Case-Control Consortia: Ways to Move Forward

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Case-Control Consortia: Ways to Move Forward

Premise: Case-control consortia can yield important scientific gains. These can be surer, faster, and less expensive than multiple sequential studies.

Questions

- What have the ongoing case-control consortia revealed about the likely benefits? The hurdles? The major common features?

  "Just-add-water" CCCs
- What should we do to help these?
- How should we build case-control consortia de novo?

Typical Consortium Goals

- Conduct specific collaborative studies
- Foster collaborative links
- Discuss common problems
- Recommend solutions

Cohorts Assembled for First Study

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:				
Physicians HS	1982	20,000	-	1,500
Nurses HS	1989	32,826	945	-
HealthProfS	1993	33,240	-	600
WomenH	1993	28,263	675	-
MULTIETHNIC	1983	100,000	1,990	2,400
PLCO	1993	75,000	-	1,000
Total		797,085	6,160	9,030

Cohort Consortium Study

Genomics Collaborating Institutions

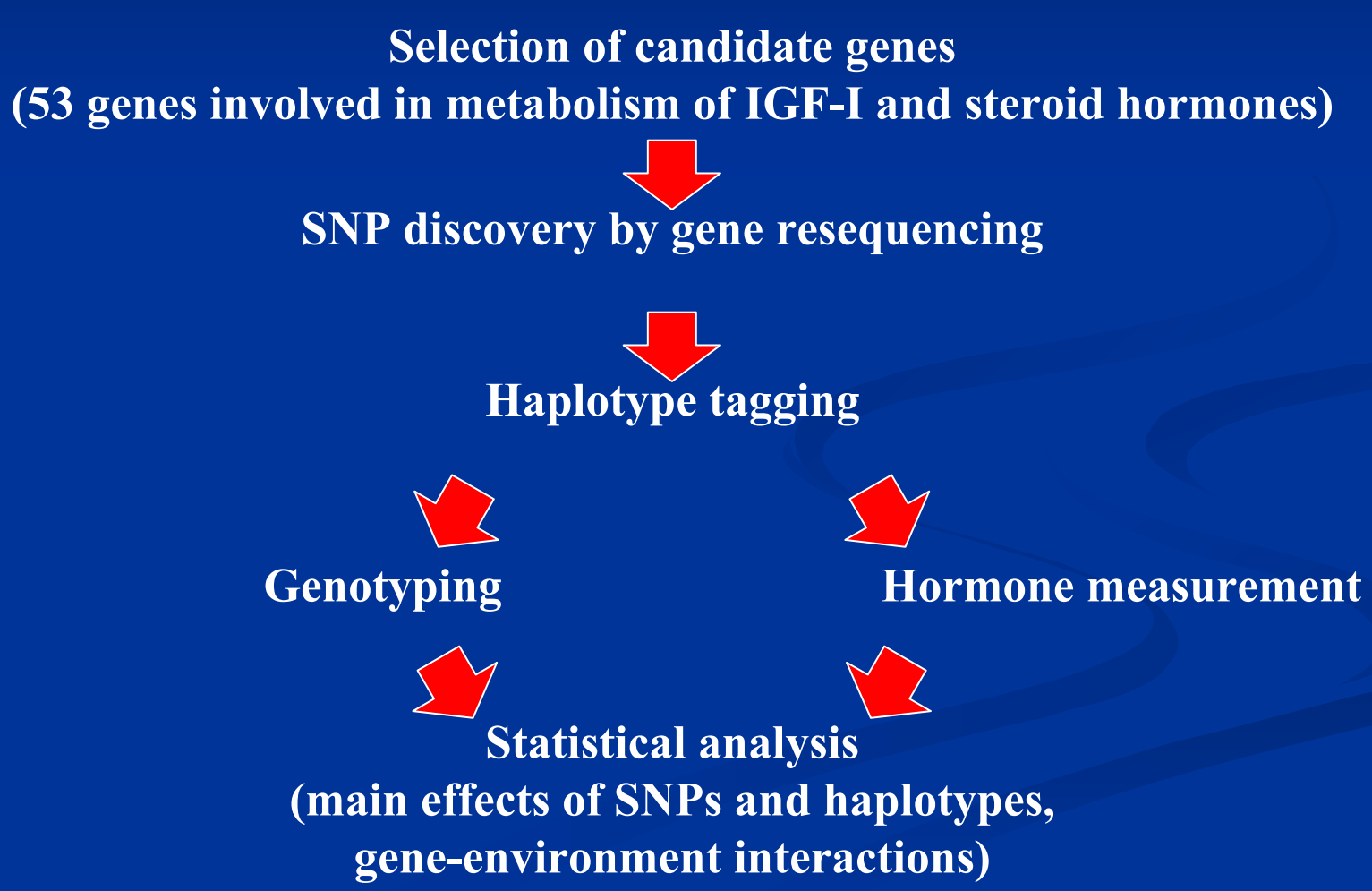
Whitehead, USA

CEPH, France

NCI, USA

Cambridge, England

Project Flowchart



Candidate Steroid Hormone Genes

- Synthesis and metabolism

StAR	: steroid accurate regulatory protein
CYP11a	: cholesterol side-chain cleavage enzyme
CYP17	: 17-alpha-hydroxylase/17, 20-lyase
EDH17B1	: 17-beta-hydroxysteroid dehydrogenase, type I
EDH17B2	: 17-beta-hydroxysteoid dehydrogenase, type II
HSD3B1	: 3-beta-hydroxysteroid dehydrogenase, type I
HSD3B2/3	: 3-beta-hydroxysteroid dehydrogenase, type II & III
CYP19	: aromatase
SRD5A2	: 5 alpha-reductase
CYP3A4	: testosterone oxidase
UGT1A1	: steroid glucuronidase
SULT1	: steroid sulphatase

InterLymph Consortium

- 20+ case-control studies
- Other lymphoma researchers
- 4 years old
- Chairs (past and current)
  - Bruce Armstrong (Australia), Paolo Boffetta (IARC), Wendy Cozen (USC), Patricia Hartge (DCEG), Carol Kasten-Sportes (DCCPS), Martha Linet (DCEG), Sandra Melnick (DCCPS)
- Includes multi-site efforts, e.g. EpiLymph, NCI-SEER

Studies Currently Included in InterLymph

★ Participating centers

Eliminating False Leads: *IL1B-511 TT* and Risk of NHL

Study	Relative Risk	P-value
A	1.7	0.02
B	0.6	0.02
C	1.4	0.2
D	1.2	0.5
E	0.8	0.6
F	1.2	0.6
G	1.1	0.7
InterLymph (combined)	1.1	0.5

The InterLymph-13

