropins, steroid synthesis, IGF, growth hormones, and some binding proteins. NIEHS is sponsoring additional resequencing of environmentally responsive genes, and NHLBI is sponsoring resequencing of inflammatory genes.
- Initial targets are 53 genes suspected of having associations with one or both cancers.
  - Work is near completion
  - Genetic data will be made public

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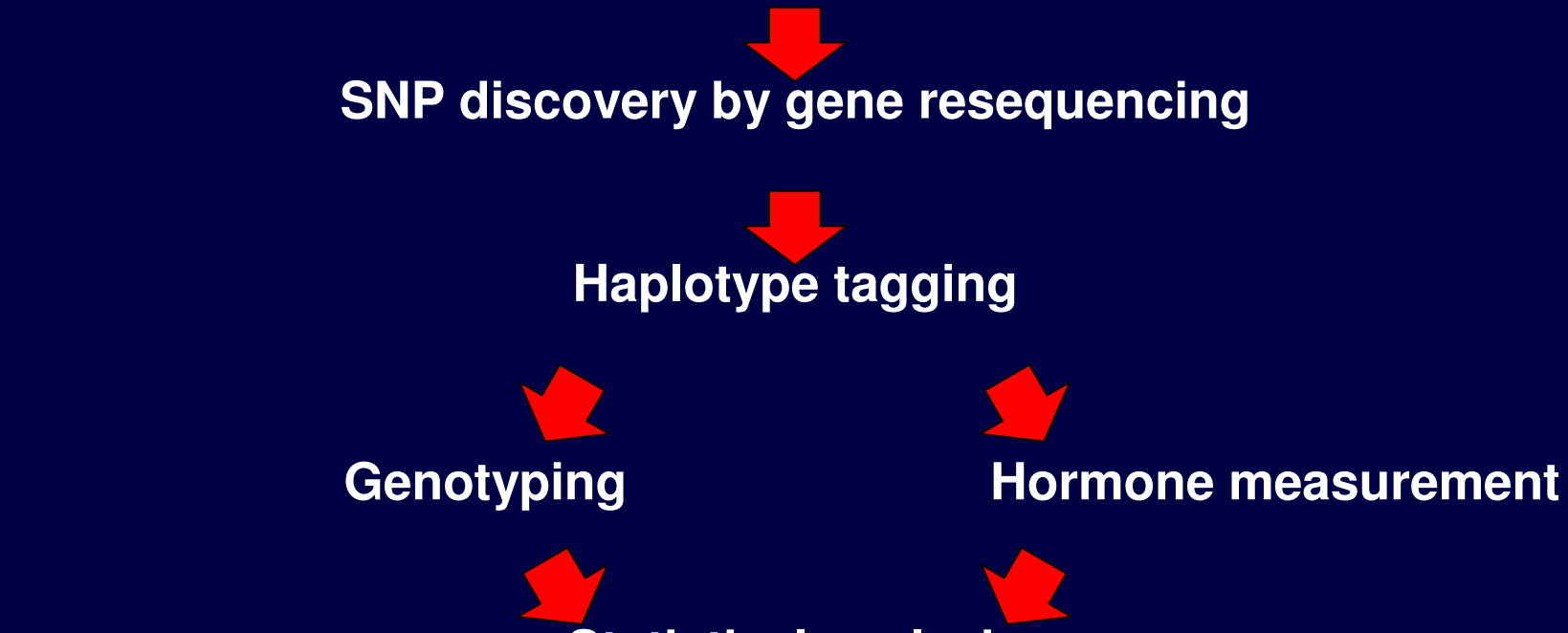
Project Flowchart



Breast, Ovarian and Colorectal Cancer Family Registries (CFRs)

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Goals

Ascertain, characterize and follow up a familial cohort spanning the whole spectrum of cancer risk, and establish a comprehensive familial infrastructure for the implementation of collaborative, interdisciplinary research protocols in the genetic epidemiology of cancer

Identify subpopulations at higher cancer risk that could benefit from enrollment in preventive and therapeutic interventions

Contribute to the development of effective Public Health measures by increasing knowledge of the genetic factors affecting cancer susceptibility and their interaction with modifiable environmental and lifestyle factors (general population).

