DETAILED ACTION

Amendment Entry

1. Applicant's amendment, filed 5/8/2012, is acknowledged and has been entered. Claims 1-3 and 7-12 were amended. Claims 4-6 and 13-14 were canceled. New claims 15-17 have been added. Accordingly, claims 1-3, 7-12, and 15-17 are currently pending and subject to examination below.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claims 1-3, 7-12, and 15-17 are rejected under 35 U.S.C. 101 because the claimed invention is directed to nonstatutory subject matter because it is not a patent-eligible practical application of a law of nature.

A claim that focuses on use of a natural principle must also include additional elements or steps to show that the inventor has practically applied, or added something significant to, the natural principle itself. See Mayo, 101 USPQ2d at 1966. To show integration, the additional elements or steps must relate to the natural principle in a significant way to impose a meaningful limit on the claim scope. The analysis turns on whether the claim has added enough to show a practical application. See id. at 1968. In other words, the claim cannot cover the natural principle itself such that it is effectively standing alone. A bare statement of a naturally occurring correlation, albeit a newly discovered natural correlation or very narrowly confined correlation, would fail this inquiry. See id. at 1965, 1971.

It is not necessary that every recited element or step integrate or relate to the natural principle as long as it is applied in some practical manner. However, there must be at least one additional element or step that applies, relies on or uses the natural principle so that the claim amounts to significantly more than the natural principle itself.

Along with integration, the additional steps must be sufficient to ensure that the claim amounts to significantly more than the natural principle itself by including one or more elements or steps that limit the scope of the claim and do more than generally describe the natural principle with generalized instructions to "apply it." See id. at 1965, 1968. The additional elements or steps must narrow the scope of the claim such that others are not foreclosed from using the natural principle (a basic tool of scientific and technological work) for future innovation. Elements or steps that are well-understood, purely conventional, and routinely taken by others in order to apply the natural principle, or that only limit the use to a particular technological environment (field-of-use), would not be sufficiently specific. See id. at 1968.

In the present case, the claims are directed to a naturally occurring correlation between NGAL levels and acute renal failure, specifically the naturally occurring correlation between certain NGAL levels and the presence of or immediate risk of developing acute renal failure.

The claims recite steps of i) determining the concentration of NGAL in a sample from a subject and ii) comparing the concentration with a cutoff value that is 250 ng/mL or a lower value. A conclusory "whereby" clause states that should the NGAL concentration fall below the cutoff value, the subject is diagnosed or determined as not having and not being at immediate risk of developing acute renal failure. See especially claim 1.

The combination of steps recited in the claims taken as a whole, including those indicated above, are not sufficient to qualify as a patent-eligible practical application as the claims cover every substantial practical application of the correlation. In particular, the step of testing a sample to determine the concentration of NGAL is recited at a high level of generality. Such a step is not sufficient to ensure that the claims amount to significantly more than the naturally occurring correlation itself since every application of the correlation would require this.

Furthermore, appending conventional steps, specified at a high level of generality, to a natural principle is not sufficient to render a claim patent-eligible. In this case, not only was the naturally occurring correlation between NGAL levels and acute renal failure recognized at the time of the invention (see prior art references discussed below) but it was also well-understood and conventional to determine levels of NGAL in a sample of urine or blood as recited instantly.

While the claim also recites a step of comparing the measured concentration with a cutoff value falling within a defined range, steps relating to the use of a cutoff value are well-understood and are routinely taken by those in the field to perform testing of a sample.

Furthermore, as noted above the additional elements or steps must relate to the natural principle in a significant way to impose a meaningful limit on the claim scope. Here, the claims encompass a very broad range of possible cutoff values (250 ng/mL or any lower value).

Moreover, NGAL cutoff values falling within the scope of the claims were also known and in use by others (see rejections under § 103 that follow). Steps that amount to instructions that are well-understood, routine, conventional activity, previously engaged in by those in the field, add nothing specific to the natural principle that would render it patent-eligible.

The claims at issue here would therefore at best set forth processes embodying researchers' findings that identified these correlations with some precision (i.e., more precisely identifying particular cutoff values to be used).

For all of these reasons, the claims do not include additional elements/steps or a combination of elements/steps that are sufficient to ensure that the claims amount to significantly more than a natural principle itself. When the claims are considered as a whole, the steps taken together amount to no more than recognizing the law of nature itself.

A claim setting forth the relationship between NGAL and acute renal failure would require additional steps that do significantly more to apply this principle than conventional body fluid sample testing or diagnostic activity based on recognizing a threshold NGAL level. Such additional steps could involve, for example, a testing technique or treatment steps that would not be conventional or routine.

