Genomics and Public Health Prior to the CDC Effort:
The Linkage of Genetic Measurements to a Health Risk Assessment

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Background

Studies of Genetic Markers and Diseases

- In the late 70's and early 80's, it became possible to measure a number of genetic markers including those in the Major Histocompatibility Complex such as the various HLA genes and alleles.
- The investigators were involved in studying immunogenetic associations and linkages in a number of diseases including Type I and Type 2 Diabetes Mellitus, Heart Disease, Leukemia, Melanoma, Rheumatoid Arthritis, Ankylosing Spondylitis, and Juvenile Periodontal Disease

Type 1 Diabetes Mellitus

Reitnauer, P.J.; Roseman, J.M.; Barger, B.O.; Murphy, C.C.; Kirk, K.A.; and Acton, R.T.: HLA Associations with Insulin-Dependent Diabetes Mellitus in a Sample of the American Black Population. Tissue Antigens 17:286-293, 1981.

Pitman, W.B.; Acton, R.T.; Barger, B.O.; Bell, D.S.; Go, R.C.P.; Murphy, C.C. and Roseman, J.M.: HLA -A, -B and -DR Associations with Primary Diabetes Mellitus in those with Onset After Age 40. Diabetes 31:22-25, 1982.

Reitnauer, P.J.; Go, R.C.P.; Acton, R.T.; Murphy, C.C.; Budowle, B.; Barger, B.O.; and Roseman, J.M.: Evidence for Genetic Admixture as Determinant in the Occurrence of Insulin-dependent Diabetes Mellitus in U.S. Blacks. Diabetes 31(6):532-537, 1982.

Murphy, C.; Acton, R.T.; Barger, B.O.; Kirk, K.A.; Reitnauer, P.; Go, R.C.P. and Roseman, J.M.: Population Genetic Analyses of IDDM using HLA Allele Frequencies. Clinical Genetics 23:405-414, 1983.

Type 2 Diabetes

Acton, R.T.; Roseman, J.M.; Bell, D.S.H.; Goldenberg, R.L.; Tseng, M.-L.; Vanichanan,C.; Harman, L.A.; and Go, R.C.P.: Genes within the Major Histocompatibility Complex Predict NIDDM in African-American Women in Alabama. Diabetes Care 17(12):1491-94, 1994.

Melanoma

Barger, B.O.; Acton, R.T.; Soong, S-J; Roseman, J.M.; and Balch, C.M.: Increase of HLA-DR4 in Melanoma Patients from Alabama. Cancer Research 42:4276-4279, 1982.

Leukemia

Budowle, B.; Dearth, J.; Bowman, P.; Melvin, S.; Crist, W.; Go, R.; Kim, T.; Iyer, R.; Roseman, J.; Barger, B.; and Acton, R.: Genetic Predisposition of Acute Lymphocytic in American Blacks. Cancer 55: 2860 -2862, 1985.

Heart Disease

Acton, R.T.; Go, R.C.P.; and Roseman, J.M.: Review of the Evidence that Immunogenetic Factors are Involved in the Etiology of Atherosclerosis. Luss, A.; Rotter, J.; and Sparks, R. (Eds.) In Molecular Genetics of Coronary Heart Disease: Candidate Genes and Processes in Atherosclerosis. Monogr Human Genetics. Basel, Karger, 14:253 -271, 1992.

Arthritis

Go RCP, Alarcon GS, Acton RT, Koopman WJ, Vitor VJ, Barger BO: Analysis of HLA Linkage in White Families with Multiple Cases of seropositive Rheumatoid Arthritis. Ar thritis and Rheumatism 30:1115 -1123, 1987.

Reveille JD, Almazor MES, Russell AS, Go RCP, Appleyard J, Barger BO (deceased), Acton RT, Koopman WJ, McDaniel DO: HLA in Ankylosing spondylitis: Is HLA -B27 The Only MHC Gene Involved in Disease Pathogenesis? A rthritis and Rheumatism 23:295-309 1994.

