Integrated theoretical model to enhance neonatal screening for sickle hemoglobinopathies in the wake of predictive, preventive, personalized and participatory medicine

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ABSTRACT: This study utilized the integrated theoretical model (ITM) to assess strategies to ameliorate screening for sickle hemoglobinopathies in the age of genomic medicine. Also discussed, is the relevance of predictive, preventive, personalized and participatory interventions. Comparison was made between universal and targeted screening. The international guidelines for neonatal screening were reiterated. The self-efficacy and empowerment of mothers is crucial in ensuring that they effectively participate in the treatment and follow-up of their new-born babies. We emphasized the compliance with the ethical, legal and social implications of newborn screening for genetic diseases.

[E. William Ebomoyi. Integrated theoretical model to enhance neonatal screening for sickle hemoglobinopathies in the wake of predictive, preventive, personalized and participatory medicine. Journal of American Science 2010;6(11):531-537]. (ISSN: 1545-1003).

Keywords: integrated theoretical model (ITM); ameliorate; sickle hemoglobinopathies; genomic medicine; neonatal screening; ethical; legal; social; genetic diseases

Background

Sickle cell disease is a recessive hereditary disorder. "This disease involves the possession of two abnormal allelemorphic genes related to hemoglobin formation, at least one of which is the sickle cell gene, the genotypes constituting sickle disease being SS, Sc, S Thal, SE, SF 'high gene' and SD."(Konotey-Ahulu, 1974). Sickle cell is usually inherited in an autosomal recessive Mendelian pattern. The clinical abnormality caused by sickle cell anemia includes manifestations of severe pain, leg ulcers, and swellings of the joints, pains in the abdomen, arms, fatigue, and sometimes death. For pediatric age, splenic sequestration, sepsis and stroke are more common and carries a high mortality, whereas for adult cohort, eye disease and organ damage and pulmonary hypertension are quite frequent (Calloway, 1977).

The observable differences between sickle cell disease and sickle cell trait (SCT) were discovered 61 years ago. The differences lie in the quantity erythrocytes of sickle cell trait and sickle cell disease and the involvement of greater reduction in the partial pressure of oxygen which is required for a significant quantity of the trait to sickle than to sickle cell disease. In sickle cell trait, a person inherits one normal hemoglobin gene (A) from one parent and one abnormal gene (S) from the other parent. With regards to sickle cell disease two abnormal genes are inherited, one from each parent. Since sickle cell disease is a hereditary disorder, the specific mechanism for this genetic inheritance follows the Mendelian pattern (Kene, 1978).

Regarding hemoglobinopathies, these are conditions that affect the nature and proportion of hemoglobin which individuals have in their red blood cells. Hmoglobinopathies is the clinical term used to describe the presence of abnormal hemoglobin

production in the blood. Although sickle cell disease is the most common hemoglobinopathy in this century, and with innovations in genomic technologies, a litany, of sickle hemoglobinopathies will be genotyped and diagnosed. We reiterate that the success of the Human Genome Project (HGP) in mapping the entire human genome is a triumph comparable to the development of the theory of relativity, and it opened the door to a new branch of biomedical science, genomics. Genomics differs from the more established discipline of genetics in that it examines not only existing characteristics of the genome but also those related to the environment (haplotypes) and biological inheritance. In particular, genomics holds out the potential for early identification of disease and disease risk, preventive strategies, "personalized medicine" and pharmacology (Ebomoyi and Ebomoyi, 2010).

Against this background, the study described here was designed to explore adoption of integrated theoretical model to enhance screening for sickle hemoglobinopathies in the age of genomic medicine, define and accentuate the crucial nature of predictive, preventive, personalized and participatory treatment of patients, assess relevance of universal and targeted screening for sickle hemoglobinopathies, identify international guidelines for neonatal screening, succinctly discuss the ethical, legal, financial and social implications of neonatal screening; emphasizing the empowerment of women and the importance of trait counseling are valid primary preventive initiatives.

