

modality with a predictive value sufficient to make it an adjunct to FNA, particularly in the setting of indeterminate cytology [8, 9].

**[0010]** 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 multivariate stepwise regression model to predict malignancy in thyroid nodules in a highly selected patient population on the basis of patient age, calcifications in a sonographically solid nodule, and FNAB cytology [10]. Another predictive algorithm applies multivariate modeling in patients with indeterminate thyroid nodules to define male gender, nodule size exceeding 4 cm, and character of the gland by palpation (dominant nodule in multi-nodular goiter) to predict the risk of thyroid malignancy [31]. The development of this predictive algorithm was limited to a narrow population of patients with follicular neoplasia by FNAB, and did not include imaging-based variables according to standard of practice in the predictive model.

**[0011]** Many electronic clinical decision support systems have been developed that rely on human expertise to develop decision-support rules rather than calculating a specific estimate of outcome using historical source data. Such “expert systems” take two forms. The first form is a system where clinical experts, following a systematic review of the literature, devise a system of static decision making rules for clinical decision support. The second form is a system where clinicians in the treating facility, usually basing their judgments on personal experience and the literature, devise a set of rules for clinical decision making in their own institution. The rules developed under both systems can either be implemented in publication format, in the form of published guidelines, or as a set of static decision rules in a clinical informatics system.

**[0012]** Transplant glomerulopathy (TG) is another disease that is difficult to diagnose. Transplant glomerulopathy is a distinctive lesion identified histologically on allograft biopsy and is associated with rapid decline in glomerular filtration rate and poor outcome. It is defined by a characteristic doubling of the glomerular basement membrane as well as increasing evidence that supports an immunologic pathogenesis; however, the molecular pathways involved have not been elucidated. Currently, transplant glomerulopathy must be diagnosed by microscopy, whether light or electron, at a minimum and thus necessitates an advanced disease stage, for which there is no cure.

**[0013]** Long-term kidney allograft function continues to improve modestly, despite dramatic improvements in acute rejection rates and short term patient and graft survivals. Measurement of serum creatinine is typically the primary monitoring modality following kidney transplantation. Significant changes in serum creatinine, and/or the development of proteinuria, result in a series of maneuvers to define the many potential etiologies of acute and chronic allograft dysfunction. Allograft biopsy is the current standard of these maneuvers, although morphologic analysis may not easily distinguish these etiologies. Furthermore, the analysis may be limited in regards to prognostic importance and functional outcome.

**[0014]** Gene expression analysis using microarrays and real-time polymerase chain reaction (PCR) has been applied

broadly in the field of renal transplantation. Gene expression changes found in renal biopsies, urine sediment, and peripheral white blood cells have been used to evaluate allografts with stable function, acute rejection, and chronic allograft dysfunction. In addition, gene expression within the renal allograft pre-reperfusion or reperfusion periods has been correlated with delayed graft function and medium term allograft survival.

**[0015]** Several well-established relationships support that such an approach to identifying TG has biologic relevance. The relationship between pathology and cell signaling (chemokine expression), cell trafficking (adhesion molecule expression) and tissue remodeling (MMP expression) is supported by current models of TG. TG is believed to be secondary to binding of donor specific antibodies to endothelium with resulting stimulation and recruiting of secondary mediators leading to an inflammatory response. This inflammatory response and subsequent tissue injury has been associated with chemokine, adhesion molecule and MMP expression. Additionally, adhesion molecule expression has been shown to be associated with both chronic disease and stable function in renal transplant recipients. Alteration of chemokine expression has been linked to costimulatory molecules (CD28, 40L, 80, 86) and IL-10 has been demonstrated to be elevated in allografts with stable function. The development of TG and Cd4 expression has also been well characterized.

**[0016]** The majority of modern war wounds are caused by blasts and high-energy ballistics [32-34]. Complex traumatic wounds require aggressive surgical care, including serial debridements to remove devitalized tissue and decrease bacterial load. Positive-pressure irrigation, negative-pressure and vacuum-assisted closure (VAC) have improved wound management [35-36]. However, despite these technological advances, the basic surgical decision regarding appropriate timing of surgical traumatic wound closure or coverage remains very subjective.

**[0017]** Poorly defined pathophysiology of acute wound failure partially contributes to the difficulties of objectively assessing wound healing. Current criteria for wound closure or coverage consider many subjective factors, which include the patient’s general condition, injury location, adequacy of perfusion, and the gross appearance of the wound. Factors used to assess the patient’s general condition include nutritional and nonspecific systemic inflammatory parameters. Relevance of injury location and visual assessment of the wound, such as the appearance of granulation tissue, are subjectively determined by the surgeon. Thus, there is considerable intra-observer variability in wound assessment. Furthermore, the decision making process used to make wound closure determination are ill-defined. After evaluating these factors, surgeons often reach a wound status determination base on his/her experience and discretion. Therefore, even in the hands of seasoned surgeons, some wounds ultimately fail. Unfortunately, other wounds with the biologic ability to heal will undergo unnecessary surgical debridements, adding treatment costs and exposing patients to additional anesthetic and surgical morbidity risk. Objective criteria and decision algorithms to define the appropriate timing of wound closure are needed.

**[0018]** The molecular landscape of the wound ultimately determines the fate of the wound healing process. Acute wounds typically heal by an interdependent sequence of events mediated by inflammatory messengers. The wound healing process generally has three phases. They are the