A summary of:
**"POPULATION-BASED CARRIER SCREENING FOR SINGLE GENE DISORDERS:
LESSONS LEARNED AND NEW OPPORTUNITIES"
February 6-7, 2008
Rockville, Maryland**

Population-based carrier screening for single gene disorders has been occurring since the 1960s, with each decade bringing new opportunities and challenges. In February 2008, approximately 125 scientists, clinicians, public health officials, and patient representatives gathered to consider population-based carrier screening in light of lessons learned and emerging technologies. The following document summarizes the content presented by the speakers, as well as the output of six breakout sessions designed to address particular challenges facing carrier screening in the decades to come.

Topics discussed were: experiences of large-scale carrier screening programs for cystic fibrosis (CF), sickle cell disease, and Tay-Sachs disease (TSD); the impact of emerging technologies on the ability to screen for disorders such as spinal muscular atrophy (SMA) and fragile-X syndrome (FXS); the ethical, legal, and social challenges raised by carrier screening; and public health perspectives on screening for genetic disorders in the setting of expanding technical capabilities.

The meeting was co-sponsored by the National Human Genome Research Institute (NHGRI), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), the Office of Rare Diseases at the National Institutes of Health (NIH), the Health Resources and Services Administration (HRSA), the Centers for Disease Control and Prevention (CDC), the Genetic Alliance, and the American College of Medical Genetics (ACMG).

In opening remarks, Co-Chair **Duane Alexander, M.D.**, Director, NICHD noted that several factors have converged in recent years, warranting renewed discussion about population-based carrier screening, including efforts to expand newborn screening (NBS) programs (which will identify more carriers), increasing use of pre-implantation genetic diagnosis and prenatal testing, and the prospect of the $1,000 genome. **Alan Guttmacher, M.D.**, Deputy Director, NHGRI, noted that a decade has passed since the last major review of a population-based carrier screening program (CF). As more tests become available for such programs, it is important to be mindful of the tensions that exist with regard to research priorities, the need for protections, and the push of technology. Further there are challenges in integrating any new technology in health care given current realities of the health care system which is in crisis. As technological advances provide the opportunities for expanded screening programs, several issues must be considered before moving forward.

Summary of Presentations

Public Health and Medical Perspectives on Population-Based Carrier Screening

Ned Calonge, M.D., M.P.H., **Chief Medical Officer, Colorado Department of Public Health and Environment**, provided a public health perspective on current applications of genomics, including:
- screening in asymptomatic individuals for genetic pre-disposition for disease
- screening for reproductive risks

- screening for acquired disease
- diagnostic testing for symptomatic disease
- testing to inform/alter therapeutic approaches (e.g., pharmacogenetics), and
- metabolic/proteomic screening for disorders.

Each of these applications provides opportunities for improved public health, for example, population-based epidemiology can take advantage of screening data and genomic registries to plan for services and design research. On the other hand, tensions between individual care and public health can become heightened in such applications as personalized medicine, where the high cost of a service that will only benefit a few might stand in conflict with the traditional goals of public health. Concerns that arise in the context of private healthcare and genomics (e.g., cost to consumers, privacy, choice) are not always consonant with the concerns of public health (e.g., public resources, population health). Nonetheless, public health practice can play a significant role by assuring the availability of services, follow up and treatment, and protection from unwarranted use of tests and test results. Meeting these challenges will require resources, accurate tests, and protections against harm. Variability in policies and practice must be addressed: for example, there are significant differences in state public health involvement in genomic application, and—with the exception of NBS—most carrier screening is conducted within the context of reproductive healthcare delivery and implemented through a medical standard of care. This means consumers are dependent on the knowledge of healthcare providers and access to care. Other applications of screening are unlikely to find a place in public health (e.g., diagnostic testing). However, an expanded public health perspective on carrier screening—beyond just the reproductive focus—could contribute to reduction of the prevalence of disease. Learning how to provide complex genetic information on a population basis will be critical to the success of any carrier screening program.   Evaluating the health value of genomic applications and prioritizing these within the larger context of health care services is essential, and will be challenging.

Louis J. Elsas, M.D., F.F.A.C.M.G., **Center for Medical Genetics, University of Miami**, provided a medical perspective of issues facing carrier screening in large populations. He noted that carrier tests remain relatively expensive, thus they generally are not appropriate as a public health strategy. A critical clinical consideration is whether therapies or interventions are available for the condition for which screening is being done—that is, what is the benefit of knowing? He added that the following criteria should be met before proceeding with carrier screening programs:

1. The disorder impairs health in the homozygous affected offspring.
2. There is a high frequency of carriers in the screened population
3. Technically and clinically valid screening methods are available and cost effective to all.
4. IVF, prenatal diagnosis, and termination are reproductive options.
5. Consent (informed and voluntary participation) is obtained.
6. Potential benefits and risks of carrier testing are communicated before and after the test.
7. Privacy is protected.
8. Stigmatization of the carrier by the community is minimized.
9. Experienced professional resources are available.