Integrated Theoretical Model

The two distinct models most applicable in neonatal screening for sickle hemoglobinopathies involve the integration of the Social Cognitive Theory (SCT) into the Health Belief Model (HBM)(Rosenstock,1974). The HBM hypothesizes that health-related actions depends upon individual's view of perceived susceptibility to a disease (X), such as sickle hemoglobinopathies particularly in a society where there is no premarital counseling. This situation is rampant in rural America, South America, Africa, South East Asia and the Mideast. The second issue is the belief that one is susceptible to a disease that is very severe. The classical symptoms of sickle hemoglobinopathies are many and varied. There are specific variants of sickle hemoglobinopathies that are life-threatening while very few variants confer mild distress on patients. At present, there is no known cure for sickle hemoglobinopathies (Ebomoyi, 2009).

The HBM also emphasizes the belief that compliance with health recommendation would be relevant in reducing the perceived threat. This process is dependent on both demographic and structural variables as education; that is, knowledge about the disease and prior contact with it. The cues to actions include mass media campaigns advice from others, illness of family members, magazine articles and reminder postcards from physicians (Maiman and Becker, 1974). Sickle hemoglobinopathies are quite rampant among people of African ancestry and this disease has a frequency of 1 in 8 African-Americans as carrier of the disease and 1 out of 400 carrying the autosomal recessive genes doubly homozygous (Ebomoyi, Cherry, 2010). The likelihood of complying with the recommended actions occurs once the perceived benefits of preventive actions outweigh the perceived barriers (Figure 1) Bandura (1977). (SCT) made two cogent contributions to the HBM. The first is emphasis on several sources of information for acquiring expectations particularly on the informative and motivational role of reinforcement and by observational learning through modeling. A second pertinent contribution is the introduction of the concept of self-efficacy; which means "the conviction that one can successfully execute the behavior required to produce the outcome."(Bandura, 1977) This integrated model has been used for many screening activities involving genetic services, family health and planning and other behavioral health problems (Bandura, 1977).

In United States, neonatal screening for hemoglobinopathies has been well established in many of the urban tertiary health care centers. At present the screening for hemoglobinopathies occurs in 43 states and in the District of Columbia, Puerto Rico and the virgin island Screening is now well established by the State Department of Laboratory and Federally mandated Newborn screening program. Implementation occurs in the hospitals where all newborns are screened for hemoglobinopathies and other disorders. Annually, screening at States' level has identified over 2000 infants with sickle diseases and additional 50,000 newborn with sickle cell trait (Day et al; 1977). Once identified, children having the disease are automatically referred to their pediatrician of record or hematologist as identified by the State Newborn screening program. In Louisiana and many other states, a medical social worker develops a follow-up plan to encourage mothers of children with sickle cell to participate in health education activities to facilitate compliance with both prevention and other medical interventions.

With existing stringent budget, not many States have followed this intervention quite religiously. Day et al,(1977) remarked that national standard have not been established for follow-up of the neonates with the heterozygous condition. Besides, several factors contribute to the unsatisfactory counseling activities at state level because screening program have shoe-string budget, and prompt identification and follow-up services for sickle cell patients is given low priority.[12] This statistics pinpoint that trait counseling and primary prevention against the sickling genes has not been intensified. Therefore, educated and affluent expectant mothers of African ancestry must utilize their self-efficacy and empowerment initiatives to encourage their counterparts to participate in neonatal screening and comply with routine medical regimen and demand that the program needs to be accorded higher priority. We must emphasize that among rural expectant mothers who use the services of traditional birth attendants, the benefits of neonatal screening could be ignored to the detriment of their newborns.