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CFRs: Participating Sites

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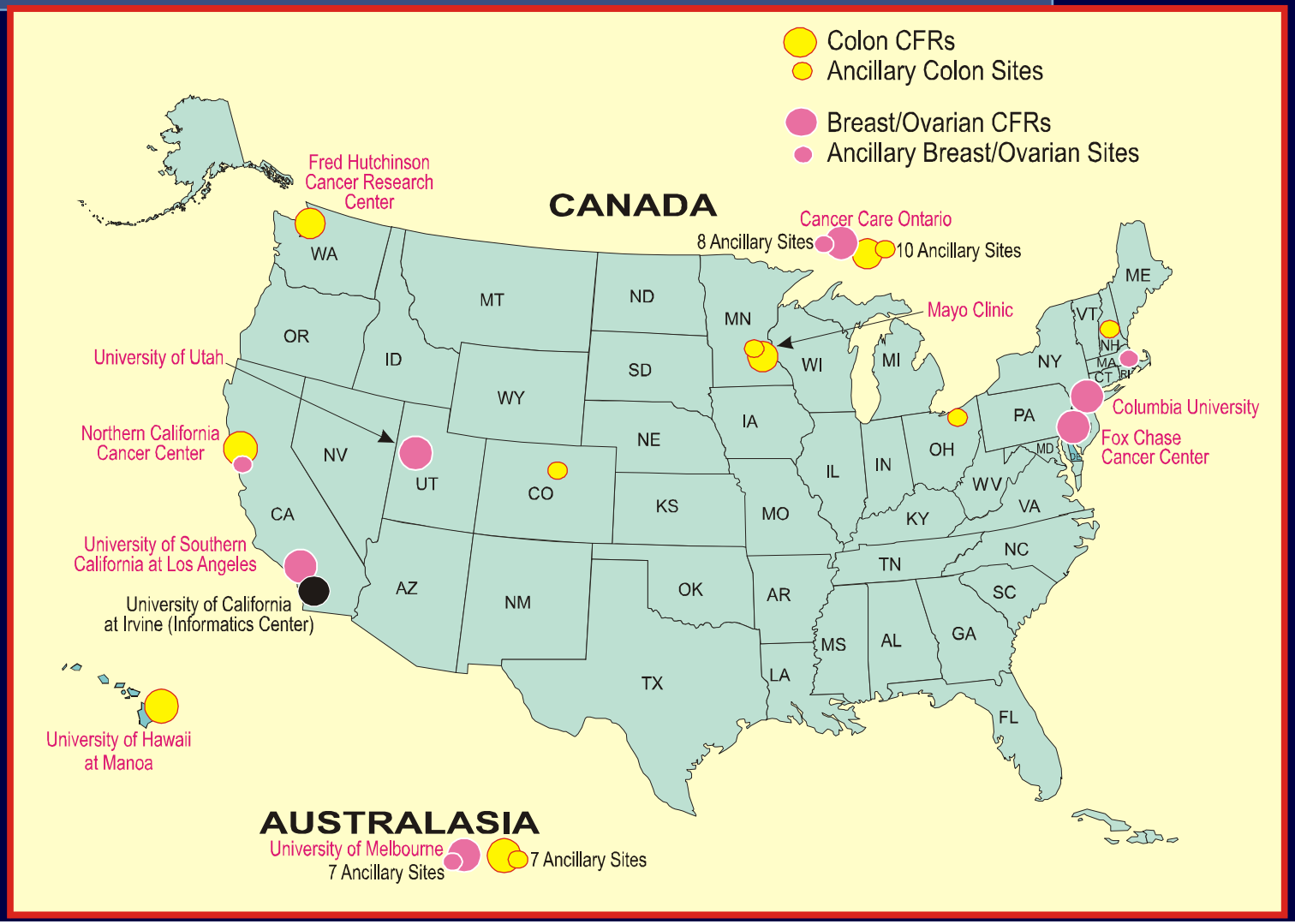