SNP Vernacular	No. studies
IL-1A -889C>T	8
IL-1B -511C>T	8
IL-1B -31C>T	8
IL1RN 9589A>T	8
IL2 -384T>G	8
IL-6 -174G>C	8
IL-6 -597G>A	7
IL-10 -1082A>G	7
IL-10 -3575T>A	8
LTA 252A>G	8
LTA -91A>C	6
TNF-A -308G>A	7
NOD2 nt1007	8

Genetic Polymorphism Working Group

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Alcohol consumption and NHL Pooled InterLymph analysis

Risk of NHL subtypes associated with alcohol consumption			
	CLL/SLL (N=814)	Diffuse (N=1972)	Follicular (N=1194)
Alcohol exposure	OR (95% CI)	OR (95% CI)	OR (95% CI)
Nondrinker	1.00	1.00	1.00
Ever drinker	0.90 (0.75, 1.09)	0.74 (0.66, 0.84)	0.83 (0.71, 0.95)
Current	0.81 (0.59, 1.10)	0.63 (0.52, 0.76)	0.80 (0.64, 1.00)
Former	1.05 (0.69, 1.60)	0.92 (0.72, 1.18)	0.94 (0.69, 1.27)

Morton LM et al. - Unpublished

Lung Cancer Consortium

- Formed at AACR 2004
- 20+ studies, 5 working groups
- Planned: Non-smoking women, early onset cases, DNA repair
- **Chairs:** Paolo Boffetta (IARC), Paul Brennan (IARC), Neil Caporaso (DCEG), David Christiani (Harvard), Qing Lan (DCEG), Margaret Spitz (MD Anderson), Erich Wichman (GSF, Germany), Zuo-Feng Zhang (UCLA)

Bladder Cancer Case-control Consortium

- Just forming (AACR 2005)
- Montserrat Garcia-Closas (DCEG), Margaret Karagas (Dartmouth), Manolis Kogevinas (Barcelona), Nat Rothman (DCEG), Xifeng Wu (MD Anderson)
- Molecular epidemiology projects hoped for
  - Tobacco x Genes (NAT2, GSTM1, GST, …)
  - Genes (DNA repair, inflammation, cell-cycle control)
  - Tumor subtypes

Esophageal Adenocarcinoma & Barrett's Esophagus Case-control Consortium

- Just forming – May meeting Bethesda, MD
- Approximately 5 EA and 5 BE studies
- Arose from cooperative agreement study (Gammon, Risch, Vaughan, Chow)
- Wong-Ho Chow (DCEG), Tom Vaughan (Fred Hutchison), Olaf Nyren (Karolinska), Ed Trapido (DCCPS)
- General aims
  - Form new hypotheses
  - Less common exposures (meds)
  - Subgroups (female, younger)
  - Comparative etiology

Case-control Consortia: Partial List

- Bladder
- Brain
- Breast
- Lung
- Esophagus
- Oral
- Lymphoma
- Multiple Myeloma

Common Issues in Ongoing Consortia

- Does look promising, e.g. first genetic findings NHL
- Not high marginal cost
- Several consortia emerging now
  - Mostly in the 1-3% lifetime risk zone
  - Some major sites, motivated by subgroups
  - Many with genetic, tobacco, or diet impetus