Predictive, Preventive, Personalized and Participatory Interventions

In the era genomic medicine these 4p's constitute precision medicine. According to Dr. ELias Zerhouni (2010), The former director of the National Institutes of Health(NIH), the new medicine must anticipate and interrupt the disease process, thereby preventing the patient from being overwhelmed by the actual disease burden. The Institute of System Medicine (ISM) (2010) defined (1) predictive approach as the development of probabilistic health projection for a person based on their DNA and protein expression. (2) preventive medicine is the creation of interventions or therapeutic that will prevent a disease that an individual is assessed to have a high probability of developing. Regarding sickle hemoglobinopathies, trait counseling of young adults of child-bearing age is one technique of making primary preventive strategy most effective. (3) Personalized medicine refers to treating individuals based on their unique human genetic variations. For example, what are their sequenced DNA and haplotype characteristics? (4) Participatory medicine implies a patient's active, informed involvement in their medical choices, treatment, and acting in partnership with their health care providers. Educated mothers of children who enroll their newborn in the neonatal screening program must ask pertinent questions about the various variances of hemoglobinopathies (FA, FAS, FS, FSC, FSA, FSD, FS OArab, FC, FAE). Questions such as the meaning of these variances of sickle hemopglobinopathies, what is the degree of severity of these diseases? At what age do the indeterminate cases become either a trait or disease? Clinically, at what time will FS convert either to SS or AS?

The mother must be able to confirm when her child can be placed on 250 milligram of oral penicillin, and what are the benefits and side effects of such prophylactic treatment and follow. Will her child be placed on this treatment plan throughout his or her pediatric age? What are the options for her regarding career choices, sporting activities and whether there could be any cognitive deficits in their newborn babies?

Many technological gadgets relevant to neonatal screening have been developed in recent times. Some of the developed technologies used to enhance personalized medical care were the 454 life sequences manufactured by Roche Diagnostics (Brandford, CT), chromatography and electrophoresis, gene amplification, capillary analysis, polymerase chain reaction tests, microarray sequencing, and iso-electric focusing. These state-of-the-science approaches and bioinformatic technologies have the potential to provide significant insights into disease manifestation in individual patients and clinical differences at the molecular level. Such knowledge will enable the physician to tailor treatment to the precise needs of patients.

DNA Vision (2010) recently created as increased technological portfolio by using next generation sequence FLX system (Roche) for genome shotgun sequencing, genome re-sequencing, transcriptome profiling and metagenomic and meta-transcriptomics. A comprehensive list of the state of the art technologies required to improve the dissemination of personalized health care services were compiled by Ebomoyi and Scrinivasan (2008).

In the era of genomic medicine, the key benefits of predictive, preventive, personalized and participatory interventions to the patient include new abilities to:

- Detect disease at an earlier stage, when it is easier and less expensive to treat effectively
- Stratify patients into groups that enable the selections of optimal therapy
- Reduce adverse drug reactions by more effective early assessment of individual drug responses
- Improve the selection of new biochemical targets for drug discovery

- Reduce the time, cost, and failure rate of clinical trials for new therapies
- Shift the emphasis in medicine from reaction to prevention and from disease to wellness.[17]

Additional benefits of the HGP are the availability of extensive genetic map which has increased the pace by which different genes are localized in the human genome. Medical geneticists are now able to identify susceptible sections of the genome which could be responsible for many disorders as sickle cell.

Universal Screening

Recommendations on the issue of universal and targeted screening evolved out of an NIH Consensus Development Conference (1987), on Newborn Screening for Sickle Cell Disease and Related Hemoglobinopathies. The conference involved 400 biomedical scientists, clinicians, public health workers, parents and public representatives. From the "consensus statement" the panel recommended universal screening of all newborns for hemoglobinopathies. As enunciated by the expert panel, programs which focused their screening on specific high-risk segments of a population are fraught with missing people who are inaccurately registered. Owing to complacency among some providers, non-screening of at-risk individuals is encouraged. The Consensus panel cautioned that the health risks to children with sickle cell disease and related hemoglobinopathies are so grave that concerted efforts are required to identify and enlist every affected child. The panel therefore recommended "that most states adopt a policy of screening all newborns."(NIH, 1987).

Many states in America have complied with the universal screening policy advocated by the consensus panel; the benefits can be appreciated from the experiences from Florida, Texas, New York and Georgia among others. The data elicited from the University of Miami/Jackson Memorial (UM/JM) Medical Center situated in a large multi-ethnic metropolitan area indicate that it is better to test all newborns for hemoglobinopathies. Because the investigators have consistently shown that it was common to find Hb S and Hb C in infants designated as White Hispanic. This study has revealed the imprecision of using the designation White or Black when screening for sickle cell disease. The need to include certain "White" populations in screening programs has become very important in situations where the possibility of detecting SCD is quite high.