See also the guidance memo of July 3, 2012 entitled "2012 Interim Procedure for Subject Matter Eligibility Analysis of Process Claims Involving Laws of Nature" available at http://www.uspto.gov/patents/law/exam/2012_interim_guidance.pdf.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

5. Claims 1-3, 7, 12, and 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Uttenthal et al. (U.S. 2009/0170143 A1).

The applied reference has a common assignee and common inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Uttenthal et al. teaches methods for diagnosing, monitoring, or determining the likelihood of a renal disorder by means of measuring NGAL in a bodily fluid sample [0002]. Uttenthal et al. further teach acute renal failure (ARF) as an example of a renal disorder that may be assessed using their methods [0007]. In addition, the reference also contemplates early detection of renal injury that may result in ARF (see [0002]-[0003], [0012]-[0013], and claim 11).

The methods of Uttenthal et al. involve comparing the measured concentration of NGAL with a predetermined cutoff value, in order to distinguish renal disorders from other disorders that do not affect the kidney [0007], [0010]. In particular, Uttenthal et al. teach cutoff levels of 250 ng/mL or more for the purpose of diagnosing renal injury [0022]-[0025]. Uttenthal et al. therefore teach comparing a subject's NGAL concentration to a cutoff level (which may be a cutoff level of 250 ng/ml), reading on the claimed comparison step of claim 1, step ii). The reference also clearly associates *increased* NGAL levels, i.e. those above the cutoff level, as being indicative of renal injury. Specifically, Uttenthal et al. state that an NGAL concentration above the cutoff value indicates a renal disorder (see, e.g., at [0009]-[0010].

The examiner notes that the conclusory "whereby" clause of claim 1 sets forth a conditional limitation that applies only "should said concentration of NGAL fall below the cutoff value". When the claim is given its broadest reasonable interpretation, therefore, this "whereby" clause does not clearly call for any additional steps to be performed in cases where the NGAL concentration is *above* the cutoff. For these reasons, the teachings of Uttenthal et al. of determining the concentration of NGAL and of comparing the concentration with a cutoff value of 250 ng/mL anticipate the claims, as the reference envisions patients with levels above this cutoff. See also MPEP 2111.04.

With respect to claims 2-3, Uttenthal et al. teach measuring NGAL in urine, plasma, or serum [0021]-[0025]. As discussed above, the reference teaches that the cutoff value may be 250 ng/mL (see at [0023], [0025], and claim 2).

With respect to claim 7, Uttenthal et al. teach that acute renal failure is a consequence of ischemic injury [0002], [0003].

With respect to claim 12, Uttenthal et al. teach measuring NGAL using one or more binding molecules specific to human NGAL, such as antibodies [0030].

With respect to claims 15-17, see claims 7-9 of Uttenthal et al.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-3, 7-12, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Uttenthal et al. (U.S. 2009/0170143 A1).

The applied reference has a common assignee and common inventors with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Uttenthal et al. anticipates the claimed invention for reasons discussed in detail above. However, in the interest of compact prosecution, the present rejection is also being made.

Uttenthal et al. teach methods for diagnosing, monitoring, or determining the likelihood of a renal disorder by means of measuring NGAL in a bodily fluid sample [0002]. Uttenthal et al. further teach acute renal failure (ARF) as an example of a renal disorder that may be assessed using their methods [0007]. In addition, the reference also contemplates early detection of renal injury that may result in ARF (see [0002]-[0003], [0012]-[0013], and claim 11).

The methods of Uttenthal et al. involve comparing the measured concentration of NGAL with a predetermined cutoff value, in order to distinguish renal disorders from other disorders that do not affect the kidney [0007], [0010]. In particular, Uttenthal et al. teach cutoff levels of 250 ng/mL or more for the purpose of diagnosing renal injury [0022]-[0025]. Uttenthal et al. therefore teach comparing a subject's NGAL concentration to a cutoff level (which may be a cutoff level of 250 ng/ml), reading on the claimed comparison step of claim 1, step ii). The reference also clearly associates *increased* NGAL levels, i.e. those above the cutoff level, as being indicative of renal injury. Specifically, Uttenthal et al. state that an NGAL concentration above the cutoff value indicates a renal disorder (see, e.g., at [0009]-[0010].

However, Uttenthal et al. do not explicitly state that when the NGAL concentration falls below the cutoff value, that the subject is diagnosed or determined as not having and not being at immediate risk of developing acute renal failure. It is noted as above that this is not currently a clear requirement of the claim, since the conclusory "whereby" clause is expressed using conditional language.

Nonetheless, Uttenthal et al. clearly associate NGAL levels *above* the predetermined cutoff level to be associated with renal injury [0022]. In particular, the reference teaches that if the measured NGAL concentration exceeds the cutoff level, this is an indication that the human has suffered renal injury and may develop or has developed ARF. Uttenthal et al. also teach that the cutoff value is chosen to exclude lower concentrations of NGAL associated with conditions that do not affect the kidney [0010], conveying that levels below cutoff indicate the absence of a renal disorder.

