National Cancer Institute

Role of Prevention Research in DCEG

National Cancer Advisory Board

Stephen J. Chanock, M.D.
Division of Cancer Epidemiology and Genetics
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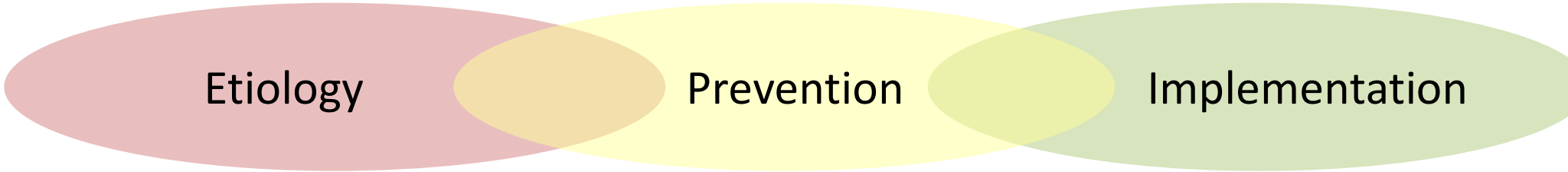
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

Prevention Research Continuum



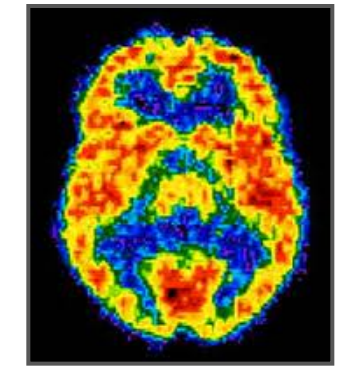
- Tobacco
- Physical inactivity, diet, and obesity
- Infectious agents
- Radiation
- Occupational carcinogens
- Hormones
- Genetics

- HPV vaccine trial
- Melanoma screening
- Genetic risk prediction
- Radiation
- Nicotine addiction
- Occupational exposure dose response and threshold levels

- HPV screening recommendations and management guidelines
- Lung cancer screening guidelines
- Radiation protection guidelines

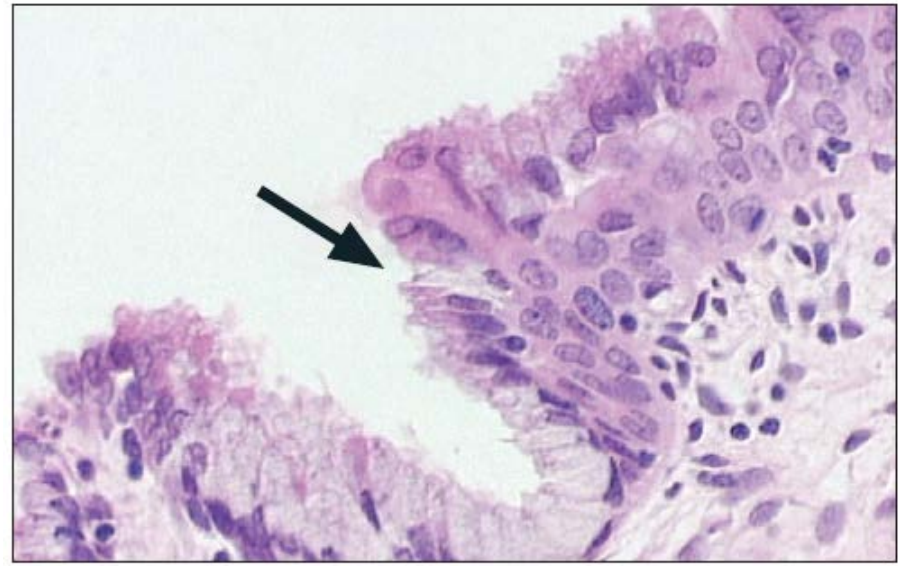
DCEG Examples that Span the Prevention Continuum

- HPV
- Tobacco
- Obesity
- Radiation



HPV Etiologic Studies

- HPV natural history
- Established HPV as necessary cause of cancer of the cervix
- Risk of cancers of the oral cavity, anus, and other sites



Schiffman MH, et al. *Lancet* 2007

Schiffman MH, et al. *JNCI* 1993

HPV Prevention Research

- HPV vaccine trial
- One dose vs. two doses vs. three doses
- Protection against anal and oral HPV infections
- Long-term follow-up