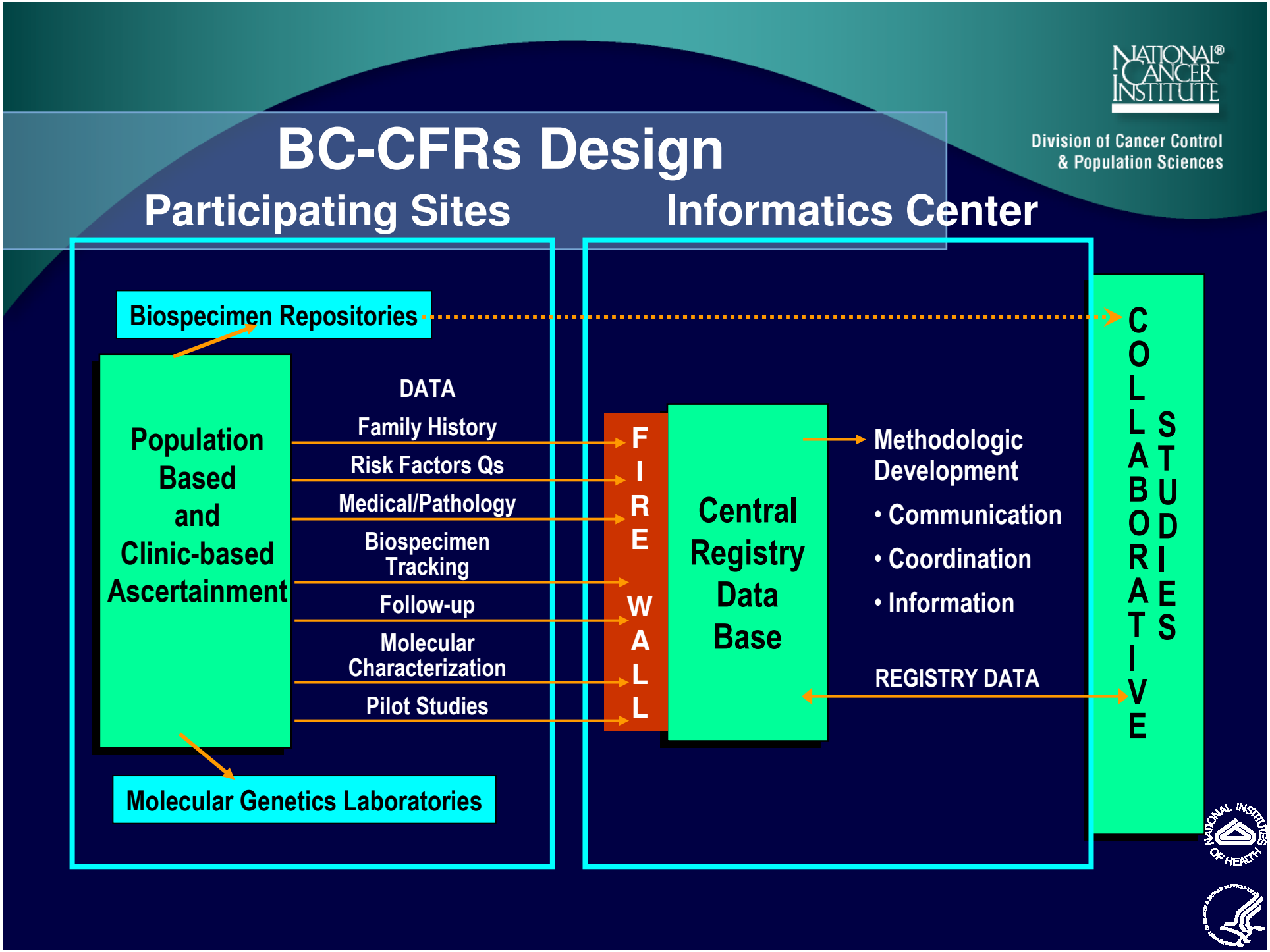
BC-CFRs Design
Participating Sites
Informatics Center
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Biospecimen Repositories
Population Based and Clinic-based Ascertainment
DATA
Family History
Risk Factors Qs
Medical/Pathology
Biospecimen Tracking
Follow-up
Molecular Characterization
Pilot Studies
FIREWALL
Central Registry Data Base
Methodologic Development
• Communication
• Coordination
• Information
REGISTRY DATA
COLLABORATIVE STUDIES
Molecular Genetics Laboratories
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Designs for Studying Association in the CFRs

D. Thomas, in preparation

- Population-based case-control studies
- Family-based designs:
  - Case-parent triads
  - Discordant sibships
  - Kin-cohort designs
  - Case-control family designs
  - High-risk family designs

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Breast CFR
Enrolled Probands, Relatives, and Population Controls