He noted that TSD carrier screening has been successful in the Ashkenazi community because many of these criteria were met. However, the population being screened was educated, motivated, and relatively homogenous. Several factors combine to caution against expanding

TSD carrier screening to additional ethnic groups, including "admixture," residual risks, and the need for functional (enzyme assay for HexA) as well as DNA-based screening tests.

CF carrier screening provides another type success story, in part because of data derived from pilot studies in the earliest stages of introduction. However, most infants with CF continue to be born to couples that do not know they are carriers, i.e., they were not offered carrier testing. Parental and professional acceptance of screening prior to pregnancy has been low in this group (parents of CF children) despite the obvious benefit of having more reproductive choices with preconception screening.

The well documented failures of the early sickle cell carrier screening programs highlighted the need for appropriate pre- and post-test counseling and greater attention to the social and clinical needs of the community and of screen-positive heterozygotes.

Dr. Elsas closed by saying that the widespread adoption of SMA carrier screening should be preceded by pilot research studies to determine community acceptance and allele frequency and to estimate the economics of testing methodology. In addition, to date, population-based carrier screening has not been recommended for FXS because of limited knowledge about intermediate expansions, inability to predict phenotype in females, lack of community and physician knowledge, limited counseling resources, lack of knowledge about community acceptance, and the costs of methods. These issues would need to be addressed prior to the adoption of a widespread screening program.

Lessons Learned from Carrier Screening for TSD

- **Robert J. Desnick, Ph.D., M.D. Professor and Chairman, Department of Genetics and Genomic Sciences**
- **Elisa Ross, President, Genetic Disease Foundation**

Dr. Desnick stated that prenatal carrier screening is currently available in the Ashkenazi Jewish population for as many as 16 recessively inherited diseases which to be at higher frequency in that group, including TSD. TSD is a fatal degenerative disorder of the central nervous system with onset of symptoms in infancy and death by age 2 to 5 years. There is no treatment available for this autosomal recessive disorder. Dr. Michael Kaback at Johns Hopkins began the first screening program in 1971, following the identification of the enzymatic defect. Education of the at-risk population and religious leaders led to wide acceptance of carrier screening. As of 2007, almost 2 million individuals had been tested, with over 65,000 carriers identified and over 1,500 at-risk couples found. Of these couples, nearly 4,000 pregnancies have been monitored and notably, over 3,200 unaffected children have been born. The screening program has been so effective that more TSD cases occur in the non-Jewish population than in the Jewish population. In 1997, the acceptance among Ashkenazi Jews of triple disease screening (for TSD, CF, and Gaucher disease) was evaluated and found to be high, which paved the way for incremental increases to the current screening panel of 16 diseases. (Individuals in the he Ashkenazi Jewish community have a 1 in 4 chance of being a carrier for 1 of the 16 disorders.)

Dr. Desnick noted that despite these successes, several challenges remain. TSD screening using an enzyme assay detects all carriers whereas DNA assays detect only specific mutations. Nearly all Ashkenazi carriers can be detected by screening for only three mutations; thus, DNA assays are preferred for screening in this population. However, as individuals increasingly marry

outside the community, the detection rate will decrease. Increasing intermarriage rates nationwide also poses new challenges for counseling, as *a priori* and residual risks change. A second challenge is the clinical variability of Gaucher disease, an autosomal recessive disorder. Carrier screening for this disease is considered controversial, because the more common Type 1 Gaucher disease is often asymptomatic and effective treatment exists. This raises the question of whether population-based programs should screen for carriers of low penetrance diseases. However, recent studies revealed this not to be the case as the prenatal carrier programs identify younger affected individuals who have disease manifestations. Finally, prenatal screening is not acceptable for Orthodox and Chassidic Jews because abortion, artificial insemination and birth control are not options. In 1982, Chevra Dor Yeshorim was established to provide compatibility testing, i.e., genetic screening prior to "matches." As of 2006, over 200,000 individuals were tested and over 800 proposed matches of carriers were averted. This model has already been transferred to the Saudi Arabian population where matches are made and certain recessive disorders are frequent.

Ms. Ross described the development of carrier screening options and guidelines and their acceptance in the Ashkenazi population, starting with the American College of Obstetricians and Gynecologists' (ACOG's) recommendations in 1976 and progressing to their 2008 technical standards and guidelines for screening. With each new issuance of guidance or standards, the number of diseases included in screening panels has expanded, often at the urging of affected families. Still, carrier screening programs vary by hospital, even in New York City, with some populations benefitting from expanded screening panels and robust education and counseling opportunities. These disparities raise issues for families who want expanded disease menus so that they can choose screening options.

