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MDL at City of Hope National Medical Center is the first lab to offer the clinical molecular test for the CHEK2 gene.

Q: What is the function of CHEK2?

A: *CHEK2* encodes a Serine/threonine-protein kinase which plays a critical role in DNA damage signaling pathways[1]. CHEK2 directly phosphorylates and regulates the functions of p53 and BRCA1[2, 3].
It has been suggested that *CHEK2* functions as a low-penetrance susceptibility gene for cancers and multiplies the risks associated with other gene(s) to increase cancer risk [4, 5, 6, 17].

Q: Are you looking only at the 1100delC or other mutations as well?

A: The entire *CHEK2* gene is analyzed by full gene sequencing. It not only detects 1100delC mutation but also other mutations. We also offer RD-PCR (Robust dosage PCR)[20] to detect deletions of exons 8 and 9 of *CHEK2* gene. A deletion of exons 9 and 10 was identified as founder mutation among the Czech and Slovak population[8].

Q: What kinds of mutations have been detected in CHEK2?

A: Different kinds of mutations have been detected in *CHEK2* including large deletions, missense mutations, and small deletions and insertions.

Q: How many mutations have been identified in your lab?

A: We have identified 12 mutations so far. The first mutation (1283 C>T, Ser428Phe) was identified in an Ashkenazi Jewish family. The patient was diagnosed with breast cancer (stage II) at age 31 with a family history of breast cancer, basal cell carcinoma, eythroleukemia and squamous cell carcinoma (nose). This mutation was reported as a founder mutation in the Ashkenazi Jewish population[7, 8]. The second mutation (1312 G>T, Asp438Tyr) was found in a breast cancer patient with family history of breast cancer and leukemia. This alteration has previously been reported as a germline mutation in a hereditary prostate cancer patient[10]. The third mutation (538C>T, Arg180Cys) was found in a breast cancer patient with family history of breast, colon and prostate cancer. This alteration has previously been reported as a germline mutation in 2 prostate cancer tumor samples[9].

Furthermore, three truncating mutations were found in families that meet the Eeles' definition of Li-Fraumeni-like syndrome (LFL)* [24], two of these frameshift mutations were novel: 1263delT (Leu421fs), 920insG (Gly307fs).

* including two first- or second- degree relatives with LFS-related malignancies at any age

Q: What is the detection rate for familial breast cancer with no mutation detected in the BRCA1 and BRCA2 genes?

A: For samples requested for detection of 1100delC mutation, CHEK2*1100delC was found in 2.1% of all cases, which is consistent with the published data[22, 23]. For 200 samples sent in for full gene sequencing, 12 mutations were found, giving a detection rate of 6% that is consistent with detection rate reported in literature[4, 5, 6, 7, 8].

Q: What is the specific contribution of colon cancer to CHEK2?

A: Although the association of CHEK2 and colon cancer is controversial, most of the negative studies only had looked at the association of families with colon cancer only and only analyzed the 1100delC mutation, but not hereditary breast *and* colorectal cancer (HBCC) with the full gene mutation spectrum.

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One study found that the 1100delC variant of the *CHEK2* gene was present in 18% of 55 families with hereditary breast *and* colorectal cancer (HBCC)* [17].

Two other groups reported that the *CHEK2* mutations were associated with a two-fold increased risk of colon cancer [18, 19]. Thus, twofold increase in cancer risk for *CHEK2* mutation carriers represents a surplus to the cancer risk among the families with CHEK2 mutations that is due to the unknown susceptibility gene[17].

*HBCC phenotype was defined as a family with breast cancer characterized by the presence of at least two patients with breast cancer who were first- or second-degree relatives and of whom at least one is diagnosed before age 60 years *and*
1. at least one patient with breast cancer and colorectal cancer diagnosed at any age; *or*
2. at least one individual with colorectal cancer diagnosed before age 50 years who was a first- or second degree relative of a patient with breast cancer; *or*
3. at least two patients with colorectal cancer diagnosed at any age of whom at least one was a first or second-degree relative of a patient with breast cancer[17].

Q: What are the clinical indications for CHEK2 testing?

A: According to the published literature, several indications are recommended for referring patients:

1. Women with bilateral breast cancer with no mutation detected in the *BRCA1* and *BRCA2* genes could be the first selection criteria.
   A study has shown that first-degree relatives of bilateral breast cancer cases who carried the CHEK2*1100delC allele had an 8.1-fold increased risk of breast cancer[1]. The cumulative risk by age 80 years was 58.8% (95% CI 33.8–85.3%) for CHEK2*1100delC carriers with a first-degree relative affected with bilateral breast cancer[6].

2. Women with familial breast and ovarian cancer (4 or more cases) with no mutation detected in the *BRCA1* and *BRCA2* genes. The likely chance to have CHEK2 mutation detected in those families would be 5%[8]

3. Men with breast cancer with no mutation detected in the *BRCA2* gene. A study has shown that a CHEK2*1100delC allele confers about a 10-fold increased risk of breast cancer in males[4]

4. Hereditary breast *and* colorectal cancer (HBCC) with no mutation detected in the *BRCA1* and *BRCA2* genes. A *CHEK2* mutation was reported in 18.2% families with hereditary breast *and* colorectal cancer (HBCC)[17] and was associated with an two-fold increased risk of colon cancer[18, 19]

5. Previous evidence suggests that mutations in *CHEK2* are also associated with prostate cancer and an increased risk for thyroid cancers [9, 10, 11]

6. Individuals with Li-Fraumeni syndrome, Li-Fraumeni-like syndrome or phenotypically suggestive of LFS with no mutation detected in p53 gene[12, 13, 14, 21]

7. If a mutation has been identified in an affected family member, with genetic counseling *at-risk relatives may* consider CHEK2 known mutation detection analysis.

Q: Do you propose to offer this test only to affected, and if so at what a priori BRCA risk as calculated by the existing models?

A: Usually, we sequence the proband first. If a mutation has been identified in an affected family member, with genetic counseling, at-risk relatives may consider *CHEK2* known mutation detection analysis. Although the available research data is limited to give a definite figure of the prior BRCA risk, women with the CHEK2*1100delC mutation have the above two-fold increased risk of breast cancer, which equal to about 16% of lifetime risk.

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Q: What are you charging and what is the turn around time?

A: Please email mdl@coh.org for a price list. The turn around time for full gene sequencing is 6 weeks and known mutation detection is 4 weeks.

Q: What is the risk for mutation carriers?

A: Available studies suggest that the *CHEK2*1100delC* mutation confers about a 10-fold risk of breast cancer in men. In women, the increased risk is about two-fold, however the lifetime risk has been estimated to be as high as 59% by age 80 if the *CHEK2*1100delC* mutation carriers had a first degree relative affected with bilateral breast cancer[6].

Q: How is CHEK2 testing relevant with clinical management?

A: de Bock et al. and Meyer A. et al. reported that a patient carrying the *CHEK2*1100delC* and other *CHEK2* mutation had poor prognosis compared with noncarriers[15, 25]. Schmidt MK. et al. found that CHEK2*1100delC carriers have an increased risk of second breast cancer and a worse long-term recurrence-free survival rate[26]. CHEK2 mutation testing may become useful when considering cancer risk screening and intensive surveillance.

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