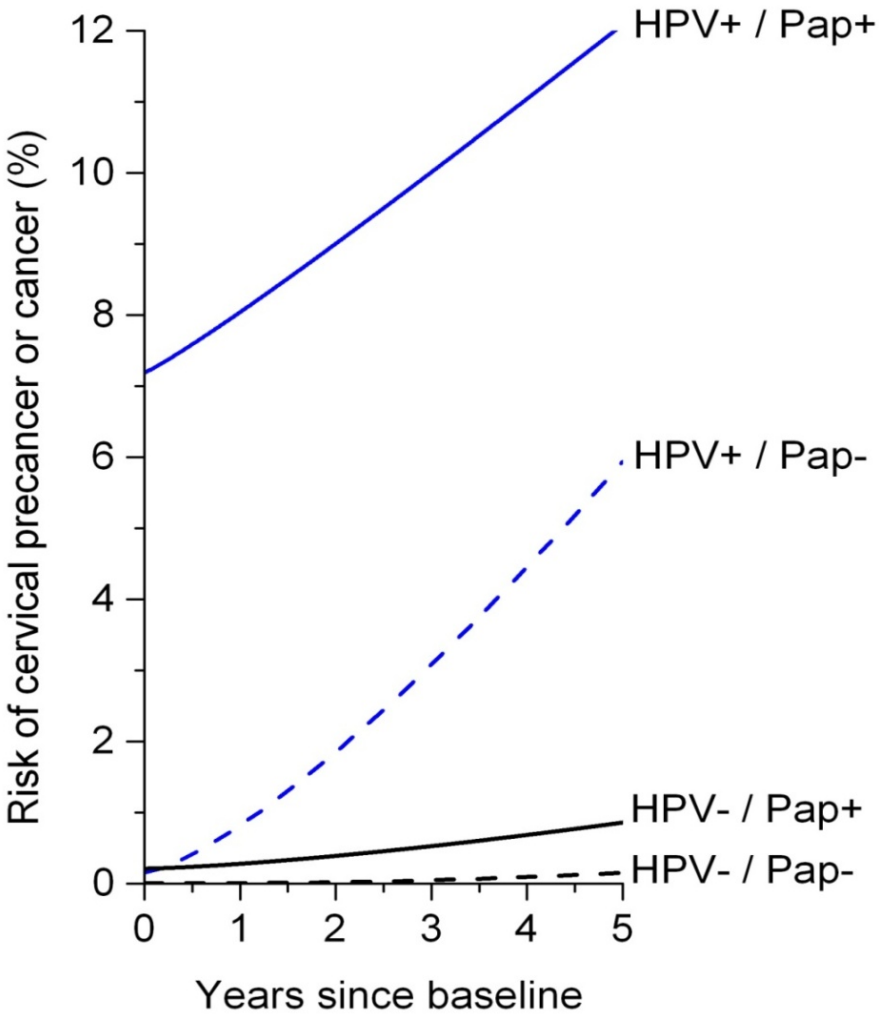
Kreimer AR, et al. *JNCI* 2011

Safaeian M, et al. *Cancer Prev Res* 2013

Kreimer AR, et al. *Lancet Onc* 2011

Herrero R, et al. *PLoS One* 2013

HPV Implementation Research



- Screening guidelines
- Clinical management guidelines

Katki HA, et al. *Lancet Onc* 2011

Gage JC, et al. *JNCI* 2014

Tobacco

- NIH-AARP cohort
- Smoking & second cancer risk
- Smokeless tobacco
- New & emerging tobacco products
- Screening guidelines

Freedman ND, et al. *Lancet Onc* 2008

Freedman ND, et al. *JAMA* 2011

Thun MJ, et al. *NEJM* 2013

Kovalchik SA, et al. *NEJM* 2013

Gu F, et al. *JNCI* 2014

Shiels MS, et al. *JCO* 2014

Carter BD, et al. *NEJM* in press

Radiation Exposure

- Medical radiation exposures
  - Diagnostic and screening procedures (low dose)
  - Radiotherapy treatments (high dose)
  - Occupational (repeated low dose)

- Environmental (nuclear testing, nuclear power plant accidents)
- Etiology of radiosensitive malignancies

Berrington de Gonzalez A, et al. *Lancet Onc* 2011

Brenner AV, et al. *Env Health Persp* 2011

Zablotska LB, et al. *Env Health Persp* 2013

Role of DCEG in Prevention Research

- Focus on *foundational, etiologic* research
- Randomized prevention trials as outgrowth of etiologic work
  - HPV
  - Chinese Nutritional Intervention Trial
- Observational studies can be critical when trials not feasible/ethical
  - Radiation
  - Chemical carcinogens

Global Alliance
for Genomics & Health

Collaborate. Innovate. Accelerate.