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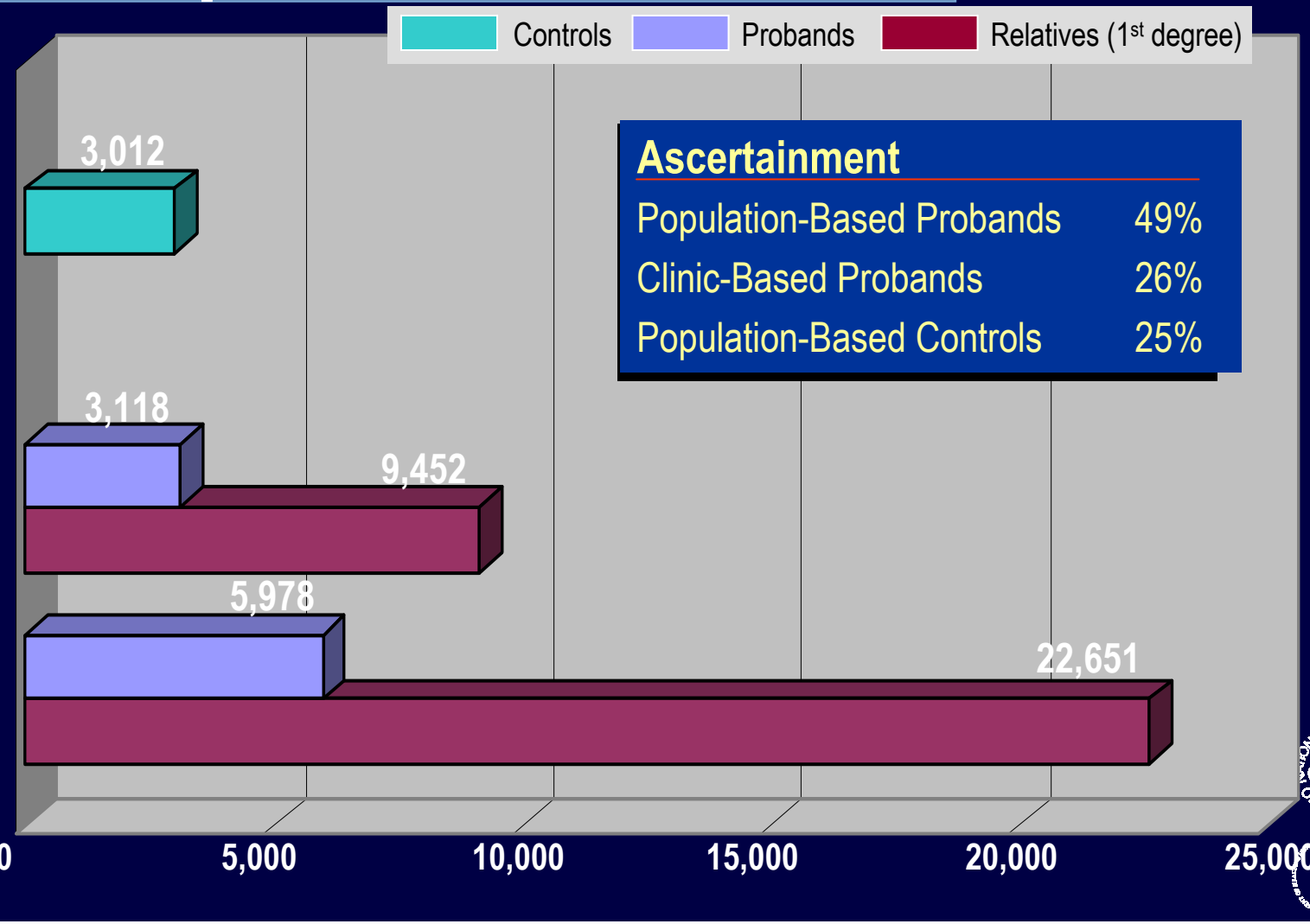

Ascertainment

Population-Based Probands	49%
Clinic-Based Probands	26%
Population-Based Controls	25%

August 2003

Breast CFR
Probands with Early and Intermediate Age at Onset

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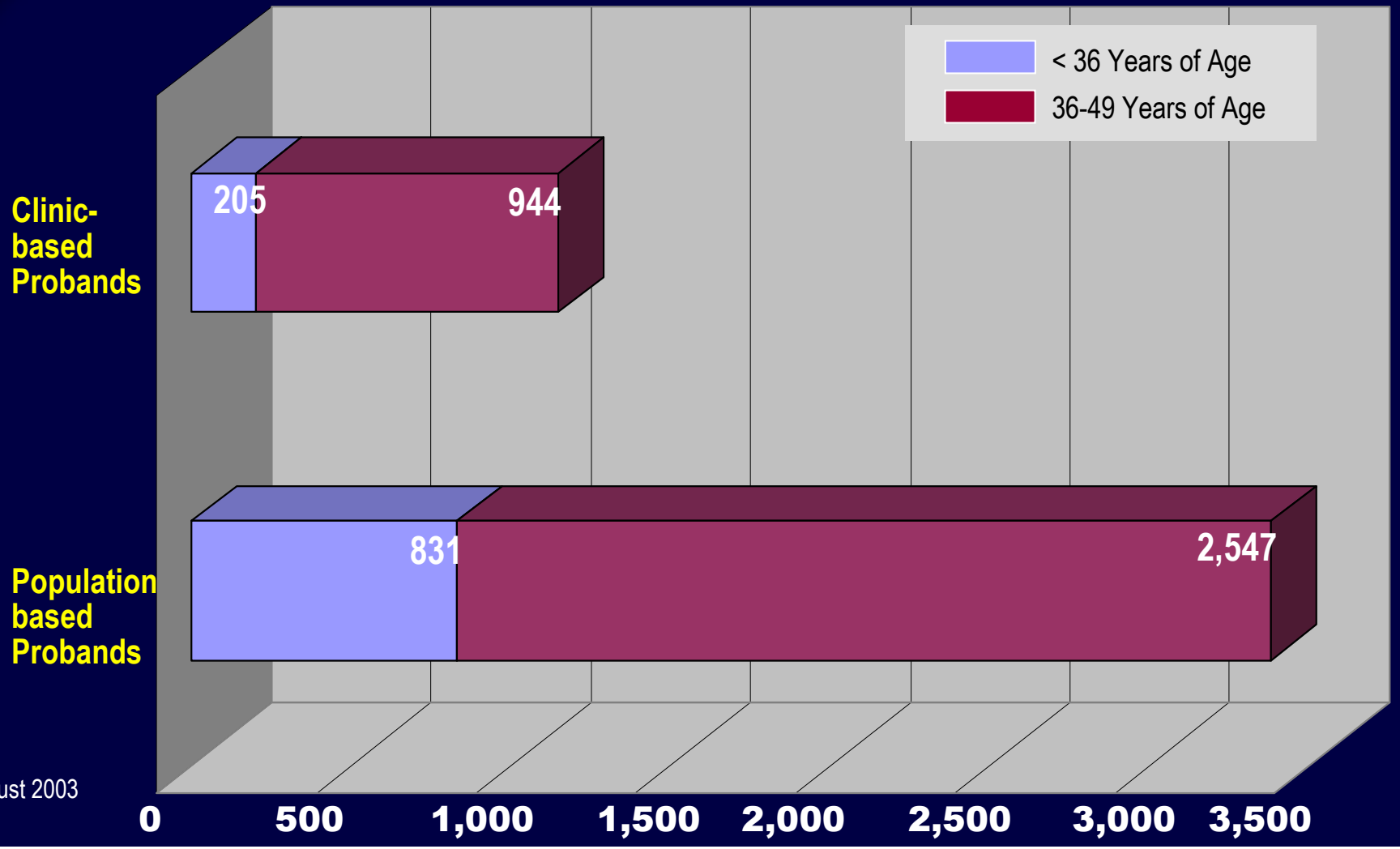