Lessons Learned from Carrier Screening for Sickle Cell Disease

- **James Eckman, M.D., Director, Georgia Comprehensive Sickle Cell Center in Grady Health System**
- **Janet Ohene-Frempong, M.S., J. O. Frempong & Associates**

Sickle cell disease and sickle cell trait were first described in 1933 and recognized as a molecular genetic disease in 1949. Early morphology tests could differentiate normal, disease, and trait status. Carrier frequency in the Black population was estimated at 8.1 percent, with normal life expectancy and no medical implications. The National Sickle Cell Anemia Control Act of 1972 aimed to reduce morbidity and mortality from sickle cell disease through increased awareness and education and through development of new modes of therapy. NIH Comprehensive Centers focused on research and treatment, and HRSA (then HSA) funded sickle cell screening and education clinics focused on screening, education, information, counseling, and referral of disease. CDC was tasked with training, proficiency testing, and development of a reference laboratory. On the surface, this seemed to be a responsible public health strategy. However, misguided efforts resulted in mass screening programs conducted with inadequate training, poor methodology, and lack of counseling. In addition, legislators pushed for policies mandating premarital and preschool testing. These early programs did not decrease the incidence of sickle cell disease. Several factors were at play in addition to poorly implemented programs, including distrust in the Black community, lack of access to selective abortion following prenatal diagnosis, and other pressing social and economic problems.

NBS for sickle cell disease and other hemoglobinopathies was recommended in 1987. Treatment of the disease had improved and the death rate in the early years of life had dropped

from 20-25 percent to 2-3 percent. As of 2005, nearly 4.2 million newborns had been screened, with 3,419 infants found to have the disease and 72,111 found to be a carrier of one of the three mutations (HbFAS, HbFAC, or HbFAE). Most states do not report carrier status.

The identification of carriers through NBS programs raises several issues regarding notification of the carrier's parents, provision of education and counseling, and follow-up when the carrier reaches reproductive age, not to mention issues related to testing extended family, nonpaternity, and risk of stigmatization or discrimination. In the early stages of screening, carriers often were followed as individuals with disease and vice versa. More recently, it is becoming evident that carrier status might not be medically neutral for all individuals. The literature has included reports of clinical manifestation of carrier status, including: decreased urinary concentrating ability; recurrent hematuria; increased incidence of sudden death at extremes of human endurance; pain, splenic infarction, and sequestration at altitude; increased incidence of pulmonary emboli; and occurrence of a rare renal medullary carcinoma. Conversely, common diseases erroneously have been linked with sickle cell trait. Clearly, challenges remain with regard to understanding the medical consequences of carrier status for this disease as well as meeting educational and counseling needs.

Ms. Ohene-Frempong presented a consumer perspective as a parent of a child with the disease and a child with the trait and, also, as a plain language and cross cultural communications consultant. She emphasized the importance of making complex information accessible when results of sickle cell status are communicated through NBS programs. Ms. Ohene-Frempong is working on a HRSA-funded program to create materials and methods of information delivery that will increase health literacy, particularly about sickle cell disease and genetics. Methodology includes reliance on a series of surveys and focus groups to identify the best use of medical terminology and messages to ensure an accurate and readable product. For example, the term "trait" is not very descriptive, and the term "carrier" implies contagion or burden, so the use of "AS" to describe carrier status might be more obvious, and highlights the importance of the "S" gene. In addition, she stressed that the message has to be sensitive not just to the genetic aspects of the information, but also to the life impact of the information. Other considerations are whether, and how, to talk about other hemoglobinopathies (e.g., AC, AD, AE, A beta-plus thalassemia, A beta-zero thalassemia). Adequately and accurately simplifying complicated and probabilistic information in the context of population-based screening programs requires many formats and approaches to account for literacy levels, context, and venues for delivery.

Lessons Learned from Carrier Screening for CF

- **R. Rodney Howell, M.D., Professor of Pediatrics, Leonard Miller School of Medicine, University of Miami**
- **Martin Kharrazi, Ph.D., Genetic Disease Screening Program, California Department of Public Health**

A 1997 NIH consensus conference resulted in the first public recommendation for population-based CF carrier screening. The process, which brought together experts from many areas of medicine, as well as patient advocates, is a model for how to approach mass screening programs, said Dr. Howell. The goal of the conferees was to address the following central questions:

- What is the current state of knowledge regarding natural history, epidemiology, genotype-phenotype correlations, treatment and genetic testing of CF in various populations?

- What has been learned about genetic testing for CF regarding (public and health professional) knowledge and attitudes, interest and demand, risks, and benefits, effectiveness, cost and impact?
- Should CF carrier testing be offered to (1) individuals with a family history (2) adults in the preconception or prenatal period; and/or (3) the general population?
- What are the optimal practices for CF genetic testing (setting, timing, and the practices of education, consent, and counseling)?
- What should be the future directions for research relevant to genetic testing, and more broadly, for research and health policies related to genetic testing?

Among several recommendations, the group suggested that carrier screening for CF should be offered to adults with a positive family history, partners of people with CF, couples currently planning a pregnancy, and couples seeking prenatal testing.

In 2001, ACOG and ACMG issued clinical and laboratory guidelines stating that carrier testing should be offered to Caucasians and Ashkenazi Jews using a universal pan-ethnic core mutation panel. The guidelines addressed the specifics of the panel, reporting of residual risks, and quality assurance standards.