Periodontal Disease

Cogen, R.B.; Roseman, J.M.; Alsobrook, W.; Louv, W.C.; Acton, R.T.; Barger, B.O.; Go, R.C.P.; and Rasmussen, R.A.: Host Factors in Juvenile Periodontitis. Journal of Dental Research, 65:394 -399, 1986.

Health Risk Assessments (HRA) or Health Hazard Appraisals

HRAs have been used in the public health setting to identify and motivate behavioral change by providing users with estimates of their risk and/or relative risk of disease, injury or death from specific causes based on their characteristics, with recommendations for reducing the risk. It was the vision of the investigators that genetic factors should be included in HRAs.

Roseman, J.M.; Go, R.C.P. and Acton, R.: The Future of Molecular Biology in Prospective Medicine. Proceedings of Society of Prospective Medicine. Society of Prospective Medicine. Proceedings of the 25th Annual Meeting. Risky Business 1989: Paying for Prevention 105-119, 1990.

Acton, R.T.; Barnberg, R.; Go, R.C.P. and Roseman, J.M.: Utilization of genetic and other laboratory tests results to predict and reduce the risk of disease. Society of Prospective Med.. Proceedings of the 22nd & 24th Annual Meetings 261-276, 1990.

Acton, R.; Barnberg, R.; and Roseman J.: Integration of Genetic Information Into the Practice of Preventive Medicine. In: Matzen R.N., Lang, R., Editors: Principles and Practices of Clinical Preventive Medicine, St. Louis, CH 40, 765-780. Mosby, 1990.

Objectives

The objectives of our program were: 1) To demonstrate that an HRA including input about genetic risk status is feasible; 2) To evaluate the validity of subject's knowledge of their family-history of specific diseases where family history and/or specific alleles have been demonstrated to add clinically significant information; 3) To evaluate the effectiveness of the HRA in motivating behavioral change; and 4) To evaluate physician knowledge of the role of genetics in disease.

Methods

Development of Health Risk Appraisal (HRA) including Genetic Information

Roseman JM, Go RCP, Acton RT, Cutler G, Louv W, Barger BO, Kramer JO, Bamberg R: A Computerized System to Assess Risk of Disease-Specific Morbidity and Mortality Utilizing Immunogenetic Marker Information Society of Prospective Medicine Proceedings of 23rd Annual Meeting Indianapolis Indiana Healthier People New Trends in Health Risk Assessment and Health Promotion pp 205-211, 1990.

Roseman, J.; Go, R.; Louv, W.; Perkins, L.; Kramer, J.; Bamberg, R.; Barger, B.; and Acton, R.: The Risk of Morbidity and Mortality Assessment (ROMMA): A Health Risk Assessment Utilizing Genetic Markers, Society of Prospective Medicine, Proceedings of the 23rd and 24th Annual Meetings 277-278, 1990.

Roseman, J.; Bamberg, Acton, R.; and Bamberg, R.: Health Risk Appraisal (HRA) Including Genetic Risk Indicators in Preventive Medicine. In: Matzen R.N., Lang, R., Editors: Principles and Practices of Clinical Preventive Medicine, St. Louis, CH 39, 784-798, Mosby, 1993.

Assessment and Validation of Family History Information

Acton, R.T.; Go, R.C.P.; and Roseman, J.M.: The use of family history of disease assessment (FHDA) instruments to target preventive measures. Society of Prospective Medicine Proceedings of the 25th Annual Meeting 86-95, 1990.

Fornage M, Lopez DS, Roseman JM, Siscovick DS, Wong ND, Boerwinkle E. Parental history of stroke and myocardial infarction predicts coronary artery calcification: The Coronary Artery Risk Development in Young Adults (CARDIA) study. Eur J Cardiovasc Prev Rehabil 2004; 11:421-6

Acton, R.; Go, R.; Roseman, J.; Perkins L.; Vanichanan, C.; Sedlacek, C.; Gore, T.; Cousins, A.; Brennan, J.; Moore, P.; Brand, R.; and Copeland, R.: Use of self-administered family history of disease instruments to predict individuals at risk for cardiovascular diseases, hypertension and diabetes. The American Journal of Human Genetics, 45:A275, 1989.