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Breast CFR
BRCA1/2 Mutational Analysis

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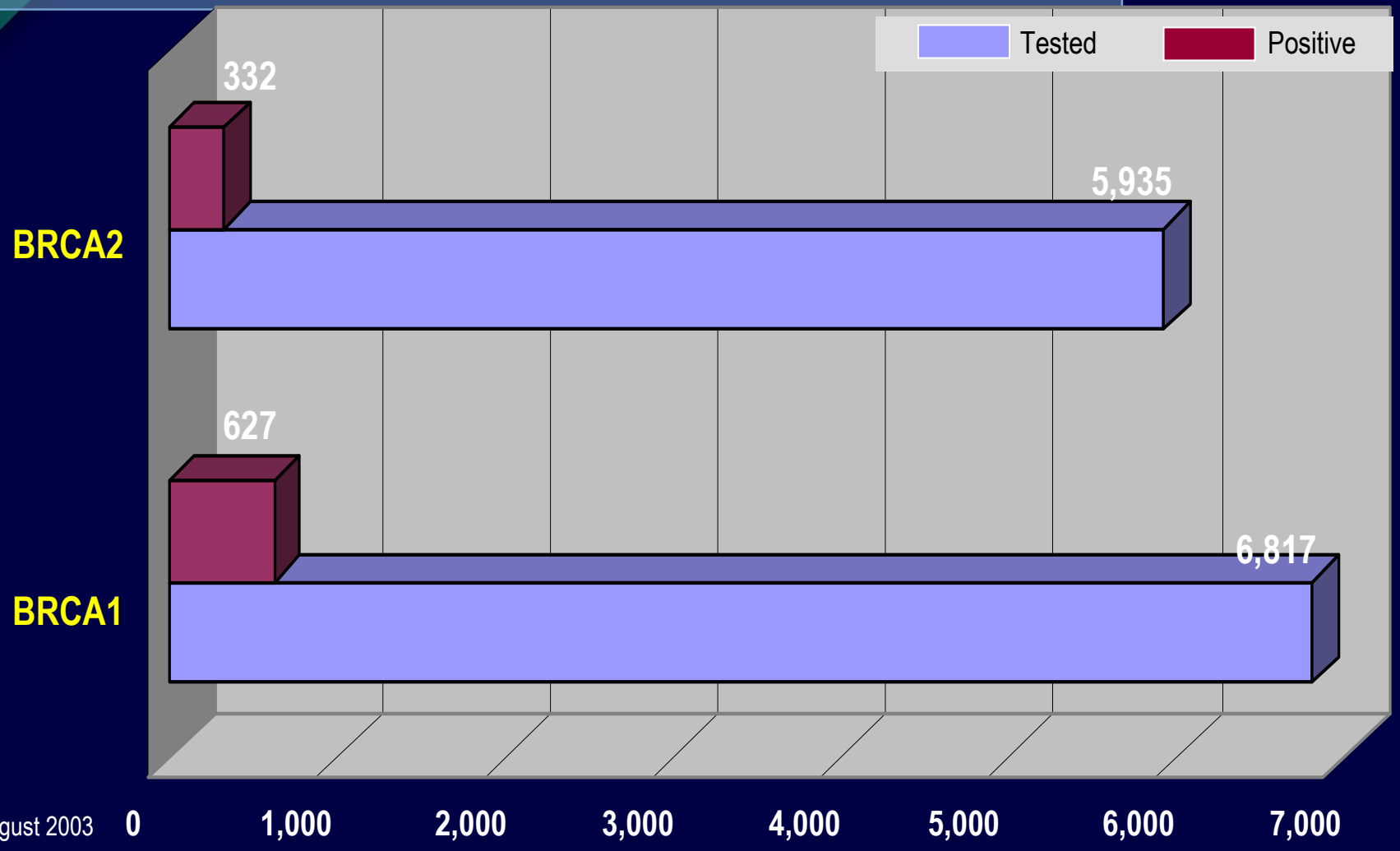