It would have been obvious to one of ordinary skill in the art to conclude as a logical corollary of these teachings that when the measured NGAL concentration is below the cutoff level, this indicates that the human subject has not suffered renal injury, has not developed ARF, and is not at immediate risk of developing ARF; given that Uttenthal et al. convey that levels below cutoff indicate a non-renal disorder rather than a renal disorder. In particular, the methods of Uttenthal et al. are designed to distinguish renal disorders from other disorders that do not affect the kidney, and employ a cutoff level in order to distinguish such disorders. The reference therefore fairly teaches that NGAL levels below the cutoff would indicate that a subject does not have a renal disorder.

As Uttenthal et al. teach the cutoff level of 250 ng/mL and indicate that this level excludes lower concentrations of NGAL associated with conditions that do not affect the kidney, it would have been further obvious to conclude that levels below this particular cutoff level would mean that the subject has not suffered renal injury, has not developed ARF, and is not at immediate risk of developing ARF. In particular, it would have been a matter of common sense to conclude that subjects with levels below cutoff (indicating no renal disorder) also would not

have ARF and would not be at immediate risk of developing ARF since they have no renal disorder. One would be motivated to draw such a conclusion in order to not only identify those subjects with a renal disorder but also to rule out renal disorder in subjects with levels below cutoff.

With respect to claims 2-3, Uttenthal et al. teach measuring NGAL in urine, plasma, or serum [0021]-[0025]. As discussed above, the reference teaches that the cutoff value may be 250 ng/mL (see at [0023], [0025], and claim 2).

With respect to claim 7, Uttenthal et al. teach that acute renal failure is a consequence of ischemic injury [0002], [0003].

With respect to claim 12, Uttenthal et al. teach measuring NGAL using one or more binding molecules specific to human NGAL, such as antibodies [0030].

With respect to claim 8, Uttenthal et al. discuss how patients that they studied may have developed renal ischemic injury because of severe infections [0043]. The reference further teaches that disorders to be diagnosed and/or monitored according to their methods include ARF of whatever cause [0007]. Therefore, it would have been further obvious to one of ordinary skill in the art to arrive at the claimed invention by employ the methods of Uttenthal et al. to assess renal disorders due to infection.

With respect to claims 9-10, Uttenthal et al. studied patients with renal disorders who were admitted to a hospital intensive care unit [0015], [0017]-[0018], [0041], [0051]. In addition, the reference teaches that surgical procedures may result in renal disorder [0029]. As above, the reference teaches that disorders to be diagnosed and/or monitored according to their methods include ARF of whatever cause [0007]. Therefore, it would have been further obvious to one of

ordinary skill in the art to arrive at the claimed invention by employ the methods of Uttenthal et al. to assess renal disorders that arise due to causes that require intensive care, including surgical procedures.

With respect to claim 11, Uttenthal et al. further teach that exposure to nephrotoxic agents may cause renal disorders (see [0002]-[0003], [0021], and claim 12). When taken together with the above teachings of Uttenthal et al. that disorders to be diagnosed and/or monitored according to their methods include ARF of whatever cause [0007], as well as the teaching of ARF as an exemplary renal disorder, it would have been further obvious to arrive at the claimed invention by employ the methods of Uttenthal et al. to assess ARF that is due to exposure to nephrotoxic agents.

With respect to claims 15-17, see claims 7-9 of Uttenthal et al.

9. Claims 1-2, 7-12, and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Devarajan et al. (U.S. 2005/0272101, of record).

Devarajan et al. teach methods for detecting the immediate or early onset of renal disease and injury, including acute renal failure, by using NGAL as a biomarker (abstract and [0029]). In particular, Devarajan et al. discuss how renal tubular cell injury can result in acute renal failure (ARF) [0001]. The reference studied patients who underwent cardiopulmonary bypass surgery, and retrospectively assessed levels of NGAL in patients who subsequently developed ARF ([0019]-[0026], Examples 3-5 in particular (note that Example 3 is mistakenly labeled "Example 4"). The reference teaches that patients who subsequently developed acute renal failure displayed a remarkable increase in both urinary and serum NGAL [0072]-[0073] and Figures 4-8).

Devarajan et al. also propose NGAL cutoff values for both urine and serum, teaching that for urine NGAL, a cutoff of either 25 or 50 ng/ml yields outstanding sensitivity and specificity, while for serum NGAL, sensitivity and specificity are optimal at the 25 ng/ml cutoff ([0075], Figures 9-10, and Table 2). The cutoff levels of 25 and 50 ng/ml taught by Devarajan et al. fall within the claimed range of "250 ng/mL or a lower value".