Developing Computer Software to Include Genetic Information Into an HRA

Roseman, J.; Go, R.; Acton, R.; Barger, B.; Louv, W.; Kramer J.; and Bamberg, R.: A Computerized System to Assess Risk of Disease-Specific Morbidity and Mortality Utilizing Immunogenetic Marker Information. Society of Prospective Medicines. Proceedings of the 22nd and 24th Annual Meeting. Healthier People: New Trends in Health Risk Assessment and Health Promotion 205-212. 1990.

Evaluation of An HRA

Bamberg, R.; Acton, R.; Goodson, L.; Go, R.; Struempler, B.; and Roseman,J.: The Effect of Risk Assessment in Conjunction with Health Promotion Education on Compliance with Preventive Behaviors. Journal of Allied Health 18:271-280, Spring 1989.

Bamberg, R.; Acton, R.T.; Roseman, J.M.; Go, R.C.P.; Barger, B.O.; Vanichanan, C.J.; and Copeland, R.B.: The effect of genetic risk information on compliance with preventive health behaviors. Health Education 21:26-32, 1990.

Bamberg, R.; Copeland, R.; Barger, B.; Roseman, J.; Go, R.C.P.; Vanichanan, C.; Brand, J.; Moore, P.; Acton, R.: Genetic Risk Information as an Impetus to Health Related Behavioral Change. Society of Prospective Medicine, Proceedings of the 23rd and 24th Annual Meetings 345-356, 1990.

Bamberg, R.; Acton, R.; and Roseman, J.: Preventive Behavior Impact from Health and Genetic Risk. In: Matzen R.N., Lang, R., Editors: Principles and Practices of Clinical Preventive Medicine, St. Louis, CH 41, 799-810, Mosby, 1993.

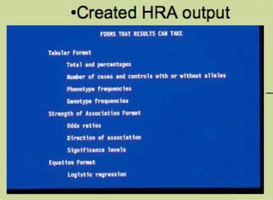
Evaluation of Physicians' Knowledge of Genetic Risk

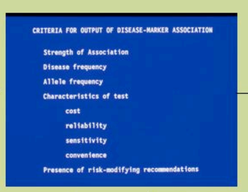
Acton RT. Burst NM. Casebeer L. Ferguson SM. Green P. Laird BC. Leviton L. Knowledge, attitudes and behaviors of Alabama's primary care physicians regarding cancer genetics. Acad Med, 75:850-852, 2000

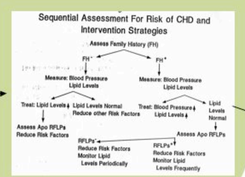
Results

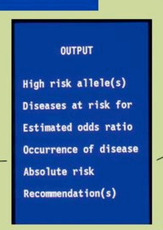
Development of the Risk of Morbidity and Mortality Assessment (ROMMA)

- Developed procedures for reviewing and abstracting publications of the associations and linkages between genetic markers and disease
- For 6 markers for which there were over 500 diseases which had been examined for associations, we reviewed over 8000 citations and abstracted over 2000 articles
- Developed process for combining the results across studies given that the results were presented in a variety of different ways. Also, often, if the association was not statistically significant in a study, the strength of the association was not reported even though it might be strong in other studies.
- Developed rules for decisions about including a particular marker and disease association in the HRA including for some diseases a sequential approach
- Developed Family History forms
- Created computer software which allowed for full customization of any HRA design
- Created computer software to output pedigrees
- Created HRA output









Validity of Family History Information

- We examined the sensitivities and specificities of the reports of probands and controls with respect to the disease status of other family members compared to the information provided by the family members themselves in three different samples with probands having three different diseases.
- The results are presented in the tables below.

