CLINICAL DECISION MODEL

I. FIELD OF THE INVENTION

[0001] The present invention relates to a model for providing a patient-specific diagnosis of disease using clinical data. More particularly, the present invention relates to a fully unsupervised, machine-learned, cross-validated, and dynamic Bayesian Belief Network model that utilizes clinical parameters for determining a patient-specific probability of malignancy, transplant glomerulopathy, healing rate of an acute traumatic wound, and/or breast cancer risk.

II. BACKGROUND OF THE INVENTION

[0002] Within this application several publications are referenced by arabic numerals within brackets. Full citations for these, and other, publications may be found at the end of the specification immediately preceding the claims. The disclosures of all these publications in their entireties are hereby expressly incorporated by reference into the present application for the purposes of indicating the background of the present invention and illustrating the state of the art.

[0003] Thyroid nodules represent a common problem brought to medical attention. Four to seven percent of the United States adult population (10-18 million) has palpable thyroid nodules, and up to 50% of American women older than age 50 have nodules visible by thyroid ultrasound [1]. The majority (>95%) of thyroid nodules are benign; however, malignancy risk increases with male gender, nodule size, rapid growth and associated symptoms, extremes of age (<30 and >60 years), underlying autoimmune disease (e.g. Graves' Disease), nodule growth under thyroid hormone suppression, personal or family history of thyroid malignancy, and radiation exposure [2].

[0004] Thorough history and physical examination, serum thyrotropin (TSH) level, thyroid ultrasound, and fine need aspiration biopsy (FNAB) are utilized to evaluate patients with thyroid nodules. Patients with thyroid nodules and normal or elevated serum TSH typically undergo thyroid ultrasound to determine if FNAB is warranted. Nodules with a maximum diameter greater than 1.0-1.5 cm with solid elements, or nodules of any size demonstrating suspicious features on ultrasound should undergo FNAB [3]. Given the increased risk of malignancy in thyroid incidentalomas detected by 18FDG-PET (Fluorodeoxyglucose or Fludeoxyglucose positron emission tomography) (14-50%) or sestamibi scan (22-66%), FNAB is indicated under these circumstances [4, 5]. Functioning thyroid nodules (suppressed TSH, hyperfunctioning on radionuclide scan) do not require FNAB in the absence of clinically suspicious findings.

[0005] Fine needle aspiration biopsy is a cost effective and accurate diagnostic tool for thyroid nodules. In experienced hands, the sensitivity and specificity of FNAB are very high, 95% and 99%, respectively, in positive and negative cases [6]. A six tiered classification system for FNAB is favored that is associated with increased risk of malignancy across the spectrum of: unsatisfactory or non-diagnostic specimen (unknown), benign (<1%), follicular lesion (atypia) of undetermined significance (5-10%), follicular neoplasm (20-30%), suspicious for malignancy (50-75%), and malignant (100%) [3]. Over 20% of patients undergoing FNAB of a thyroid nodule have indeterminate cytology (follicular neoplasm), and they require and are exposed to the function-limiting complications (impaired voice and swallowing) of thyroid lobectomy/isthmusectomy conducted purely for the purpose of attaining a more definitive diagnosis. Given that the majority of patients with follicular neoplasms have benign surgical pathology, thyroidectomy in these patients is conducted principally with diagnostic intent [7]. Electrical impedance scanning (EIS) is another tool for scanning thyroid nodules [9, 10]. Utilization of EIS can result in a significant reduction (67%) in the number of purely diagnostic thyroid resections for follicular neoplasms [8, 9].

[0006] Fine needle aspiration cytology has a high diagnostic accuracy and is a practicable test for the initial evaluation of thyroid nodules. However, the efficacy of FNA for the differential diagnosis of follicular and Hurthle cell neoplasms remains imperfect. As the majority of detected thyroid nodules are benign and cytology, even in the best of hands, is indeterminate in 20% of fine needle aspirates, the frequency of diagnostic or non-therapeutic thyroid resection is increasing.

[0007] As the majority of patients with indeterminate FNA cytology have benign nodules, surgical operations are undertaken primarily with diagnostic intent. Thus, it is difficult to non-invasively differentiate benign and clinically inconsequential low-risk malignant nodules from those that indeed stand to benefit from resection. Color Doppler sonography with quantitative analysis of tumor vascularity, in conjunction with conventional ultrasonographic assessment of echogenicity, halo, microcalcifications, and tumor size, may provide a means for differentiating malignant from benign solid thyroid nodules in the pre-operative setting [11-14]. However, the predictive value of this combined technique is achieved by compromising diagnostic sensitivity [15]. The predictive value of ultrasonography may be enhanced significantly through the application of ultrasound thyroid elastography [16-17]. The application of 18F-FDG PET shows high sensitivity for the diagnosis of malignancy in thyroid nodules demonstrating indeterminate cytology on pre-operative FNA. However, the low specificity of the technique limits its utility [18-19].

[0008] Cellular changes alter the flow of electrical current through living tissue, and differences in cellular electrical signature between malignant and non-malignant tissue has been identified and studied extensively since the 1920's [20]. EIS devices measure tissue impedance characteristics and identify irregularities in conductance and capacitance that are associated with increased levels of cellular activity and malignant transformation [21]. EIS measurements are obtained by introducing a known, low-level, biocompatible, alternating current to the body via a hand-held electrical signal generator. The signal is directed through the measured tissue and collected via a non-invasive surface probe. EIS is safe, feasible, and diagnostically accurate in detecting differences in the bioelectrical signature of benign and malignant tissue through body surface measurements of suspicious skin lesions and lymph nodes, and breast abnormalities [22-30]. EIS is a safe, rapid, realtime, and non-invasive imaging modality with a predictive value sufficient to make it an adjunct to FNA, particularly in the setting of indeterminate cytology [8, 9].

[0009] Recognizing that individual variables, though independently associated with thyroid cancer, are insufficient in predicting the risk of malignancy in any given thyroid nodule, multivariate predictive algorithms have been developed to determine the cumulative risk of malignancy for this clinical problem [10, 31]. One predictive algorithm utilizes a multi-