The teachings of Devarajan et al. differ from the claimed invention in that the reference fails to specifically exemplify comparing a subject's NGAL concentration with these cutoff values. In particular, the studies of Devarajan et al. were *retrospective* in nature, designed to assess the usefulness of NGAL as a biomarker of acute renal failure. However, since Devarajan et al. concluded from their studies that NGAL can be used not only to diagnose renal injury but to predict acute renal failure (see, e.g., [0074]), it would have been obvious to one of ordinary skill in the art to employ NGAL levels in a prospective manner in order to diagnose and/or predict ARF in subjects in whom it is not yet known whether ARF is present or not.

As Devarajan et al. teach that their cutoff values yielded outstanding sensitivity and specificity in early diagnosis of acute renal injury, and further report both positive predictive value and negative predictive value [0075] for NGAL in this context, one skilled in the art would have found it obvious to conclude that NGAL levels in a subject that are above cutoff values would indicate acute renal injury. Conversely, one skilled in the art would have found it obvious to conclude that NGAL levels in a subject that are below cutoff would indicate the absence of current or imminent acute renal injury. One would be motivated to do this in order to not only identify subjects with acute renal injury, but also to rule out acute renal injury in subjects who do not have this disease. As Devarajan et al. provide statistical data establishing that NGAL has

both high positive predictive value (i.e., patients with a positive test result who are correctly diagnosed) as well as high negative predictive value (i.e., patients with a negative test result who are correctly diagnosed), one skilled in the art would have had a reasonable expectation of success in using NGAL levels to diagnose subjects as either having or not having acute renal failure.

The examiner also notes that the conclusion of claim 1 is a conditional limitation that would only be applicable in the event that NGAL levels are below the cutoff value. In other words, for subjects with NGAL levels found to be above cutoff, the conclusion step does not apply and does not clearly require any conclusions or steps to be performed. As such, the diagnosis of acute renal injury in subjects with NGAL levels above cutoff, as fairly suggested by Devarajan et al., would also read on the claim. See also MPEP 2111.04.

With respect to claim 2, the cutoff level of 50 ng/ml for urinary NGAL taught by Devarajan et al. falls within the claimed range of "between 50 ng/ML and 250 ng/mL".

With respect to claims 7 and 11, Devarajan et al. teach assessing ARF that is due to ischemic as well as nephrotoxic injury (see especially [0001], [0033] and [0040]-[0041]).

With respect to claim 8, Devarajan et al. contemplate detecting NGAL in patients who are at risk of developing ARF, including use in sepsis (i.e., an inflammatory disease; see especially [0033] and [0040]-[0041]).

Regarding claims 8 and 11, it would have been obvious to assess ARF due to administration of a nephrotoxic agent or sepsis by comparing a subject's NGAL levels to a predetermined cutoff level in the same manner exemplified by Devarajan et al. for cardiac surgery-induced ARF. In particular, as Devarajan et al. contemplate NGAL as a marker in ARF

due to a wide variety of causes, including nephrotoxic injury and sepsis, it would have been obvious to measure and compare NGAL levels in order to diagnose and predict ARF in other subjects also known to be at risk of ARF, such as those at risk of ARF due to these other causes.

With respect to claims 15-17, Devarajan et al. exemplify taking serial NGAL measurements, including several measurements made within 24 hours ([0073], Figures 7-8); and also contemplate measuring NGAL in samples taken at intervals throughout the course of treatment to monitor changes in renal health ([0041], claims 7-8).

10. Claims 1-2, 7, 9-10, and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mishra et al. ("Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery" Lancet 2005; 365: 1231–38).

Mishra et al. teach NGAL as a biomarker for predicting acute renal injury. In particular, the reference teaches NGAL as an early biomarker for the initiation phase of acute renal failure (see page 1232, left column, first paragraph). In particular, the reference studied patients undergoing cardiac surgery, some of whom developed ARF as a result of the ischaemia-reperfusion injury that occurs during the surgery (see page 1232, left column). Patients were classified into those who did and who did not develop ARF (see especially pages 1234, right column; and Figures 2-3). Samples of urine and serum were assayed for NGAL at various time points after cardiopulmonary bypass (ibid). Mishra et al. found that those patients who subsequently developed acute renal failure had a striking increase in both serum and urinary NGAL as compared with the patients who never developed acute renal failure (see page 1234, right column to page 1235, left column; and Figures 2-3).

From their data, Mishra et al. also derived various cutoff values for both serum and urine (page 1235, Table 2, and Figure 4). The reference concludes that for urine NGAL, a cutoff of either 25 or 50 μg/L (i.e., 25 or 50 ng/mL) yielded good sensitivity, while for serum NGAL, sensitivity and specificity were best at the 25 μg/L cutoff (i.e., 25 ng/mL).

