workshop c3: saturday, march 11

Genetic Screening: The Future Is in Prevention

What's new in newborn screening? E.R.B. McCabe, Mattel Children's Hospital at UCLA, Los Angeles, CA.

The goal of newborn screening (NBS) is identification of those at risk for genetic disease to provide diagnosis and treatment. Diseases selected for NBS include disorders in which newborns appear normal, untreated neonates die or suffer severe morbidity, effective treatments are available, inexpensive and reliable screening tests exist, and a significant number of neonates are affected. All U.S. NBS programs include PKU and congenital hypothyroidism, but additional tests vary from state to state. The American Academy of Pediatrics and the Maternal and Child Health Bureau sponsored a Task Force on NBS to consider national standards for inclusion of diseases in NBS and criteria for evaluation of new diseases and new technologies. Molecular genetic testing is used as a follow-up test for sickle cell disease NBS, providing confirmation from the original NBS blood blotters. New screening tests include tandem mass spectrometry, which is capable of quantitating a large number of analytes. A critical issue will be to determine which should be reported. Only four states test for cystic fibrosis (CF) at this time, but other states are planning CF pilot screening. Mutation screening for CF is another example of molecular follow-up testing for a positive newborn screen. Another new disease that is being added to the NBS battery is congenital adrenal hyperplasia with testing for elevated serum 17-hydroxyprogesterone. DNA confirmation helps to determine which infants have severe disease and require immediate treatment. Initial hearing screening involves physiologic testing in the newborn nursery. However, follow-up testing for connexin 26 mutations is being suggested for nonsyndromic, genetic deafness. Public health genetic screening in neonates is facing new applications and must consider ethical issues accompanying population-based genetic testing.

Adult Genetic Screening: Are we ready for hemochromatosis? L.A. Bradley[1], G.E. Palomaki[1], W. Burke[2] and J.E. Haddow[1]. [1]Foundation for Blood Research, Scarborough, ME, and [2]University of Washington, Seattle, WA.

Since the discovery of the *HFE* gene and two common mutations, clinicians, researchers, and public health policy makers have debated the role of genetic testing in the identification of hereditary hemochromatosis (HHC). With provision of appropriate information about benefits and risks of testing, mutation analysis is moving into routine practice, both as a diagnostic test for persons presenting with biochemical evidence of iron overload or clinical symptoms, and as part of risk assessment in families with a diagnosed case. Efforts to improve education of health care providers and consumers about HHC and available diagnostic testing are underway. However, HHC is often not recognized before the onset of serious clinical symptoms, and the public health impact of improved diagnosis alone may be limited. HHC is relatively common, potentially serious, and preventable with presymptomatic identification. For these reasons, some within the medical community and patient support groups have advocated immediate implementation of population screening for HHC. Many others, however, are urging caution until sufficient data are collected through intervention trials, both ongoing and planned, to adequately answer certain key questions, including: 1) the penetrance of the disorder by gender and age; 2) the impact of genetic and environmental modifying factors; 3) the extent to which certain associated clinical symptoms can be attributed to HHC; 4) the appropriate target populations for screening; and 5) the effectiveness, costs, benefits and risks of different screening strategies. This last question includes collecting information as diverse as whether it is more effective to use mutation analysis as the initial screening test or part of diagnostic follow-up, the psychological effects of positive screening results on "healthy" persons, whether screen positive individuals will be compliant over 10-20 or more years of monitoring and/or phlebotomy treatment, and how data might be collected to assess the ongoing safety and effectiveness of such a screening program. HHC would appear to be an ideal model for addressing a range of issues related to the integration of adult genetic screening into routine practice.

Genetics and Public Health in the 21st Century: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease? Muin J. Khoury M.D., Ph.D., Office of Genetics and Disease Prevention, CDC, Atlanta, GA 30333

With the completion of the Human Genome Project in the next few years, numerous DNA-based tests will become available in medical practice. Over 700 tests are currently used. An important challenge for the years to come is the appropriateness of using genetic information in disease prevention, the fundamental mission of public health. Using examples from genetic susceptibility to chronic diseases, I will discuss three main themes that serve as the scientific foundation for integrating genetics into disease prevention activities. The themes are: 1) human diseases results from the interaction of genetic variation and environmental factors, broadly defined to include physical, chemical, infectious, nutritional, and behavioral factors; 2) there is an urgent need for public health research agenda to define the appropriate medical, behavioral, dietary and environmental interventions that can be targeted to individuals with various genetic backgrounds; 3) the development of genetic tests can then be guided by evidence-based requirements for clinical validity (calculating positive and negative predictive values of predictive tests) and clinical utility (demonstrating reduction in morbidity and morality following testing). Using these themes, I will describe CDC scientific initiatives to provide intramural and extramural support for research in human genome epidemiology, prevention effectiveness, communication research and dissemination of information on genetic tests.