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Colon CFR
Accrued Probands, Relatives, and Controls

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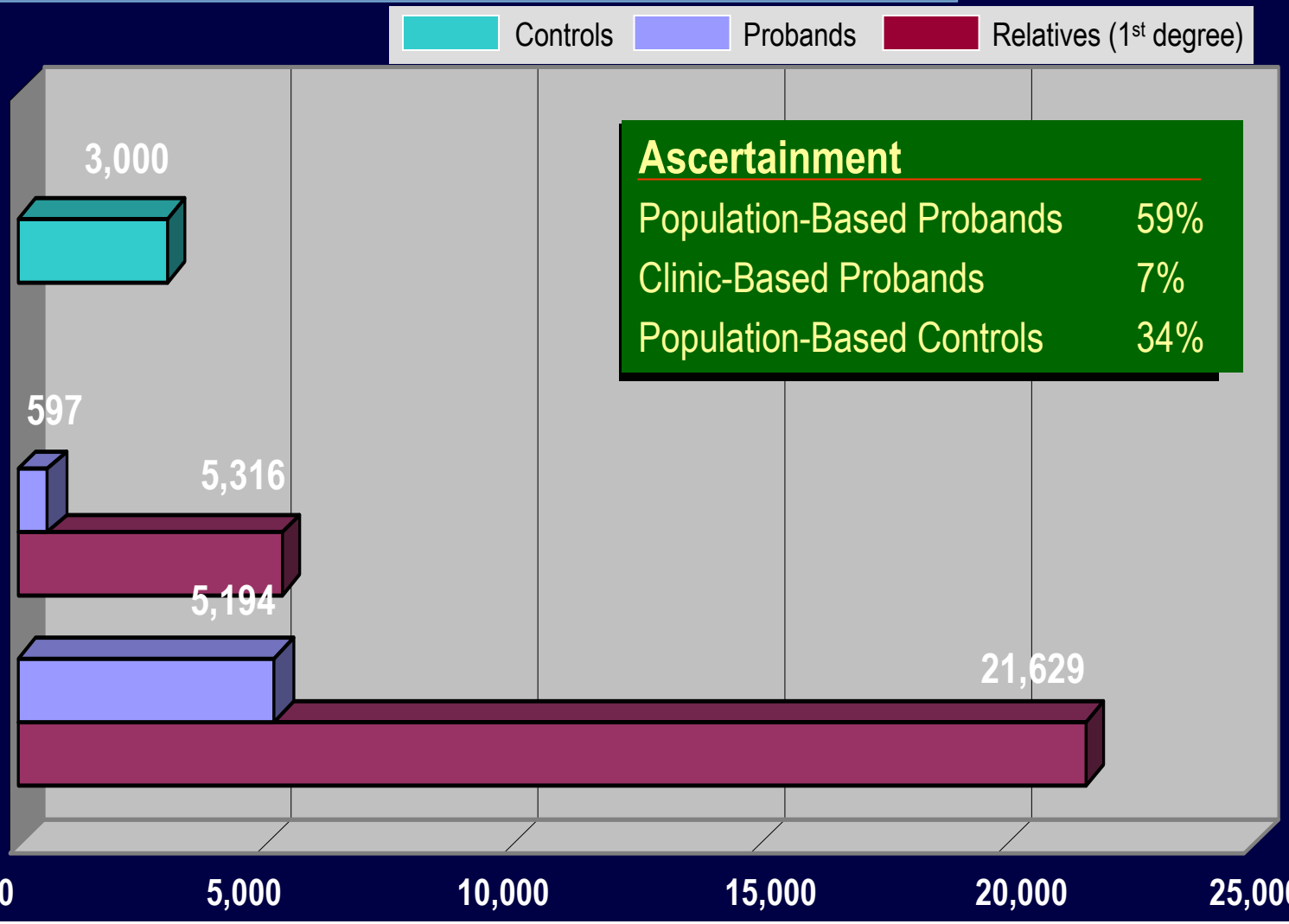