Mission

To accelerate progress in human health by helping to establish a common framework of harmonized approaches to enable effective and responsible sharing of genomic and clinical data, and by catalyzing data sharing projects that drive and demonstrate the value of data sharing

Goals of the BRCA Challenge

1. Synchronize BRCA data in federated public database
   - Existing and future data
2. Review existing variants
   - Curate reference list
3. Create an API for display of annotated variants
4. Create a template for other genes

Coordinated Activities

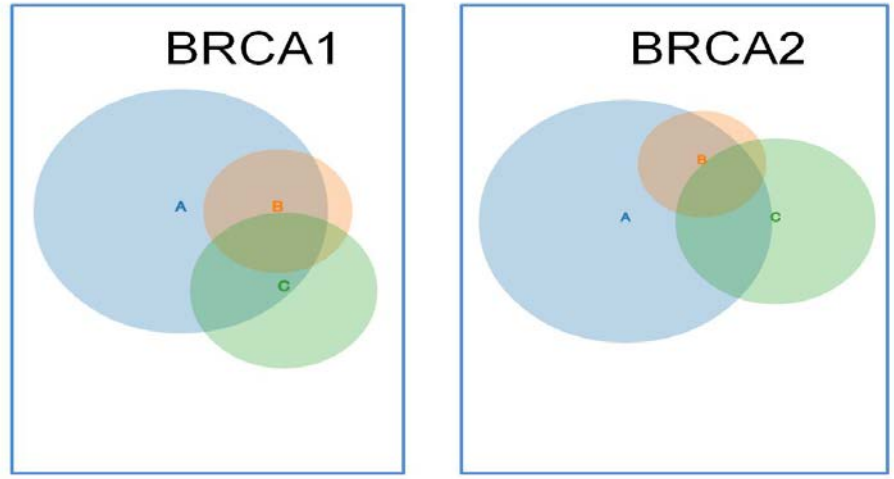
1. Data Collection
    - Evidence Group
    - Variant Classification Group
2. Interpretation of Variants
3. Community Engagement and Regulation

BRCA 1/2 Variants in Public Databases

NCBI ClinVar database:
6431 variants

LOVD Databases:
3262 variants

French Universal Mutation Database: 3913 variants

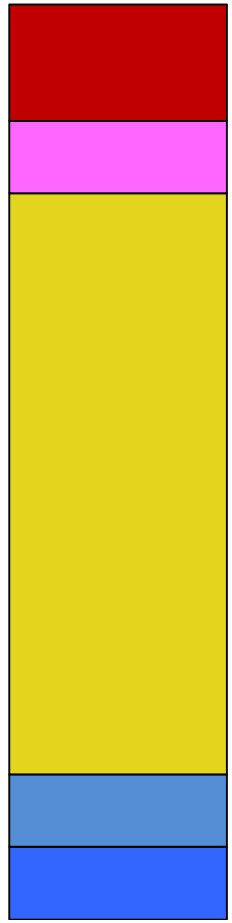


GOAL:

Expand to include ENIGMA, CIMBA, & other data sets from around the world

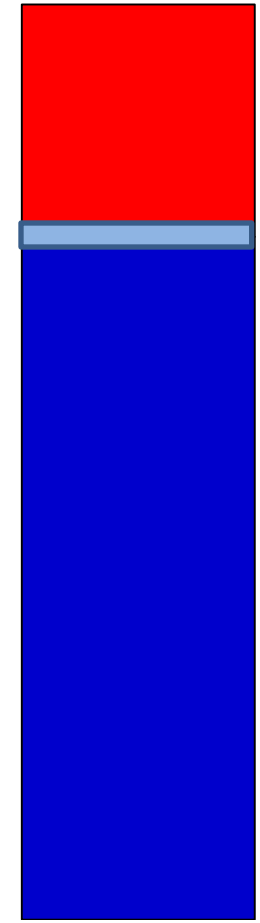
2 ‘Views’ of Variant Classification

Scientific



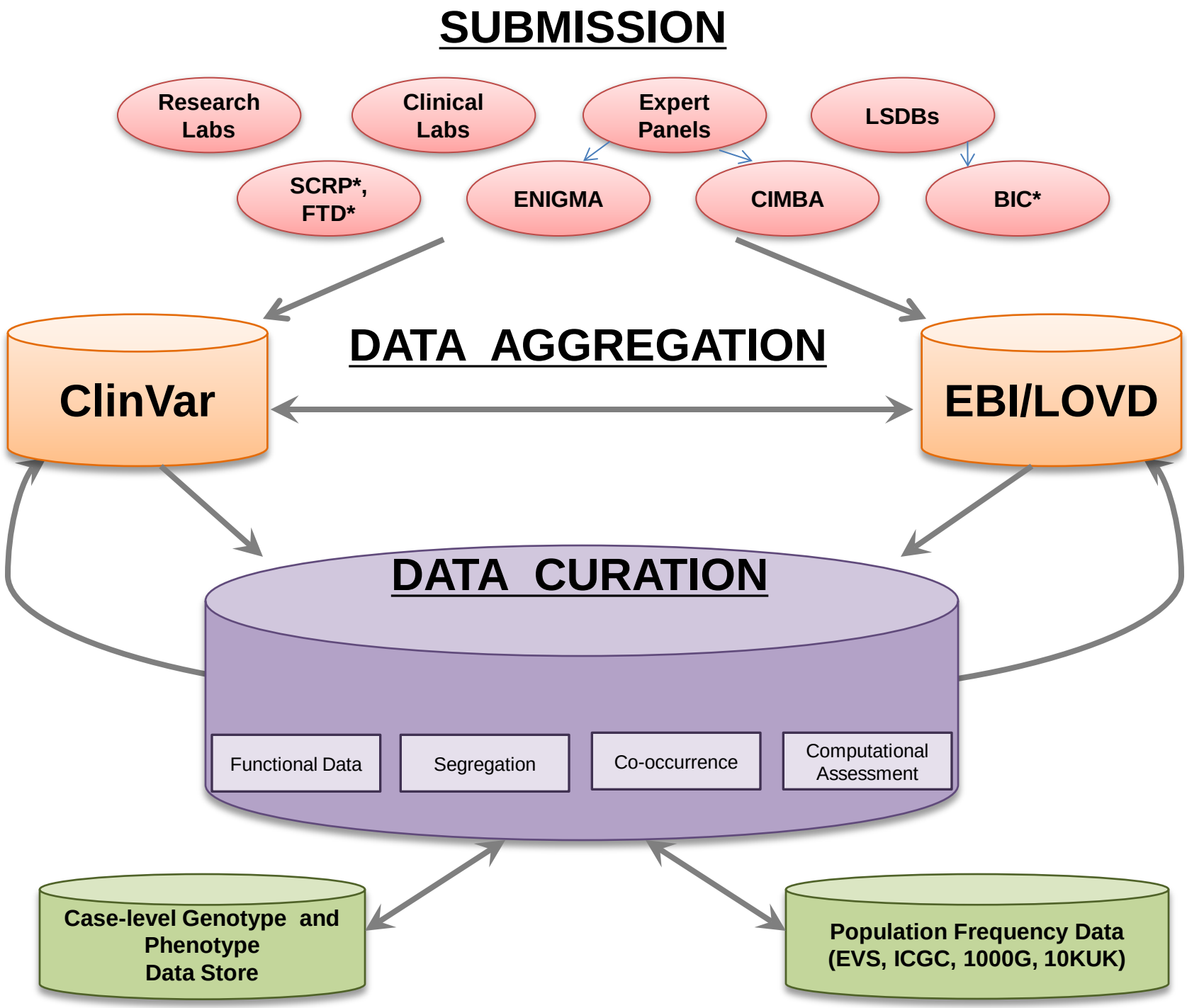
- Pathogenic
- Likely pathogenic
- Variant of Uncertain Significance
- Unlikely pathogenic
- Non-pathogenic

Clinical



Custom management

- Manage as pathogenic
- Manage as not pathogenic


SUBMISSION
Research Labs
Clinical Labs
Expert Panels
LSDBs
SCRP*, FTD*
ENIGMA
CIMBA
BIC*
DATA AGGREGATION
ClinVar
EBI/LOVD
DATA CURATION
Functional Data
Segregation
Co-occurrence
Computational Assessment
Case-level Genotype and Phenotype Data Store
Population Frequency Data (EVS, ICGC, 1000G, 10KUK)

Deliverables

1. Display population-based allele frequencies using available sequencing resources
    - Prototypes being tested
2. Federated collection of Pathogenic Variants for *BRCA1/BRCA2*
    - In development
3. Improve penetrance estimates
    - Long-term goal

BRCA Challenge Steering Committee

Antonis Antoniou, University of Cambridge (United Kingdom)
Larry Brody, National Human Genome Research Institute (United States)
Sir John Burn, Newcastle University (United Kingdom)
Stephen Chanock, National Cancer Institute (United States)
Fergus Couch, Mayo Clinic (United States)
Johan den Dunnen, Leiden University Medical Center (Netherlands)
Susan Domchek, University of Pennsylvania (United States)
Douglas Easton, University of Cambridge (United Kingdom)
William Foulkes, McGill University (Canada)
Judy Garber, Dana Farber Cancer Institute (United States)
David Golgar, Huntsman Cancer Center (United States)
Robert Nussbaum, University of California, San Francisco (United States)
Ken Offit, Memorial Sloan Kettering Cancer Center (United States)
Sharon Plon, Baylor College of Medicine (United States)
Nazneen Rahman, Institute of Cancer Research (United Kingdom)
Heidi Rehm, Harvard Medical School (United States)
Mark Robson, Memorial Sloan Kettering Cancer Center (United States)
Wendy Rubinstein, National Institute of Health (United States)
Amanda Spurdle, QIMR Berghofer Medical Research Institute (Australia)
Dominique Stoppa-Lyonnet, Curie Institute (France)
Sean Tavtigian, University of Utah (United States)