In the early stages of widespread screening concerns emerged about the mutation panel because mutation frequencies differ in the general population. In addition, a survey of OB/GYN practice patterns revealed that while many practitioners were familiar with the recommendations, they were not always offering carrier testing, although they were more likely to do so during, rather than before, pregnancy (i.e., they were not using the recommended selection criteria). This highlighted the importance of continuing education and the need for simple and clear language in guidance.

Dr. Kharrazi provided a parent's perspective as well as the results of two California obstetrical provider surveys. The percentage of obstetrical providers offering prenatal CF carrier screening increased from 17 percent in the one-year period before the ACOG/ACMG guidelines to 53 percent 1-2 years after the release of the guidelines. In the second survey in 2003, inadequate provider knowledge and time, lack of patient knowledge, lack of CF screening educational materials, and high cost of the test were the most common reasons for not offering CF carrier screening.

Since 2001, many developments have changed the context of CF carrier screening in 2008. CF NBS has increased from 8 state programs in 2001 to over 40 in 2008. Because CF case detection rates (sensitivity) are lower for prenatal carrier screening than for NBS there are more parents being told that they are test negative for CF carrier status but who later find out that they have a newborn with CF according to NBS. This is causing parental confusion, denial about their child's CF status, and distrust of the medical profession. CF clinical care has improved and predicted median age of survival has risen from 32 years in 2001 to 37 years in 2006. As such, CF is being perceived more as a manageable chronic disease than a fatal genetic disease, but this perception varies by medical specialty so different messages are a source of confusion for parents. Knowledge about CFTR mutation frequencies and genotype-phenotype correlations has improved and this has revealed that the widely-used ACMG-23 CFTR mutation testing panel includes mutations with varying degrees of severity, is not equitable across geographic subgroups, and is not comprehensive for the non-White population. Together, these factors place even greater demands on limited educational and counseling resources, particularly preconception counseling and testing. In addition, they highlight the need to revisit the composition of the mutations on the panels used for carrier screening to achieve higher test sensitivity, specificity and equitability, to improve interpretability of the test results, to reduce

current levels of provider and patient confusion, to the lower the cost of the test, and to reduce the time for genetic counseling.

An Update on Technologies Relevant to Carrier Screening

- **Eric Hoffman, Ph.D., Children's National Medical Center, Washington, D.C.**

In general, the technology for gene variant screening used in NBS programs can be used in population-based carrier screening. Several factors are critical in distinguishing which technology or technique is most relevant, including whether the screening is for a monogenic versus polygenic disorder, whether or not a high *de novo* mutation rate exists for the disorder and to what extent copy number variation plays in the disorder. Available technologies include genotyping assays, sequencing, and comparative genomic hybridization (CGH). Each has its advantages and disadvantages. Genotyping assays are most appropriate for allele discrimination, sequencing is best suited when dealing with a high mutation rate that is widely distributed, and high copy number variations call for CGH.

Genotyping assays include TaqMan ® - based assays as well as molecular diagnostic microarrays (SNP chips containing panels of mutations). Although costs are coming down for these assays, especially for SNP chips, it doesn't make sense to genotype 1 million SNPs for population-based carrier screening, said Dr. Hoffman. Current SNP chips do not sequence disease genes and do not contain common disease gene mutations. Custom chips could be constructed, however, that target mutations of interest. Cost and pragmatism are key considerations.

Sequencing is best for testing for dominant disorders and disorders for which there is a high new mutation rate. Duchenne Muscular Dystrophy is an X-linked recessive disorder with a high *de novo* mutation rate and could be the first X-linked disorder placed into population-based screening. However, because of the high mutation rate and the size of the gene, high-throughput screening will be difficult. Targeted sequencing using a shotgun method, and sequencing by hybridization are the most promising approaches in the near term.   Advances in whole genome sequencing do not necessarily advance targeted sequencing.

CGH is best used when there is copy number variation. There are numerous examples of disease-associated copy number variations, but most are not reflective of carrier status. Thus, CGH is best suited for patient diagnosis.

Hybrid chip-based assays are likely to emerge as the best tool for population-based carrier screening because they can detect all common mutations in recessive disease and provide quantitative assays (CGH-type information) for common copy number variations.

Current Challenges in SMA Carrier Screening

- **Thomas W. Prior, Ph.D., Ohio State University**
- **Deborah Heine, Claire Altman Heine Foundation, Inc.**

SMA is the most common autosomal recessive genetic disorder lethal to infants. It is caused by a homozygous absence of the survival motor neuron gene (SMN1). SMA has a carrier frequency of approximately 1 in 40 individuals; this prevalence shows neither racial nor gender

preference. The disorder manifests itself through anterior horn cell degeneration resulting in progressive weakness and muscle atrophy. Only supportive treatment is available currently.