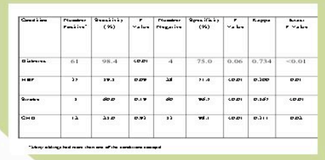
The first sample is middle-aged white males with an MI. The second sample is black and white adults who have hemochromatosis or iron-overload. The third sample is African-American females with diabetes.

Disease	Cases (N=405) Sensitivity %	Cases (N=405) Specificity %	Controls (N=298) Sensitivity %	Controls (N=298) Specificity %
CHD	79	99	67	98
Hypertension	70	97	58	95
Diabetes	89	99	83	99

Comparisons of proband's report of relative's condition and relative's self-report

Condition	No. Reporting (%)[a]	Sensitivity (%)[b]	No. Not Reporting (%)[c]	Specificity (%)[b]	Kappa[b]
Hemochromatosis or iron overload	13 (81.25)	81.43	519 (97.37)	97.34	0.5896
Arthritis	57 (54.29)	55.01	348 (78.38)	78.49	0.2781
Liver disease	2 (18.18)	18.39	536 (99.63)	99.62	0.2587
Diabetes	29 (58.00)	57.86	476 (95.39	95.72	0.5245
Heart Disease	19 (35.85)	37.35	467 (94.15)	94.22	0.3132

[a]The number and percent of probands who reported that a family member had the condition for which the family member also reported having the condition.
[b]The p-values for sensitivity, specificity and Kappa exact values are <0.0001 for all comparisons.
[c]The number and percent of probands who reported that a family member did not have the condition for which the family member also reported they did not have the condition.



Evaluation of Genetic Risk Information Impact

In a randomized trial, we compared the compliance with preventive recommendations between a "treatment" group that was given risk information based in part on family history and/or genetic information and a group which was given risk information not based on the family history or genetic information. The results are presented in the table below. The treatment group was more compliant with respect to a number of behaviors.

Table 2. Significant and Dissimilar Compliance Levels Comparing All Control Subjects and All Treatment Subjects

Behavior	Number Complying (%) Control Group	Treatment Group	p Value	Odds Ratio
Significant				
*CHOL CHK (BCL > 200)	5(16)	12(44)	.0318	4.32
Dissimilar				
WT ASK	2 (6)	9(27)	.0538	5.62
†CHOL CHK	5(12)	12(30)	.0805	3.17
LIM FAT (BCL < 200)	3(43)	8(100)	.1536	10.67
LIM CHOL (BCL < 200)	1(20)	4(67)	.3474	8.00
CALM (Not Type A's)	6(67)	8(100)	.5708	4.00

*Chi-square = 4.61, critical value at p < .05 is 3.84
†Includes both subjects with BCL < 200 mg/dl and subjects with BCL > 200 mg/dl

Physician Knowledge of and Attitude Toward Genetic Risk

In order to determine how knowledgeable physicians were about the genetic aspects of diseases, we conducted two separate surveys of Alabama physicians with respect to their knowledge of the genetic aspects of cancer in one and hemochromatosis in the other. We found with respect to cancer that the vast majority (94%) of respondents took a cancer family history with a new patient, but only about half updated it during any follow-up. The majority had not sent a patient for genetic testing within the previous year and were concerned about the effect of any test results on the patient's emotional well-being, employment and insurance. With respect to hemochromatosis, the vast majority (>90%) of physicians did not ask their patients about a family history of hemochromatosis.

Conclusions

- An HRA with genetic risk factors is feasible
- The validity of family history of disease information depends on the disease being studied and the characteristics of the type of people being queried. For the diseases examined the specificity is generally quite good although the sensitivity may be low.
- The provision of genetic risk information might lead to increased frequency of behavioral compliance in those who are at increased risk.
- Physicians do collect family history information with respect to some, but not all. familial -related diseases when seeing a new patient, but rarely update it, and their knowledge of genetics is often insufficient to convey genetic information to the patient.
- The issues which surround the use of genomics information in the public heath setting today are similar to those we faced in the past and still need further exploration.

Funding Sources:
Immunogenetics Program
Center for Health Risk Assessment and Disease Prevention