The teachings of Mishra et al. differ from the claimed invention in that the reference fails to specifically exemplify comparing a subject's NGAL concentration with these predetermined cutoff values. In particular, the studies of Mishra et al. were *retrospective* in nature, designed to assess the usefulness of NGAL as a biomarker of acute renal failure. As such, development of ARF was assessed by conventional methods (see page 1232, "Procedures"). However, since Mishra et al. concluded from their studies that NGAL is a powerful independent predictor of acute renal injury (abstract and page 1236, right column), it would have been obvious to one of ordinary skill in the art to employ NGAL levels in a prospective manner in order to predict ARF in subjects in whom it is not yet known whether ARF is present or not.

Further, as Mishra et al. propose cutoff values for NGAL for distinguishing subjects who developed ARF from those who did not, it would have been obvious to conclude that subjects with NGAL levels below these cutoffs do not have ARF and are not at immediate risk of developing ARF. In particular, since Mishra et al. teach that NGAL levels taken as early as 2 hours after cardiopulmonary bypass (i.e., after the insult causing ARF) were capable of distinguishing subjects who developed ARF from those who did not, it would have been obvious to conclude that NGAL levels below the cutoff values proposed by Mishra et al. would indicate that subjects did not have ARF and were not at immediate risk of developing ARF.

With respect to claim 9, Mishra et al. teach that acute renal failure accounts for 30-50% of patients in intensive care units (see page 1231, left column). It would also have been at once envisaged that the patients studied by Mishra et al. would have been subject to intensive care due to the serious cardiac surgery procedures they underwent. In view of these teachings, it would have been further obvious to perform the methods of Mishra et al. on subjects at risk of developing ARF due to critical illness requiring intensive care, given that Mishra et al. taught that ARF frequently arises in such a setting.

With respect to claim 12, Mishra et al. measured NGAL by ELISA, which involved the use of a monoclonal antibody raised against human NGAL (see page 1232, right column, "ELISA for NGAL quantitation").

11. Claim 3 is rejected under 35 U.S.C. 103(a) as being unpatentable over either one of Devarajan et al. or Mishra et al. in view of Fraser ("The Utility of Population-Based Reference Values", Chapter 4 in: Biological Variation: From Principles to Practice, AAAC Press (July 1, 2001), pages 91-116, of record), Wu et al. ("Analytical and clinical evaluation of new diagnostic tests for myocardial damage" Clinica Chimica Acta 272 (1998) 11–21, of record), Elneihoum et al. ("Leukocyte activation in atherosclerosis: correlation with risk factors" Atherosclerosis, (1997 May) Vol. 131, No. 1, pp. 79-84, of record), Kunis et al. "NGAL (Neutrophil Gelatinase-Associated Lipocalin) as a Marker for Tubular Damage in Patients with Acute Tubular Necrosis (ATN), Abstract SU-PO204, poster presentation at The American Society for Nephrology Renal Week 2004 (October 27-November 1, 2004, of record), and Holvoet et al. (US 6,309,888, of record).

Devarajan et al. is as discussed in detail above, which teaches a cutoff value for serum NGAL of 25 ng/ml cutoff ([0075], Figures 9-10, and Table 2). The reference fails to specifically teach a serum cutoff value that is between 100 ng/mL and 250 ng/mL.

However, it is noted that the studies of Devarajan et al. were performed on pediatric patients (see especially [0061]-[0062], [0064]-[0065], [0067]). The cutoff value of 25 ng/mL was therefore arrived at by studying levels of NGAL in children in the context of acute renal failure.

Similarly, Mishra et al. also report a cutoff value of serum NGAL of 25 ng/ml (see page 1235, right column) which they arrived at through statistical analysis of their clinical data from pediatric subjects.

Those of ordinary skill in the art at the time of the instant invention recognized the importance of establishing cutoff levels tailored to the particular clinical situation; cutoff levels derived from age- and sex-matched cohorts may be necessary since analyte levels can vary with age and/or sex

For example, Fraser discusses how many analytes change over the lifespan of an individual, or depending on sex. This has consequences for the reference or cutoff values used to interpret test results. In addition to these endogenous factors, other exogenous factors, laboratory-specific factors, and the type of statistical approach used can also affect cutoff values. See pages 97-98, "Factors Affecting Reference Values". Fraser discuss how age and sex in particular are "important factors", such that sub-sets of reference values may be needed (ibid and page 100, item 4). For example, Fraser discusses how the biomarker serum creatinine is higher in elderly people than in younger people, such that age stratified cutoff values are most likely required (pages 102-103).

Wu et al. also indicate that the normal reference range and cut-off concentrations for any laboratory marker should be examined on an age- and sex-matched cohort group of healthy individuals (pages 14-16, section 3.1).

In the case of NGAL, it was further known that levels of NGAL may vary depending on age. For example, Elneihoum et al. teach that plasma levels of NGAL are correlated with age, as well as with hypertension for women (abstract; section 3.1; and page 82, right column).