There are three types of childhood SMA: Type I (the most prevalent and most severe form, also known as Werdnig Hoffmann disease) – 50-70% of all SMA children suffer from Type I – these infants have severe generalized muscle weakness, can never sit unaided, over time become unable to swallow or control their own secretions, and generally die from respiratory failure within the first two years; Type II, the next most prevalent form, in which children cannot walk or stand unassisted, are generally very frail, and survivability is variable; and the mildest and least common form, Type III (also known as Kugelberg-Welander), in which children are ambulatory and typically walk unassisted for a period of time before needing a wheelchair for mobility. There is also an adult onset form, Type IV, in which symptoms appear after age 35; this form is very rare.

Humans possess a nearly identical SMN2 gene that provides insufficient amounts of fully functional SMN protein that is necessary to maintain survival of motor neurons throughout development. There is a genotype/phenotype correlation in SMA; milder phenotype has been associated with increased copy number of SMN2.

Carrier testing was first offered in 1997, and to date over 1,500 test have been conducted, the majority on family members of previously affected individuals. Widespread carrier screening is possible, though there are two limitations: 2% of SMA cases arise as a result of de novo mutation events, and the copy number of SMN1 can vary on a chromosome, about 5% of the normal population possesses three copies of SMN1 – thus, it is possible for a carrier to possess two copies of SMN1 on one chromosome and no copies on the second chromosome. However, carrier testing can detect 90 to 95 percent of carriers since 95-98% of all cases result from a common single deletion event.

Education is the key missing component to implementing a successful pan-ethnic carrier screening program for SMA. The Claire Altman Heine Foundation Pilot Program for Population SMA Carrier aims to improve education, estimate carrier frequencies, determine allele frequencies, and assess technical and cost feasibility.

Ms. Heine explained that the Claire Altman Heine Foundation was founded in 2005 in memory of her daughter, who died as a result of SMA Type I. The Foundation uses its funding to advocate for the implementation of pan-ethnic, population-based SMA carrier screening, to raise awareness of SMA, and to educate the public and professional communities. Ms. Heine emphasized that the need for pan-ethnic SMA carrier screening recommendations and/or guidelines by governmental and professional communities is compelling.

The impact of SMA is severe and clinically significant; Type I is fatal in early childhood; and currently there is no treatment or cure available. Carrier screening would provide options to couples where both partners are carriers of the SMA gene mutation. Since SMA is present in all populations, carrier testing should be offered to all couples regardless of race or ethnicity. Ideally, the testing should be offered before conception or early in pregnancy. The primary goal is to reduce the prevalence of SMA by allowing carriers to make informed reproductive choices.

Current Challenges in FXS Carrier Screening in the Prenatal Population

- **Tom Musci, M.D., San Francisco Perinatal Associates, University of California, San Francisco**
- **Don Bailey, Ph.D., RTI International**

FXS is the most common cause of inherited mental retardation, with an incidence of approximately 1 in 4,000 males and 1 in 8,000 females, in which it is less severe. It is found among all ethnic groups and occurs in families with no history of mental retardation. There is a spectrum of clinical involvement and FXS-associated conditions are found among carriers, including premature ovarian failure, and tremor and ataxias. One in 259 women is a carrier of the FXS premutation; however, most will have a negative family history. Only the mother has to be a carrier for the fetus to be at risk. The fragile X mutation is an unstable CGG repeat that can expand dramatically when a premutation allele is passed from mother to offspring. The risk of expansion of the repeat is influenced by the gender of the carrier and the number of repeats in the premutation; the higher the repeat number the greater chance of expansion to a full mutation .

ACOG/ACMG has recommended carrier testing only for individuals with: a family history of FXS or undiagnosed mental retardation, developmental delay, or autism; and prenatal diagnosis when the mother is a known carrier (of either the premutation or full mutation). However, risk factors based on screening alone are not effective in detecting carriers. For example, based on one published model, the maximal rate of detection of female premutation carriers by active cascade screening is 6 percent, compared with prenatal screening (60 percent). Moreover, the largest proportion of FXS births occurs in families without index cases. In addition, 50 percent of women have more children after having a child with FXS, but before that child has been diagnosed.

Thus, a case can be made for population-based carrier screening as FXS appears to meet the criteria applied to other common screening programs, i.e., the disorder is considered a significant health problem or carries a burden of disease, screening could be accomplished in a simple manner, and screening could be cost-effective. Pilot studies have shown that participants are in favor of testing or screening. Arguments against population-based screening are: 1) the genetics are too complex; 2) current education and counseling resources are inadequate; 3) the phenotype for female fetuses with full mutations cannot be predicted; and 4) time and costs.

Dr. Bailey described a study to assess the benefit of including FXS in NBS programs. Benefit to the infant is a fundamental tenet of NBS—historically this has been a necessary condition for screening. Although there is no cure for FXS, children with the full mutation are likely to experience a range of impairments that could be reduced, delayed, or prevented through early intervention. What should the policy be if there was a relatively inexpensive test that could accurately screen newborns for FXS? What if the test was DNA based and accurately reported CGG repeat length, thereby differentiating children with a full mutation from those with a premutation? A critical question is how carrier status would be reported. Because there are some phenotypic characteristics found in the carrier population, could early identification reduce or prevent risks?