Ascertainment

Population-Based Probands	59%
Clinic-Based Probands	7%
Population-Based Controls	34%

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Colon CFR
Age at Onset of Probands

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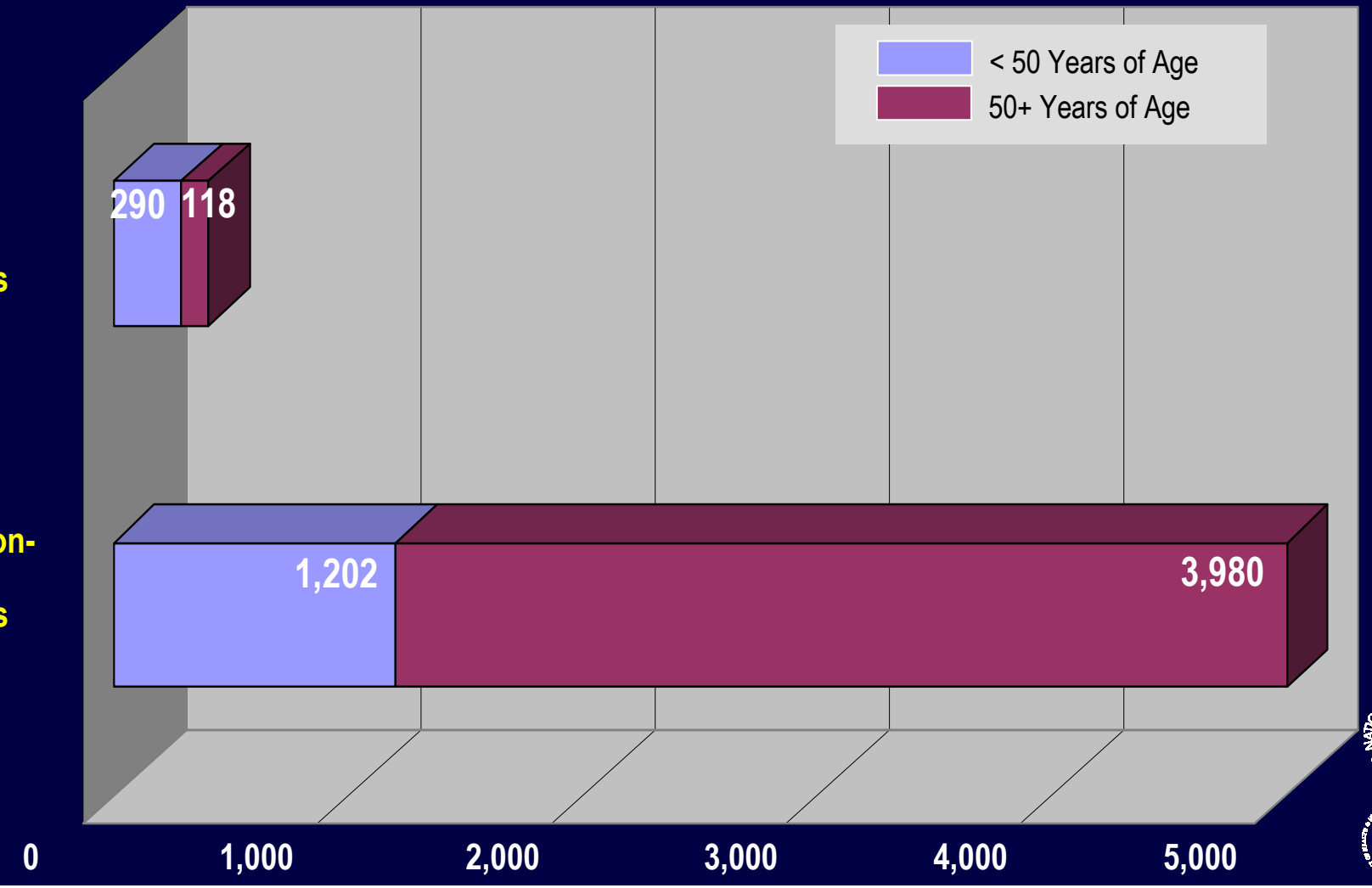

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Colon CFR
MSI and IHC Analysis

