INTRODUCTION:

Every cell type has a unique molecular signature, which has identifiable characteristics such as levels or activities of a myriad of genes, proteins or other molecular features, can referred as biomarkers. Biomarkers are an objective measure or evaluation of biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention[1-3]. It includes diagnostic tests, imaging technologies, and any other objective measures of a normal person’s health status. Biomarkers are used to dynamic modulation, and are expected to enhance our understanding of drug metabolism, drug action, efficacy, and safety. These can also explain molecular definition of diseases, provide information about the course of disease and predict response to therapies.

Technologies to recognize and understand the features of normal cells and how these become cancerous, promises to provide specific insights into the aetiology of cancer that can be useful for early detection, diagnosis, and treatment. Biomarkers are therefore invaluable modern tools for cancer detection, diagnosis, patient prognosis and treatment selection [4]. These can also be used to identified the tumor and determine its stage, subtype, and response to therapy. A major & risky challenge in cancer diagnosis is to establish the exact relationship between cancer stage and its clinical pathology. It is very tough to detect cancer non-invasively at an early stage. Similarly, identification of subtle changes in the genomics and proteomic status specific to malignant transformation will allow molecular targets to be used for developing therapeutics.

Biomarkers:

Diagnostic and prognostic biomarkers are quantifiable traits that help clinical oncologists at the first interaction with the suspected patients. These particularly aid in (i) identification (ii) diagnosis (iii) selection of treatment (iv) monitoring of treatment [5]. Molecular genetics approaches have played significant role in the diagnosis and prognosis of cancer. Molecular genetics techniques can provide information about the specific and subtle genetic changes; have been quite useful in the identification of certain tumors.

There are several types of biomarkers exist, but they are broadly classified in three categories. 1) Biomarkers provide information on disease status. 2) Biomarkers quantified the effect of a drug or other intervention on a biological process. 3) Biomarkers estimate the direct interaction of a drug with its target molecule, or receptor. But development of biomarkers is a challenging measurement.

Thyroid Cancer:

Certain modifications in a person’s DNA can cause thyroid cells to
become cancerous. DNA is the chemical in each of our cells that makes up our genes – the instructions for how our cells function. Certain genes that help cells grow and divide or make them live longer than they should are called oncogenes. Other genes that slow down cell division or make cells die at the right time are called tumor suppressor genes [6]. Cancers can be caused by DNA mutation that turn on oncogenes or turn off tumor suppressor genes.

Thyroid cancer is a cancer of thyroid gland. The medical term for an abnormally large thyroid gland is known as goiter. Goiters are of different types viz diffuse, nodular. There are many reasons the thyroid gland might be larger than usual, and most of the time it is not cancer. Both diffuse and nodular goiters are usually caused by an imbalance in certain hormones. For example, deficiency of iodine in the diet can cause changes in hormone levels and lead to a goiter. People can develop thyroid nodules at any age, but they occur most commonly in older adults [7].

Basically thyroid cancer is differentiated type of cancer, but in some cases it may be undifferentiated. In this cells look like a normal thyroid tissue when seen under a microscope.

1. Differentiated thyroid cancers

A. Papillary carcinoma:
About 8 out of 10 thyroid cancer cases are papillary carcinomas. Papillary carcinomas tend to grow very slowly and usually develop in only one lobe of the thyroid gland. Although they grow slowly, reaches to the lymph nodes in the neck. These kinds of cancers can often be treated successfully [8].

B. Papillary thyroid cancer (PTC)
Many DNA changes have been found in papillary thyroid cancer. These type of cancer mainly caused by alteration in specific parts of the RET gene. The altered form of this gene, known as the PTC oncogene, is found in about 10% to 30% of papillary thyroid cancers overall. Prevalence of this cancer more in children and/or mainly linked with radiation exposure. Many papillary thyroid cancers have a mutated BRAF gene. The BRAF mutation is less common in thyroid cancers in children. Cancers with BRAF changes tend to grow and spread to other parts of the body more quickly changes in other genes have also been tied to papillary thyroid cancer, including those in the NTRK1 gene and the MET gene [9].

C. Follicular carcinoma:
Follicular carcinoma, also called follicular cancer or follicular adenocarcinoma. It is observed common in iodine deficient areas. This cancer usually spread to lungs or bones. The prognosis for follicular carcinoma is not quite as good as that of papillary carcinoma [8].

D. Follicular thyroid cancer:
A change in the RAS oncogenes causes follicular thyroid cancer.

2. Undifferentiated thyroid cancers

A. Medullary thyroid carcinoma:
It accounts only about 4% of thyroid cancers. It develops from the C cells of the thyroid gland, which normally make calcitonin, a hormone that control, the level of calcium in blood [10]. Sometimes this type of cancer can spread to lymph nodes, lungs, or liver even before a thyroid nodule is discovered.

B. Medullary thyroid cancer:
People who have medullary thyroid carcinoma (MTC) have mutations in different parts of the RET gene.

C. Anaplastic carcinoma:
Anaplastic carcinoma (also called undifferentiated carcinoma) is a rare form of thyroid cancer, found only 2%. It is thought to develop from an existing papillary.

D. Anaplastic thyroid cancer:
This type of cancer possesses some kind of the mutations and often has changes in the TP53 tumor suppressor gene and the CTNNB1 oncogenes as well.