Kunis et al. determined the concentration of NGAL in serum and urine samples taken from adult patients with acute tubular necrosis (ATN) during the first 48 hours of acute renal failure (ARF). The reference reports that as compared with controls, NGAL levels were increased in these ATN patients from 20 to 145 ng/ml in serum. In patients in whom ATN was caused by sepsis, NGAL levels were even higher (331 ng/ml in serum).

In addition, Applicant is reminded that generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05.

In the case of cutoff values, the prior art recognized that cutoff values were routinely used as a point of reference against which measured values of a biomarker may be compared, in order to objectively interpret the results of laboratory tests. Moreover, the cutoff level selected for an assay was recognized in the prior art to be a result effective variable in diagnostic testing, having effects on both assay sensitivity and specificity. In particular, there was a known trade-off

between sensitivity and specificity, in that increasing the sensitivity by lowering the cutoff value decreases the specificity, and vice versa.

For example, Holvoet et al. teach that the diagnostic accuracy of a test or assay, i.e. the ability of the test or assay to distinguish between patients having a disease, condition or syndrome from those that do not, is based on whether the patients have a clinically significant amount of an analyte. A "clinically significant" amount refers to an amount higher than a predetermined cut point or threshold value for that analyte. See column 8, lines 37-50. Changing this cut point or threshold usually changes the sensitivity and specificity of the diagnostic test. For example, if the threshold is lowered, sensitivity (true positive rate) will be increased while specificity (true negative rate) will be decreased. Similarly, raising the cut point will tend to decrease sensitivity and increase specificity (column 9, lines 5-33).

Therefore, while Devarajan et al. and Mishra et al. exemplify a cutoff value of 25 ng/mL, it would have been obvious to employ cutoff values within the claimed range of 100 ng/mL and 250 ng/mL for the following reasons.

Devarajan et al. and Mishra et al. arrived at their optimal cutoff value of 25 ng/mL by studying pediatric patients. It was known, however, that concentrations of analytes may vary with age (Fraser, Wu, Elneihoum). In the case of NGAL, it had in fact been documented that NGAL levels increase with age (Elneihoum).

When taken together with the guidance of Wu et al. that cut-off concentrations for any laboratory marker should be examined on an age- and sex-matched cohort group of healthy individuals, as well as the teachings of Holvoet et al. which indicate that the cut-off value was known to be a result-effective variable, it would have been obvious to one of ordinary skill in the

art to optimize the cutoff value when performing the methods of Devarajan et al. or Mishra et al. on older subjects such as adults. One would be motivated to do this in order to assess acute renal failure not only in pediatric subjects but also in adults. While Devarajan et al. and Mishra et al. exemplify a cutoff value of 25 ng/mL for their pediatric subjects, one of ordinary skill in the art would have found it obvious to employ a cutoff value derived from an age-matched cohort when seeking to diagnose non-pediatric subjects. As older subjects would be reasonably expected to normally have higher levels of NGAL, optimal cutoff values derived from age-matched cohorts in older subjects would similarly be expected to be higher than the cutoff value of 50 ng/mL derived by Devarajan et al. from their studies on children.

Moreover, the prior art provides specific direction to serum NGAL levels within the claimed range, in that Kunis et al. observed that adult patients with acute tubular necrosis (ATN) during the first 48 hours of acute renal failure (ARF) had serum NGAL levels of 145 ng/ml, as compared with control levels of 20 ng/ml. It would have been obvious to arrive at cutoff levels within the claimed range by optimizing levels in order to achieve a desired sensitivity and/or specificity, depending on clinical goals and for the particular patient population under study.

Double Patenting

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined

application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The following are <u>provisional</u> obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

13. Claims 1-3, 7, 11-12, and 15-17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-13, 15, and 30 of copending Application No. 11/722,025. Although the conflicting claims are not identical, they

are not patentably distinct from each other because copending Application No. 11/722,025 claims a method of determining whether a human subject has a renal disorder by determining the concentration of NGAL in a body fluid sample and comparing the measured concentration to a cutoff value that is 250 ng/ml or a higher value. The copending application further recites that a concentration of NGAL in the sample that is greater than or equal to the cutoff value indicates that the human being has a renal disorder. See especially claim 1. In addition, the renal disorder to be determined may be one that may cause acute renal failure (see claim 11).

Copending Application No. 11/722,025 therefore sets forth a method in which a cutoff value of 250 ng/ml may be used to assess a renal disorder, and in which measured NGAL levels higher than this cutoff value 250 ng/ml indicate that the subject has a renal disorder (which may be a renal disorder that may cause acute renal failure).

The copending application fails to specifically recite diagnosing or determining the risk of developing acute renal failure. More particularly, the copending application fails to specifically state that the subject is diagnosed or determined as not having or not being at immediate risk of developing acute renal failure when the concentration of NGAL is below the cutoff value.