Guidelines on neonatal screening

The guidelines recommended by the World Health Organization (2006), for most screening programs worldwide must meet a number of requirements before implementation:

- The condition in question should portray high prevalence
- The condition in question should impose a significant health and economic burden on the population
- The gene in question should be easily and inexpensively tested, the analytical validity of the test should justify screening(WHO, 2006)

Screening in the Age of Genomic Medicine

Newborn screening has become one of the nation's most successful public health programs. Very well established screening centers now exist in the urban areas. However, an effective mechanism is needed to extend such services to rural areas. In centers with highly qualified medical geneticists, physicians have been able to sequence the DNA of sickle cell patients so as to determine the order of the base pairs on the globin gene of the patient with sickle cell disease and characterize how it differs from the other children without sickle cell.

In compliance with WHO (2006) guidelines, clinical epidemiologist, and Centers for Disease Control and Prevention scientists continue to advise medical laboratory technologists and the screening team to carry out inexpensive test with acceptable sensitivity and specificity. Sensitivity is when the technology indicates that the genetic disease is present, when it is actually present. Whereas, specificity is when the technology indicates the genetic disease is absent when in fact, the disease is not present in the newborn. In the first two to three months of birth there could be a few indeterminate cases of "FS", "FA". Sometimes, these few cases turn out to be cases of the heterozygous status of the sickling gene. One must encourage screening centers to accurately compile the results for scientific investigation and reporting.

Dr Francis Collins and others (2010) the current Director of the National Institutes of Health,

and the United States Department of Energy (2004), have cautioned clinicians and providers to be quite sensitive to analytic validity of a test, which focuses on the ability of the genetic test to measure accurately and reliably the genotype of interest. Clinical validity of a test assesses the ability of a procedure to detect or predict the presence or absence of a phenotype, clinical disease or predisposition for a disease. Clinical utility of a genetic test indicates the probability that the test will lead to an improved outcome for the patient. Screening for sickle hemoglobinopathies and other diseases in the United States major hospitals, in the wake of preventive, predictive, personalized and participatory medicine must take into cognizance the ethical, legal, financial and social implications of neonatal screening.

Health Education Implications Using the Integrated Model

The integrated model has all the relevant constructs to enable any expectant mother to participate in neonatal screening for sickle hemoglobinopathies. As people of African ancestry, there is the perceived susceptibility to sickle cell disease if one had not participated in premarital screening to ensure that one's partner does not have the trait for sickle cell. Since there is no known cure for the disease, the perceived seriousness of the diseases is quite authentic bearing in mind that the classical signs and symptoms of the diseases are life-threatening and costly to managed. Participation in screening is to enable people engage in primary preventive behaviors. The integration of the social cognitive theory into this model further augment the predictability of this model by insisting that we use persuasion and copious information and motivations to focus on one's self-efficacy to carry-out the preventive behavior. Therefore, among high school students of child-bearing age, health education intervention must reinforce counseling students about premarital genetic screening. Efforts must be devoted by educators to intensify trait counseling so as to reduce the frequency of the deleterious gens in the society. The education of women and their empowerment can be most useful in avoiding being impregnated by partners with the allele of any hemoglobinopathies.

The Ethical, Legal, Social Implications

With the availability of cutting edge biotechnology and genomic science, it is prudent to predict that genetic variation within the human genome can be characterized and genotyped for for many ethnic groups. Through the use of molecular techniques, and genomic techniques scientists expect to detect increasing number of genetic diseases. Therefore, there is the urgent need to train more scientist with the capabilities to provided the relevant genomic services.

Acknowledgement

The information used in this study is a component of neonatal screening conducted with Professor Flora F Cherry (Retired) at the Tulane Medical Center, School of Public Health and Tropical medicine. I am very grateful to Dr. Cherry for serving as my preceptor and for her commitment to the success of our neonatal screening for sickle hemoglobinopathy in New Orleans Louisiana.