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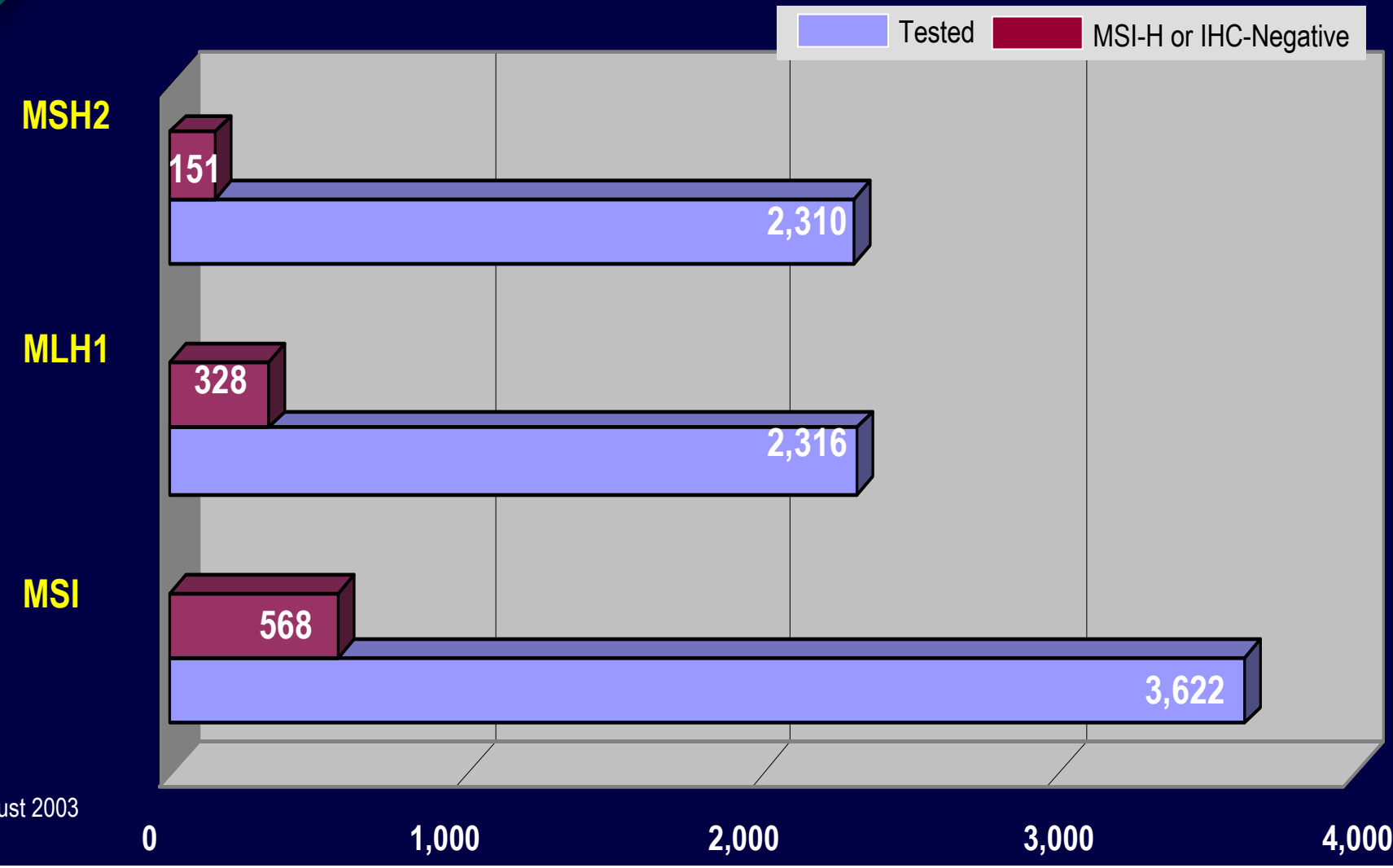

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Access to Collaborative Research

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- Proposal for collaborative protocols are strongly encouraged from national and international groups with appropriate expertise.
- Access requires formal application. Information at http://www.cfr.epi.uci.edu/
- CFRs tools and protocols are available

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"The "PERFECT" population resource/dataset does not exist… "

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But we can strive to support desirable and feasible elements:

- LARGE datasets (consortia) from well ascertained caucasian and non-caucasian populations, from diverse geographical areas
- Accurately and prospectively assessed risk factors
- Ever improving genetic profile (biospecimen availability, technology integration)
- Pathology, biomarkers data
- Data on preventive interventions, treatment

And….improved methodology to compensate for opportunistic design (often current reality)

Future Challenges/Goals for Cancer Risk Prediction

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- Direct observation of impact of many interacting factors on risk
- Rapid and seamless translation of genetic epidemiology research data into model construction
- Efficient and effective translation of risk prediction models into clinical practice

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Thank You

- Sandra Melnick
- Ed Trapido
- Debbie Winn
- Andrew Freedman

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