However, as the copending application makes clear that levels above the cutoff of 250 ng/ml indicate the presence of a renal disorder, the ordinary artisan would have found it obvious to conclude that levels below this cutoff indicate that the subject does not have a renal disorder, and in particular that the subject does not have a renal disorder that may cause acute renal failure. One of ordinary skill in the art would have therefore found it obvious to conclude that such patients determined not to have a renal disorder as per the methods of Copending Application

No. 11/722,025 would not have acute renal failure (since this is a renal disorder). Similarly, it would have been obvious to conclude that patients determined not to have a renal disorder that may cause acute renal failure as per the methods of Copending Application No. 11/722,025 would also not be at immediate risk of developing acute renal failure.

With respect to claims 2-3 and 13-14, Copending Application No. 11/722,025 teaches sampling either urine, plasma, or serum (see claim 1).

With respect to claim 7, see claim 10 of Copending Application No. 11/722,025.

With respect to claim 11, see claim 12 of Copending Application No. 11/722,025.

With respect to claim 12, see claim 15 of Copending Application No. 11/722,025.

With respect to claims 15-17, see claims 7-9 of Copending Application No. 11/722,025.

14. Claim 8 is provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-13, 15, and 30 of copending Application No. 11/722,025 in view of Devarajan et al. (U.S. 2004/0219603 A1; hereafter, "Devarajan et al. 2".

Application No. 11/722,025 is as discussed in detail above, which renders obvious a method substantially as claimed, but does not teach that the risk of developing ARF is due to an inflammatory disease.

Devarajan et al. 2 teach that NGAL measurements can be applied to all patients who are at risk of developing ARF, including risk in sepsis and nephrotoxins [0038].

The teachings of Devarajan et al. 2 indicate that those of ordinary skill in the art recognized both nephrotoxins (which are also recited in Application No. 11/722,025, see claim 12) as well as sepsis to be associated with risk of ARF. As such, it would have been obvious to

arrive at the claimed invention by performing the methods of Application No. 11/722,025 on those subjects at risk of ARF due to sepsis (i.e., an inflammatory disease). One would be motivated to do this in order to ascertain risk in this population known to be susceptible to ARF.

15. Claims 9-10 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4-13, 15, and 30 of copending Application No. 11/722,025 in view of Mishra et al.

Application No. 11/722,025 and Mishra et al. are as discussed in detail above. Application No. 11/722,025 renders obvious a method substantially as claimed, but does not teach that the risk of developing ARF is due to critically illness requiring intensive care or due to a surgical intervention.

However, Mishra et al. teach that ARF may result from cardiopulmonary bypass surgery. It would have been at once envisaged that patients undergoing such surgery would be critically ill and require intensive care.

As such, it would have been obvious to one of ordinary skill in the art to arrive at the claimed invention by performing the methods of Application No. 11/722,025 on subjects at risk of developing ARF due to cardiopulmonary bypass surgery. One would be motivated to do this in order to ascertain risk in this population known to be susceptible to ARF.

16. Claims 1-3, 7-12, and 15-17 are directed to an invention not patentably distinct from claims 1, 4-13, 15, and 30 of commonly assigned Application No. 11/722,025. See the preceding obviousness-type double patenting rejections.

The U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300). Commonly assigned Application No. 11/722,025, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(e), (f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee can, under 35 U.S.C. 103(c) and 37 CFR 1.78(c), either show that the conflicting inventions were commonly owned at the time the invention in this application was made, or name the prior inventor of the conflicting subject matter.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g), or 35 U.S.C. 102(e) for applications pending on or after December 10, 2004.

Response to Arguments

17. Applicant's arguments filed 5/8/2012 have been fully considered.

18. The rejections under 35 U.S.C. 112 (first and second paragraphs) as set forth in the previous Office action are withdrawn in response to Applicant's amendments.

19. With respect to the rejections under 35 U.S.C. 102(e) and 35 U.S.C. 103(a) based upon the Uttenthal et al. reference, Applicant has submitted a Declaration under § 1.132 by inventors Uttenthal and Bangert purported to show that the Uttenthal et al. reference is not prior art. See the Declaration and Applicant's reply at pages 8-10.

Response to Amendment

20. The Declaration under 37 CFR 1.132 filed 5/8/2012 is insufficient to overcome the rejections of claims 1-3 and 7-14 based upon 35 U.S.C. 102(e) and 35 U.S.C. 103(a) as set forth in the last Office action (now applied to claims 1-3, 7-12, and 15-17 above) for the following reasons.

In the Declaration, inventors Uttenthal and Bangert state that any subject matter described in U.S. 2009/0170143 that is equivalent to the subject matter recited in claims 1-3 and 7-14 of the present application is solely their invention, as is the subject matter in U.S. 2009/0170143 upon which the Office has relied upon in the 35 U.S.C. 103 rejection. The Declaration further states that Margarita Ghiglione Juanes did not make an inventive contribution to such subject matter. Declaration, items 2-3.