Key questions to be answered include:

- Will parents agree to have their children screened for FXS, knowing that carriers could be detected?

- Why do parents accept or decline screening, and are these reasons associated with socio-demographic variables?
- Do families of identified children feel they were adequately informed about possible results?
- Are families of identified children satisfied with their decision to participate?
- To what extent do mothers suffer adverse mental health outcomes from disclosure of carrier status?
- Are parent-child relationships affected by knowledge of FXS carrier status?
- How do parents and extended family members respond to, share, and use information from screening?

In sum, screening for full mutation FXS would likely benefit children and families. However, screening for carriers evokes important questions about benefit—for whom? and how? FXS is a good prototype to use in a prospective study of screening benefits. However, rather than thinking strictly in terms of cost-benefit, said, Dr. Bailey, we might need to assess family adaptation to information gained through screening.

Carrier Screening: Populations, Stigmatization, and Eugenics

- **Keith A Wailoo, Ph.D., Martin Luther King Jr. Professor, Rutgers University**

Previous population-based screening efforts have illustrated the importance of balancing the interests of individuals, communities, and society, and the need to recognize historical sensitivity and cultural competence among health practitioners who engage in screening. Deciding which populations to target and the potential emergence of "hidden" subpopulations (e.g., sickle cell carriers) warrants focused attention. Moreover, one-size does not fit all—screening must be considered in light of group values and concerns. We also have learned the importance of competent screening programs among populations whose group identities are invested in the maintenance of values that are distinctively different than that of the majority culture, said Dr. Wailoo. Importantly, despite the many similarities in the evolution of carrier screening programs for sickle cell disease, CF, and TSD, each disease is linked to a specific racial/ethnic group, thus the term "genetic disease" does not do full justice to their complexities. Lurking in the background has always been the ultimate goal of developing therapies, so that the emphasis on prevention can be alleviated. In fact, treatment has improved for CF and sickle cell patients and life expectancy has improved. Behind the curtain of prevention lie the more challenging ethical dilemmas of prenatal diagnosis and selective abortion, artificial insemination by donor, adoption, or childlessness.

Clearly, each genetic disease and each population follows a unique trajectory: shaped by complex interactions among science, technology, medicine, values, subculture, and society. Histories of therapeutic advancement reveal that they solve some problems while creating others in their wake. For each of these three diseases, different interests and social, political, economic investments in screening resulted in different kinds of stigma and different meanings for each population. Thus, each carrier screening program comes to have different political, social, and cultural meanings.

Reports from Small Group Sessions

A. What to screen for and when to screen? Developing criteria for disorder selection in the setting of economic and social constraints.

Criteria for screening should be established before generating a list of disorders to consider. A framework for criteria development already exists through the ACMG Report on Newborn Screening, which included: test accuracy; financial burden of testing; prevalence and carrier frequency; the natural history of the disease, including its severity, burden, and course; homozygous and heterozygote phenotypes; and whether an intervention is available for those identified as carriers. The top three considerations should be carrier frequency, disease burden, and cost of screening.

What to screen for depends on the rational for screening, i.e., what actions can be taken and when would screening occur across the life spectrum? Screening to date has been large ethnocentric; thus, one obvious criterion is ethnicity as well as personal and family history. When to screen depends on several factors, including cost, and the meaning of the information to the individual being screened. Consent/assent issues differ across the prenatal, neonatal, child, and adult populations. There can be risks with screening too early, either in the life of the individual, or the life of the technology. Benefit to the individual should be paramount, but the "family" nature of genetics blurs that requirement.

An expert panel should be convened to develop a scoring system for selection, based on review of data collected from stake holders, economists, patients, and providers, as well as surveys of potential target populations. Guidelines should be developed as soon as possible and revisited and revised as more data become available.

B. How should we balance the screening interests of individuals, communities, and society?

The first order principle is to engage the relevant communities. While consumer-driven special interest might be major force, the medical model is an equally significant force; thus, identifying the rightful gatekeeper is challenging. In any case, the gatekeeper should be trusted by the community, which can be difficult to define. State public health programs are not surrogates for the community, and in some cases communities are self-defined rather than neatly categorized along clinical or demographic lines. Some communities are more tightly knit and organized than others (e.g., Amish, Ashkenazi Jews). Many are proactive, wanting to be actively involved in research designs, development of registries, and development of public policy.

There are different screening models along the spectrum of community involvement, from the loosely defined newborn community for which screening is mandatory to communities requesting screening before it is technically or economically feasible.

In considering the interests of individuals, communities, and society we must consider the disorder being screened for, the time of screening (preconception, prenatal, newborn, adult), who will pay, who has access, and post-test consequences (e.g., counseling, planning, elective termination).

