Breast cancer is the most common cancer among women worldwide. About 10-15% of breast cancer is caused by hereditary genetic predisposition [1]. The most penetrable predisposition is the germline mutation in *BRCA1* and *BRCA2* (*BRCA*) [2-5], which is responsible for 20-30% of hereditary breast cancer [6]. Women carrying the predisposition in *BRCA1* have 55-65% and in *BRCA2* 45-47% risk of developing breast cancer by age 70, comparing to the rates in general population of 12% and 1.4%, respectively [7,8]. Besides breast cancer, *BRCA* mutation also causes other types of cancer including ovarian cancer, prostate cancer, melanoma, and pancreatic cancer. With the known cause for the disease, the effective treatment options of blocking cancer development through enhanced cancer screening [9], chemoprevention [10], and preventive surgery [11], identification of germline *BRCA1* mutation carriers becomes the key for early prevention of hereditary breast cancer.

In the developed countries, *BRCA* mutation test is applied routinely in clinical practice through the family history-based approach. Here, a physician first determines if a breast cancer patient has familial history of this disease. If yes, the patient is referred for *BRCA* test. If the result is positive, family members of the affected person (proband) are referred to take the same test [12-14]. However, this approach misses the majority of the mutation carriers, due to factors of the smaller size of modern nuclear family that prevents tracking family history, lack of the mutation information if it is inherited from the father who has much lower probability of developing breast cancer, lack of insurance coverage for *BRCA* test, and lack of awareness of the disease in both medical professionals and general public [15]. In the United States, only 19% of the estimated half-million *BRCA* carriers have been tested [16]; in Israel, the test rate is about only 35% even with the awareness for the high prevalence of *BRCA* predisposition in Ashkenazi Jewish population, the well-developed genetic testing system and the smaller population size [17]. The failure in identifying mutation carriers misses the best time for early prevention. As a result, these mutation carriers missed the test will only be identified after they develop breast cancer, and their family members will only be tested for the same mutation after the proband developed breast cancer. "To identify a woman as a carrier only after she develops cancer is a failure of cancer prevention" [18].

To overcome the dilemma situation, Dr. King et al. [18] recently proposed a revolutionary concept for prevention of *BRCA* predisposition-caused breast cancer. That is, using population screening approach to determine the *BRCA* status for every woman once in her life. This concept is built upon the deep understanding for the roles of *BRCA* predisposition in breast cancer after decades’ extensive study, and the next-generation DNA sequencing (NGS)-based technology development that enables population screening practically possible for the first time.

The proposed population screening concept triggered public and academic debates to address various related issues [19-20]:

- **Scientific issue.** Although the prevalence of *BRCA* carriers in general population is believed to be 1 in 200-400, the actual rate is largely unknown as the estimates are largely based on the data from breast cancer patient population rather than cancer-free general population [21-23];
- **Cost-effectiveness issue.** Studies demonstrated that population screening is more cost-effective than family history-based approach does to control *BRCA* mutation-caused breast cancer [24-26]. However, screening a population over multi-millions is still costly although sequencing cost has dramatically decreased;
- **Psychological issue for the identified mutation carriers.** A study concluded that no long-term psychological effects exist in these identified as the mutation carriers [27];
• Ethics issue for privacy protection [28];
• Over-diagnosis issue.
• Policy issue. These include ethics guideline for implementing population-level genetic screening, and changing insurance policy to cover the screening cost for individuals without cancer symptom.

A proof-of-principal population screening study was performed in Israel [17]. The study analyzed three hot-spot predispositions (BRCA1: 185delAG, 5382insC; BRCA2: 6174delT) in 8,195 Ashkenazi Jewish individuals, and identified 178 mutation carriers (2.17%). Fifty percent of families harbored the mutations had no family history of cancer. Further test in 629 family relatives of the identified mutation carriers identified 211 female mutation carriers (33.5%). In 2015, Hudson Alpha Institute in Alabama, USA initiated a voluntary-based screening project with 23 cancer genes including BRCA1 and BRCA2 for the women in Madison county with a population size of 334,811, Alabama. Of the 1,500 screened in the first phase study, 44 cases (3%) were identified as the carriers with mutations in one of the genes. The study is expanded into phase two in 2016 by offering test for all voluntary female and male over 19 years old [29]. In 2016, the Moon shot Cancer Program selected the hereditary breast and ovarian cancer (HBOC, the majorities are caused by BRCA mutation) as one of the two demonstration projects for cancer prevention and plan to identify 7,000 HBOC proband and their 28,000 family member carriers out of the estimated 250,000-450,000 HBOC cases [30].

As indicated above, screening a population over multi-millions is still too costly. Restricted by this single factor, it is unlikely that population screening for BRCA mutation carriers will be applied for breast cancer prevention in countries with large population size, such as China (1.35 billion), USA (300 million), Japan (126 million), and even Singapore (5 millions). Therefore, the family history-based system will likely remain as the major tool to identify BRCA mutation carriers in the populations in these countries, in which two third of the BRCA mutation carriers are predicted to remain unidentified before cancer occurs in them. In the near term, however, population screening does provide a powerful tool to reach comprehensive identification of the BRCA mutation carriers in the populations with smaller size, such as the population at specific geographically isolated region like the Iceland population, specific ethnic group like certain American Indian tribes, specific group with hot-spot predisposition like the Ashkenazi population. The results from these populations will also provide valuable information to know better the prevalence of BRCA mutations in human population and to screen in larger population in future when the obstacles are overcome.

In short, the population-based screening indicates a direction for eradicating hereditary cancer at the population level.

References
23. Yurgelun MB, Hiller E, Garber JE. Population-Wide Screening for