This evidence is not sufficient because:

The statements made in the Declaration are vague and fail to establish a clear or conclusive record about who invented what specific subject matter. It is not explained, for example, what specific contribution inventor Juanes made to U.S. 2009/0170143 and what specific contribution inventors Uttenthal and Bangert made. The Declaration does not provide an explanation as to why inventor Juanes is an inventor of U.S. 2009/0170143 but not of the present application. References to “the subject matter…upon which the Office has relied upon" and to “any subject matter…that is equivalent to the subject matter recited in [certain of the pending claims]” are non-specific inconclusive and do not clearly indicate what particular subject matter was invented by whom.

In addition, the Declaration fails to establish that the disclosure of U.S. 2009/0170143 is a description of Applicant's own previous work because there is no showing that Inventor Juanes was associated with Applicant (e.g. worked for the same company) and learned of applicant's invention from applicant. In re Mathews, 408 F.2d 1393, 161 USPQ 276 (CCPA 1969). See MPEP 2136.05.

Finally, the subject matter at issue here is not limited to unclaimed subject matter but rather, includes that recited in the claims of U.S. 2009/0170143. Applicant's reply on page 8 references MPEP 2136.05, which discusses the possibility of a showing under 37 CFR 1.132 "when the unclaimed subject matter of a reference is applicant's own invention". Similarly, Applicant also refers here to MPEP 716.10, quoting a passage that begins "When subject matter disclosed but not claimed in a patent application...". Because the subject matter at issue here also appears in the claims of U.S. 2009/0170143, the evidence presented is insufficient to overcome the rejection.

Applicant may wish to consider the possible applicability of a showing under 35 U.S.C. 103(c) in order to address this rejection. See MPEP 706.02(l).

21. The rejections based upon the Devarajan et al. reference were incorrectly listed in the previous Office action under 35 U.S.C. 102; the rejections are under 35 U.S.C. 103 and the rejection heading has been corrected accordingly as set forth above.

Applicant argues that the reference clearly teaches away from employing a cutoff value of 250 ng/mL for determining that a subject does not have renal disorder since all of the patients of Figures 2, 4, 7, and 8 of Devarajan et al. would be diagnosed as not having renal failure if this

cutoff value were used. Applicant further argues that Devarajan et al. teaches in several places that any elevation in NGAL indicates acute renal failure, See Reply, pages 9-10.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., employing a cutoff value of 250 ng/mL) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Rather, the claims recite "a cutoff value of 250 ng/mL or a lower value". This terminology encompasses a genus of possible cutoff values, including not only the upper limit of the range (250 ng/mL) but any value lower than 250 ng/mL. The cutoff values of 25 and 50 ng/mL taught by Devarajan et al. fall within this claimed range.

22. With respect to the rejections under § 103 based upon the Mishra et al. reference, Applicant argues that the claims are directed to a method in which a concentration below 250 ng/ml identifies the subject as not having and not being at immediate risk of developing ARF. Applicant argues Mishra et al. teach cutoff values of 25 or 50 ng/ml and therefore fail to teach a cutoff value of 250 ng/ml. See Reply, pages 10-11. This is not found persuasive because as discussed immediately above, the claims recite "a cutoff value of 250 ng/mL or a lower value". As such, the claimed methods encompass not only cutoff values of 250 ng/ml *per se* but any cutoff values lower than this, such as the cutoff values of 25 or 50 ng/ml taught by Mishra et al.

Applicant further argues that the purpose of Mishra et al. is to identify individuals suffering from acute renal failure, and that the reference does not envision the necessity of identifying the population that does not require medical intervention (Reply, pages 10-11). This

is not found persuasive because Mishra et al. teach using cutoff values to distinguish populations with acute renal failure from those without renal failure. Although Mishra et al. focus on identifying those subjects with ARF, it is maintained that the ordinary artisan would have found it obvious to conclude that subjects with NGAL levels below the cutoff do not have ARF and are not at risk for immediate development of ARF. From the teaching of Mishra et al. of a cutoff level above which NGAL levels are indicative of disease, the ordinary artisan would have at once envisaged the obvious logical corollary; i.e. that levels below the cutoff are indicative of the absence of disease.

23. Applicant acknowledges but does not presently address the obviousness-type double patenting rejections (see Reply, page 11), which are therefore maintained at this time for reasons of record.

24. Applicant's attention is also directed to the Advisory Information relating to Applicant's copending Application No. 11/722,025 (set forth above and in the previous Office action at page 27, item 30). Applicant's reply does not address the Advisory Information.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Christine Foster/
Examiner, Art Unit 1641