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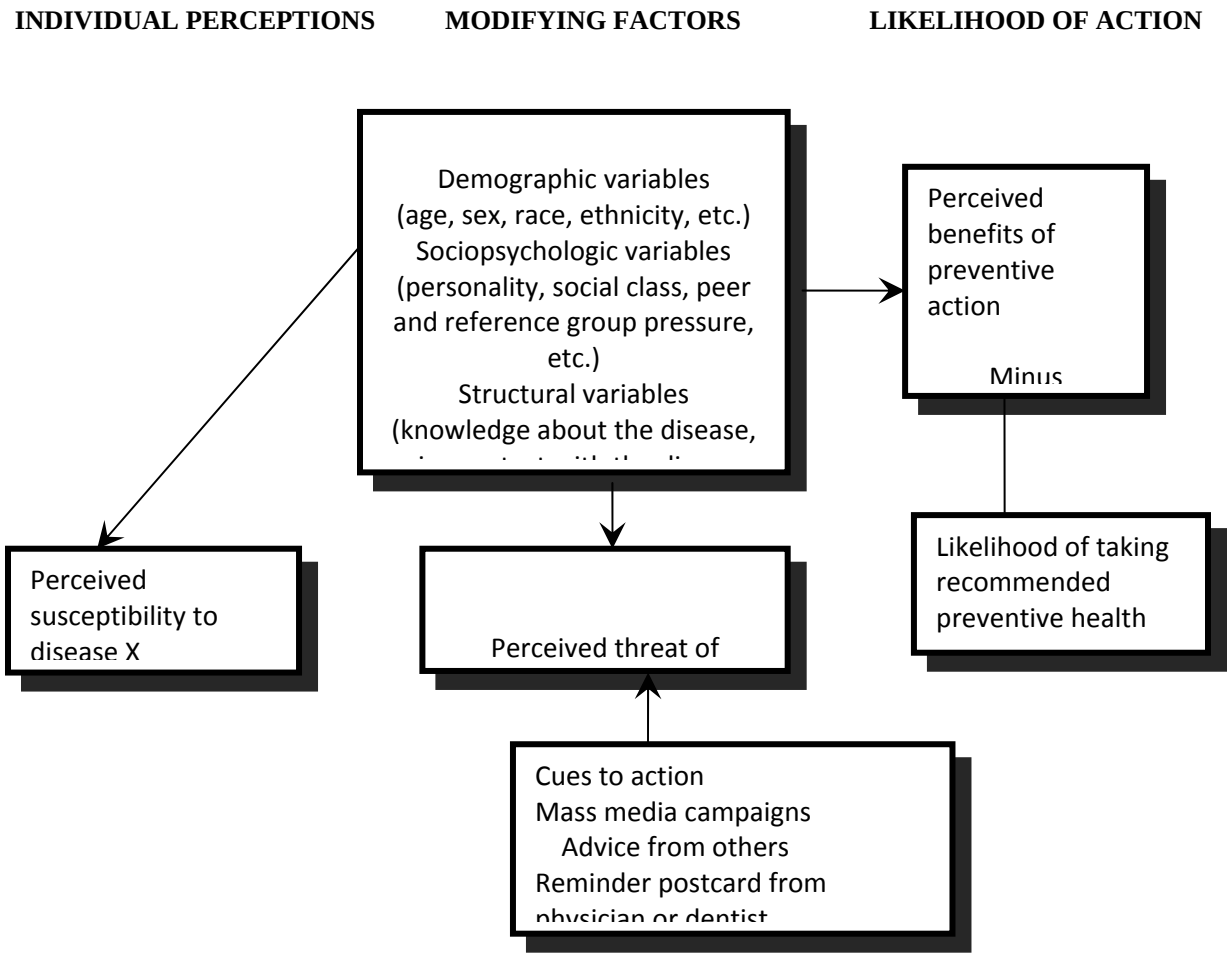

Figure 1. The Health Belief Model

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