Diagnosis of Thyroid cancer

The diagnosis of thyroid cancer, generally done after the doctor recommendation, otherwise it’s often ignored. The common diagnosis methods are immunohistochemical based, which includes galectin-3, Hector Battifora mesothelial cell-1 (HBME-1), and cytokeratin-19 [8]. The common symptoms, which suspect Thyroid cancer are lump in the neck, swelling in the neck, pain in the front of the neck, sometimes going up to the ears, hoarseness or other voice changes that do not go away, trouble swallowing, trouble breathing and constant cough that is not due to a cold [7].

Role of Genetic Biomarkers in Thyroid Cancer Diagnosis

Genetic mutations in thyroid tumors can be divided into two categories a) Inheritable (germline) mutations b) sporadic (somatic) mutations. Investigations into the inheritable and sporadic mutations in thyroid cancer have proceeded in parallel with one another. Although many gene mutations have been studied, only one inheritable genetic mutation and five to eight sporadic mutations are significant.
The first sporadic mutation identified in thyroid cancer was described in 1987 and involved a genetic defect in the RAS protein family. In 1990, somatic RET/PTC translocations were identified in papillary thyroid cancer. In 1992, P53 mutations in anaplastic thyroid cancer and NTRK1 mutations in papillary thyroid cancer were identified. There was a subsequent lull in the discovery of genetic mutations in thyroid cancer until the year 2000, when PAX8/PPAR gamma translocations were found in follicular thyroid findings in thyroid cancer research. Several investigators have continued to search for the genetic mutation responsible for familial non-medullary thyroid cancer, but the responsible genetic mutation has not yet been identified.

### Table 1. List of Biomarkers used for diagnostics & prognostics of Thyroid Cancer

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Biomarker Name</th>
<th>Function</th>
<th>References</th>
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<tbody>
<tr>
<td>1.</td>
<td>BRAF</td>
<td>RAF family (A,B,and C) of serine/threonine kinases. regulators of the MAPK pathway that ultimately control the expression of several genes responsible for cell proliferation, differentiation, and apoptosis. Mutation occurs uniquely in 600 position. Mostly it replaces valine for glutamic acid at position 600, and is designated as BRAFV600E.</td>
<td>Adrienne L. Melck et al., 2010, Xing, M. 2005, Kebebew E et al. 2007</td>
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<td>2.</td>
<td>RET-PTC</td>
<td>Encodes the RET receptor: a plasma membrane bound tyrosine-kinase, which is expressed in neuroendocrine and neural cells</td>
<td>Takahashi M et al. 1985</td>
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<td>3.</td>
<td>PAX8</td>
<td>Paired box gene 8, important tumor suppressor that regulates cell cycle arrest and apoptosis. Typically associated with follicular thyroid cancers that present at an earlier age and with a high frequency of vascular invasion.</td>
<td>Nikiforova M N.et al. 2003</td>
</tr>
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<td>4.</td>
<td>EGFR</td>
<td>EGRF overexpression (EGFR-H) is implicated thyroid disease progression. Significance of EGFR-H in tumors that harbor EGFR AND v-Raf murine sarcoma viral oncogenes homologB1 (BRAF/EGFR-H should used for histological &amp; immunochemical methods</td>
<td>Wells S A.2007</td>
</tr>
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<td>5.</td>
<td>P53</td>
<td>P53 mutations may play an important role in malignant transformation of thyroid cells &amp; tumor progression. Cause the thyroid cancer to progress to an undifferentiated state. Mutation of TP53 has been implicated as a late event in thyroid carcinomas</td>
<td>Jossart GH et al. 1996</td>
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<td>6.</td>
<td>NTRK1</td>
<td>Mutation in NTRK1 leads to rearrangement in TPM3, TPR &amp; TFG gene. This causes formation of TRK oncoproteins which form PTC. Exclusive to papillary thyroid cancer, but with a much lower frequency (5–15%) than RET translocations or BRAF point mutations</td>
<td>Greco A et al. 2010</td>
</tr>
<tr>
<td>7.</td>
<td>RAS</td>
<td>RAS proteins are as essential components in cellular proliferation, differentiation, or survival. Oncogenic mutation of H-ras, N-ras or K-ras gene found in PTC. RAS mutations are found in the N-RAS gene, followed by H-RAS, and least frequently, K-RAS. frequently associated with follicular tumors than papillary tumors</td>
<td>Garcia R. G et al. 2003</td>
</tr>
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<td>8.</td>
<td>VEGFR</td>
<td>An essential peptide in new vessel growth in physiology &amp; pathological conditions as well as in tumor cell growth, particularly distant metastases.</td>
<td>Lin J.D et al. 2005</td>
</tr>
</tbody>
</table>

**Epigenetic Biomarkers**

Epigenetics is defined as the study of heritable changes in gene expression that occur independently with the other changes. Mechanisms of epigenetic regulation include DNA methylation, histone protein modification, nucleosome positioning, and microRNA silencing. One of the most exciting aspects of epigenetic regulation is that unlike genetic mutations, these processes are easily reversible with various therapeutic agents & these can be used to detect thyroid cancer at early stage.

**CONCLUSIONS**

The evolution of thyroid biomarker research reflects the standard thinking of the time and their need, have changes in parallel with the advancement of technology. Although thyroid cancer is one of the most recent forms of cancer, research in the field has remained on the cutting all the edges of science and technology, but better diagnostic & prognostic tests and predictors of tumor aggressiveness are necessary. “Finding a cure” for thyroid cancer should remain a strong
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impetus for continued research to identify new biomarkers and therapeutics for this disease.

REFERENCES


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