Other screening models to consider in developing criteria are imaging, cholesterol, blood pressure, and obesity, as indicators of future disease. Immunization policy and seatbelt laws are public heath models that bypass individual interest in favor of public health and societal

interests. It is important to recognize that sometimes genetics will be overshadowed by behaviors; thus, education efforts and community involvement will vary depending on where they occur (e.g., school, clinic), when they occur (e.g., newborn, during pregnancy), and who leads them (e.g., consumers, health care providers, researchers).

"Market" pressures come from technology (e.g., $1,000 genome), special interest consumer/advocacy organizations, professional society guidelines, and specific community concerns.

Can we devise a set of criteria to determine when something rises to the level of available, optional, or mandated carrier screening? We need a framework for making these determinations. We need to be clear about the incentives for screening, determine the appropriate intervention, and establish who pays. There was a strong consensus for voluntary programs with education to make informed choices. Screening programs must be balanced, ensure access, account for health disparities and cultural differences, accommodate technology advances, recognize market pressures, address public health needs, respect individual autonomy, be economical, and address potential for discrimination. Education is essential as is community consultation.

Important considerations are discerning the difference between offering screening versus making it available, planning for the long-term, and developing registries and mechanisms for surveillance and risk assessment. A significant challenge is developing strategies for interventions for carriers identified through NBS programs, as this is not a well-defined or well-understood community.

C. Should services be targeted to subpopulations? If so, on what basis can subpopulations be accurately identified? Balancing science, ethics, and clinical utility.

Decision making regarding population-based screening must balance science, ethics, and clinical utility. A key consideration is when to address targeting issues—at the time when screening is offered or when interpreting the results of screening. If you cannot categorize people on the front end of screening, you can at least customize the interpretation on the back end. There is always the need to balance the desire for equitability with constraints. Should it be a public health activity or a clinical program, and how will that constrain or facilitate delivery?

The community should drive what is offered, but defining community is difficult—is it ethnicity, self-identity, or based on scientific markers? Another way of defining community is through point of service (e.g., newborn, prenatal). Carrier screening made available only through the prenatal settings favors those with access to prenatal care. However, education limitations and the priorities of primary care limit the ability to make screening widely available.

Subpopulations should be targeted only if population characteristics (e.g., reproductive isolates, specific geographic origin of ancestors) justify such an approach. Over time, DNA markers integrated with screening markers might change the targeting strategy by modifying the *a priori* risk and clinical validity.
Carrier screening resulting from NBS is a by-product that produces another subpopulation.

It will be important to assess the long-term effects of carrier detection, e.g., the outcomes of cascade carrier detection versus screening on the basis of increased risk versus offering screening to all. The intended use is the first limitation to a programmatic approach and lack of

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clinical validity data in larger populations will limit our understanding of the most effective approach.

D. How is informed consent defined and obtained? Models for multiple complex tests applied to the general population.

The informed consent process provides information to the recipient, including risks and potential benefits of either being tested or not being tested, and the anticipated outcomes of testing. The information provided should be appropriate to the literacy level of the patient and culturally sensitive. Information can take many forms: multimedia, personal instructions, and written materials. There need not be a signature on a consent form for informed consent to occur. Consent should be obtained and discussed by personnel knowledgeable about the issues involved. All methods and approaches used for informed consent should be evaluated for effectiveness.

Informed consent for testing is the standard of care and perhaps even a statutory requirement in some states. Consent to diagnosis is distinct from consent to research.

When a carrier is identified during the course of NBS, "accidental detection of a carrier" occurs. Such incidental findings can also reveal nonpaternity. There is wide variation in policies in this area, which are made more complex because there was no prior consent for such screening, during which the potential for such results could be disclosed. Some programs provide specific information about the carrier state with verbal or written materials. One program advises the family that there is additional information available that might be of value should they want it— about half of families follow through. The group expressed general concern about the level of effort required for follow-up and counseling for infants being screened for FXS if the premutation were identified rather than the full-mutation. A California laboratory has been mandated to reduce the number of carriers identified in order to reduce the burden on follow-up. To accomplish this it has modified its mutation panel and cut-off values.

Key elements of informed consent for carrier screening include: the meaning of the term carrier, its meaning to you and your family, risks and potential benefits of the information, where to get follow-up information, levels of uncertainty about the test, and the future of the disease. These elements become more complex with the use of multiplex tests. It is not practical to discuss and describe each disease for which carrier screening might be done in multiplex panels. Templates should be developed that describe that carrier screening will be done for a group of conditions that might adversely affect your offspring.
In the event that one of the carrier tests is positive, then detailed counseling about that condition should be carried out.

With regard to research, a national or central IRB could be created for carrier screening studies.

E. How can we measure the success of carrier screening programs? Developing an evidence base.

Do we define success in terms of public health or individual benefit? Should we measure net health benefit (i.e., balance between positive and negative outcomes)? Is one goal to reduce disease frequency in the population for lethal conditions? Key variables in answering these questions are clinical severity, longevity, and quality of life for treatable conditions. Other factors to consider are reproductive options and maximizing therapeutic approaches. One measure of success is participation by the target population when choice is an element. Another measure of

success is adequate understanding by participants. At the systems level, a measure of success is appropriate follow-up by health care providers and the grass roots community as well as fair access to screening and counseling.

