

Integrating personalized genomics into Turkish healthcare system: A cancer-oriented pilot activity of Istanbul Northern Anatolian Public Hospitals with GLAB

**Levent Doganay,¹ Kamil Ozdil,² Kemal Memisoglu,³ Seyma Katrinli,⁴
Emre Karakoc,⁵ Emrah Nikerel,⁶ Gizem Dinler Doganay⁴**

¹Genomic Laboratory, Umraniye Training and Research Hospital, Istanbul, Turkey

²Secretary General, Istanbul Association of Northern Anatolian Public Hospitals, Istanbul, Turkey

³Director of Health, Health Directorate of Istanbul, Ministry of Health, Istanbul, Turkey

⁴Genomic Laboratory, Istanbul Technical University, Istanbul, Turkey

⁵Genomic Laboratory, Bioinformatics, Medipol University Faculty of Medicine, Istanbul, Turkey

⁶Genomic Laboratory, Bioinformatics, Yeditepe University Faculty of Medicine, Istanbul, Turkey

Cancer is a major health problem worldwide. The annual number of newly diagnosed cancer cases has reached approximately 14 million people, according to the World Health Organization [1]. The incidence rates are growing, and the estimated annual number of cancer cases in the next 20 years is 22 million. According to the World Cancer Report, 8.2 million people died due to cancer in 2012, and the annual number of deaths is expected to increase to 13 million within 20 years [1, 2]. In Turkey, cancer is the second leading cause of death after cardiovascular diseases. Data from the Turkish Statistical Institute revealed that 79,628 people lost their life as result of cancer in 2013 [3]. The cancer incidence rate in Turkey is around 200 for every 100,000 people according to the Cancer Department of the Public Health Institution of Turkey, and Istanbul has the most cancer-related deaths

with respect to entire population [4]. The most observed type of cancer in women is breast cancer, with an incidence rate of 40 cases for every 100,000 women. While the most diagnosed cancer types in men are respiratory system cancers, prostate, and colorectal cancers, with an incidence rate of 66, 26, and 21 cases, respectively, for every 100,000 males. There is inherited factor in 5% to 10% of breast and colorectal cancer cases [5]. When an accumulation of breast or colorectal cancer cases is observed in a family, the diagnosed patient should be screened for hereditary cancer gene mutations, and if the patient has a pathogenic mutation, family members who are at risk should also be screened. Cancer statistics of Turkey showed that only 47% of breast cancers and 29% of colorectal cancers have early diagnosis. In case of early diagnosis, the cure rate for breast and colorectal cancer is 90% and 80%, respectively.



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Correspondence: Dr. Levent DOGANAY. Umraniye Egitim ve Arastirma Hastanesi, Istanbul, Turkey.

Tel: +90 216 - 632 18 18 e-mail: levent.doganay@ueh.gov.tr

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Hereditary cancers are generally caused by mutations in genes that are related to a high probability of cancer development, vertical transmission from parents, and an association with other tumor types [6, 7]. Once an individual is suspected of carrying a risk for hereditary cancer, genetic counseling should be offered [8]. For example, in Istanbul, each year 6000 people are estimated to be diagnosed with breast or colorectal cancer. As many as 10% of these cancer patients, 600 cases, are expected to have a genetic background of predisposition for cancer. If these 600 patients have 3 siblings and 3 children, that estimation reveals 3600 healthy individuals that may have a cancer-predisposing mutation who are at risk of developing cancer. The current developments in molecular genetics, and especially next-generation sequencing (NGS) technologies, allow screening of multiple genes and multiple individuals very quickly, which in turn, greatly supports preventive medicine.

To support this vital need for genomic screening of hereditary breast and colorectal cancers, Genomic Laboratory (GLAB) was founded in Istanbul under the constitution of the Istanbul Association of Northern Anatolian Public Hospitals with the cooperation of Istanbul Technical University with a grant from the Istanbul Development Agency in 2015. The main objective of GLAB is to use NGS to screen breast and colorectal cancer patients for hereditary cancer mutations, and if a patient has such a mutation, the other family members are screened to determine whether they have risk of developing hereditary cancer. Currently, the genes screened for are BRCA1/2 (breast cancer 1/2), TP53 (tumor protein p53), PTEN (phosphatase and tensin homolog), ATM (ataxia-telangiectasia mutated), PALB2 (partner and localizer of BRCA2), CDH1 (cadherin 1), RAD51C/D (RAD51 homolog C/D), BRIP1 (BRCA1-interacting protein 1), STK11 (serine/threonine kinase 11), and CHEK2 (checkpoint kinase 2). For colorectal cancer, MUTYH (mutY DNA glycosylase), EPCAM (epithelial cell adhesion molecule), MSH2/6 (DNA mismatch repair protein 2/6), MLH1 (MutL homolog 1, colon cancer, nonpolyposis type 2), APC (adenomatous polyposis coli), PMS2 (mismatch repair endonuclease PMS2), BMPR1A (bone morphogenetic protein receptor, type IA), PTEN (phosphatase and tensin homolog), ATM (ataxia-telangiectasia mu-

tated), BLM (Bloom syndrome protein), TP53 (tumor protein p53), SMAD4 (SMAD family member n°4), STK11 (serine/threonine kinase 11), and CHEK2 (checkpoint kinase 2). GLAB also gets further support for bioinformatics analysis from Yeditepe University and Medipol University.

Currently, GLAB provides service to patients from Umraniye Teaching and Research Hospital and Goztepe Teaching and Research Hospital. The blood samples of breast and colorectal cancer patients are collected in these hospitals, and DNA isolation from the samples is performed in the GLAB laboratory located in Umraniye Teaching and Research Hospital. Isolated DNA samples are then transported to the GLAB laboratory located in ITU, with appropriate care to maintain the cold chain. Further NGS analysis is performed at this GLAB site, and the data generated are analyzed with bioinformatics tools. In this process, two different bioinformatics analysis pipelines are in use to minimize false positive and false negative results. Each observed variation is screened in multiple public databases for its phenotypic effect (i.e., whether the variation is benign, pathogenic, or of uncertain significance). In the end, a genetic report is created based on the recommendations of a medical genetics doctor that includes the patient's genetic screening result indicating that the mutation profiles are uncertain significant, possibly pathogenic, or pathogenic variations, according to bioinformatics results. If a patient has a pathogenic variation and a risk of hereditary cancer, the patient may be offered a surgical option (prophylactic mastectomy, oophorectomy, colectomy etc.) in discussion with medical genetics doctor and surgical committee [8]. Moreover, family members of this patient are offered genetic screening and counseling. Umraniye Teaching and Research Hospital, which specializes in oncological genetic counseling, currently provides this service.

As a result, GLAB is creating the foundation for preventive medicine in hereditary breast and colon cancer in Turkey, and is integrating personalized medicine into the Turkish health care system. The services provided by GLAB will prevent and detect cancer at early stages, thus reducing health care expenses and lowering cancer mortality rates.

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