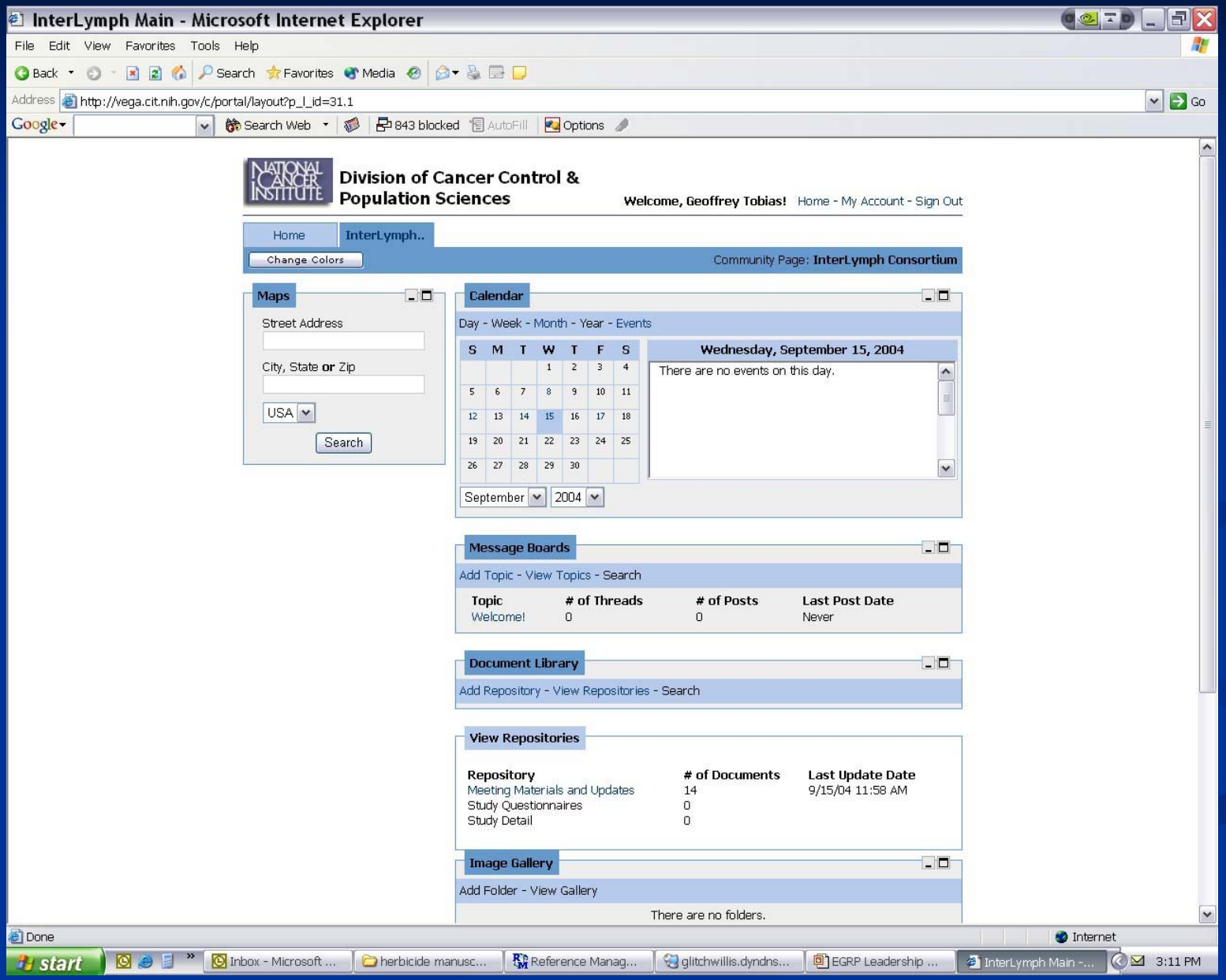
Common Scientific Issues

Genes x Environment	• How strong should E be? • How strong should G be?
Many genes	• Which genes to study? • Haplotypes, pathways, density of SNPs • Staying current is a challenge
Subgroups	• Histology, expression profiles • How meaningful age, sex, race? • Compare within each exposure, or look across all exposures within type
Analysis approach	• Too soon to standardize

Common Logistic Needs

1) Studies	• Surveys of interest • Timelines • Leadership, writing • Protecting frank exchange
2) Communications	• Correspondence • Web portals • Working groups, overall
3) Decisions executive committees working groups	• Membership classes • Rotations • Flexible but reliable
4) Support	• Umbrella organization needs • Specific studies and mixed models
5) Evaluation	• Benefits and costs

InterLymph Portal Under Construction



Building from Scratch

- Hospital-based for caners with poor survival, e.g. cancer center.
- Population-based, e.g. registries
- Existing mechanisms awkward