Major issues to consider in adopting a new screening program include: development of well-defined positive and negative outcomes; demonstrated ability of providers to educate consumers about screening; the burden of disease in the population; genotype-phenotype correlations; long-term follow-up from screening (longitudinal outcomes); insurance coverage and implications for carriers; and measures of quality of life for carriers who do not have children with conditions.

Methods for measuring success include: evaluations of pre- and post-testing education; surveys to determine whether tests are being appropriately offered; assessment of opt-in and opt-out rates; costs per net health benefit measurements; qualitative measures of "choice" in carriers and the general population (individuals who are screen negative); evaluations of enhanced genetics competency of health professionals; cohort studies (follow-up of screened populations) for rare diseases; population-based studies for other conditions; community-based research (e.g., public consultation).

F. What will be the "next generation" screening methods? Technology development, screening, and the $1,000 genome.

New methodologies must be robust enough to qualify for population-based use; i.e., high analytic validity, replicable in many settings, high-throughput, cost-effective (including sample acquisition and preparation). If the near-term answer is hybrid chip-based assays, what approaches should be pursued in the long-term? DNA-based testing may not always be the best or complete answer. Analyte-based testing may play a role. Ideally, a two-stage approach should be used—DNA-based screening followed by analyte-based (or other) confirmatory testing.

Who develops a test and their motivations (e.g., economic and/or public health) might influence how evaluations of clinical validity and utility are performed and who will pay for such assessments. Addressing issues of specificity and false positives are complex when hundreds to thousands of tests are being run simultaneously. Who will decide which tests to read out, especially when a test has no incremental cost but the information it provides may not (yet) be clinically useful (e.g. CF tandem mass spectrometry experience in newborn screening)? How and when should such information be "released" and might there be staged release that is partially dependent on individual preferences, life stage, and clinical need.

Is the "$1,000" in the $1,000 genome the cost of the test to the tester or the person being tested? Does it account for counseling and other health care provider costs? Does the focus on cost over emphasize the technology rather than the need for clinical validity/utility, provision of relevant clinical services, and potential for genetic discrimination? The $1,000 genome might not be the answer for population-based carrier screening—will it be population based or population targeted? It might be more useful to consider an assortment of $1,000 (or, $100) genetics-based assays, each of which has clinical utility for differently defined populations, or, one "test" (potentially, whole genome sequencing) with an assortment of "subpanels" that are read out in various specific situations.

Clearly, new technologies will blur the distinctions between single-gene and common disease testing. If, that is the case, defining the needs of a "population" will become more difficult,

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requiring more of a focus on primary care. In moving forward with screening programs, it is critical to recognize the distinctions between predisposition screening, carrier screening, and diagnostic testing, and screening adults versus children. In addition, because carrier status is not always clinically neutral, the clarity between carrier status and unaffected is diminished.

Finally, is technology driving too much of the conversation and research agenda? New technologies may require new safeguards, or at least reinforce the need for ones we already are aware of (e.g., GINA).

Concluding Comments

In closing remarks, Dr. Alexander reiterated the numerous factors pushing for a more coherent and systematic approach to introducing new tests into population-based carrier screening programs. The history of current programs informs these discussions by highlighting the need for better techniques, more education, and access to counseling. He expressed concern that the largest screening program to date—NBS—has no consistent policy across programs, especially with regard to "incidental" identification of carriers. At some point this incidental identification might become intentional, and we should be better prepared than we are. And, as NBS panels are expanded, the issue becomes more critical. Dr. Alexander noted that several federal bodies are already reviewing screening programs, such as the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children (ACHDGDNC). This group was chartered to advise the Secretary regarding the most appropriate application of universal NBS tests, technologies, policies, guidelines and standards for effectively reducing morbidity and mortality in newborns and children having, or at risk for, heritable disorders. In addition, new legislation requires the Secretary to assess the impact of NBS screening for FXS.

Dr. Francis Collins, Director, NHGRI, closed the conference by also emphasizing the importance of developing more uniform policies with regard to carriers detected through NBS programs. He also stressed that the environment is likely to become even more complicated as technology advances and the market places more pressures on the healthcare system and consumers. In moving forward we must recognize that criteria for screening programs rightfully should differ depending on the context within which a program is offered. As a next step, discussions should focus on what additional conditions are now appropriate for population-based carrier screening? These discussions should involve the public, perhaps under the guidance of an expert panel tasked to identify research needs and define the criteria for screening.

There was some discussion as to whether CDC's Evaluation of Genomic Applications in Practice and Prevention (EGAPP) project could undertake reviews of screening for specific disorders (e.g., SMA, FXS), or whether the Secretary's Advisory Committee on Genetics, Health, and Society might be asked to review issues surrounding expanded carrier screening programs.