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(71) Applicant: **HYCOR BIOMEDICAL, INC** [US/US];  
3021 E. 98th St., Suite 220, Indianapolis, IN 46280 (US).

(72) Inventor: **VAN CLEVE, Mark, David**; 3348 E. 1st St.,  
Long Beach, CA 90803 (US).

(74) Agents: **CULLMAN, Louis, C.** et al.; K&I Gates LLP, 1  
Park Plaza, 12th Floor, Irvine, CA 92614 (US).

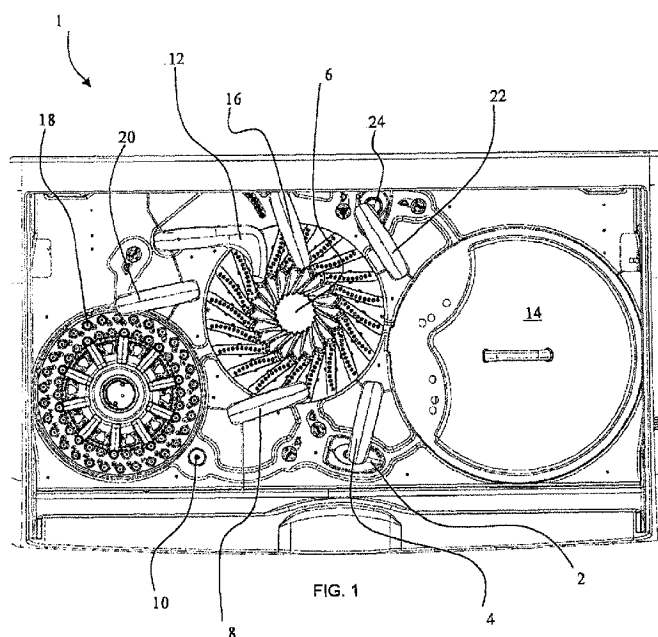
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(57) Abstract: Methods and apparatus that mix a plurality of individual capture reagents for the diagnostic assays are described herein. In an embodiment, a system for optically analyzing a patient sample includes an automated immunochemistry analyzer storing a plurality of capture reagents and a plurality of paramagnetic particles, a user interface configured to allow a selection of a combination of two or more of the capture reagents, and a logic implementer configured to cause the automated immunochemistry analyzer to (i) mix together each capture reagent of the combination of two or more of the capture reagents; (ii) bind the mixture of the combination of two or more of the capture reagents to the paramagnetic particles; (iii) bind the patient sample to the bound mixture of the combination of two or more of the capture reagents; and (iv) optically analyze the patient sample.

## ON-BOARD KITTING

### FIELD OF THE DISCLOSURE

**[0001]** The present disclosure relates generally to methods and apparatuses for performing diagnostic assays, and more specifically to methods and apparatus that mix a plurality of individual capture reagents for the diagnostic assays.

### BACKGROUND OF THE DISCLOSURE

**[0002]** Many immunochemistry analysis systems require that analyte molecules in a patient's biological sample (e.g. serum or plasma) attach to paramagnetic particles. To bind analyte molecules of interest to the paramagnetic particles, a capture reagent is first bound to the paramagnetic particles, and then the patient sample is bound to the capture reagent. The analyses performed by such systems, however, are relatively slow and inefficient because the systems do not provide the capability for a user to customize a mixture of multiple capture reagents and therefore optimize the analysis of the patient sample for different types of analyte molecules of interest.

### SUMMARY OF THE DISCLOSURE

**[0003]** Described herein are methods and apparatus that mix a plurality of individual capture reagents for diagnostic assays so that the analysis of a patient sample can be optimized for different types of analyte molecules of interest.

**[0004]** Disclosed herein is a system for *in situ* preparation of a plurality of analytical substrates customizable for a particular disease profile, the system comprising: an instrument configured to store a plurality of capture reagents, each capture reagent specific for an immunogen, and a plurality of paramagnetic particles, wherein the instrument comprises; (a) a user interface configured to allow a selection of a capture reagent, or a combination of two or more capture reagents, from the plurality of capture reagents based on input by a user; and (b) a logic implementer configured to cause the instrument to (i) mix together each capture reagent of the combination of two or more capture reagents, and (ii) bind the capture reagent or the combination of two or more capture reagents to the paramagnetic particles; wherein at least one analytical substrate is formed by the instrument.

**[0005]** In other embodiments of the system, the instrument is adapted to prepare a plurality of custom analytical substrates simultaneously. In yet other embodiments, the plurality of custom analytical substrates are simultaneously prepared for the same disease profile. In other embodiments, the plurality of custom analytical substrates are

simultaneously prepared for different disease profiles. In some embodiments, the immunogens are selected from allergens, infectious disease antigens, and autoantigens.

**[0006]** In other embodiments, the instrument is an automated immunochemistry analyzer. In other embodiments, the logic implementer is configured to limit the number of capture reagents that the user interface allows for selection. In other embodiments, the logic implementer is configured to limit the number of capture reagents that the user interface allows for selection based on the availability of the capture reagents within the automated immunochemistry analyzer. In yet other embodiments, the logic implementer is configured to adjust the number of capture reagents that the user interface allows for selection as the selection is being made. In some embodiments, the logic implementer is configured to store a plurality of preprogrammed combinations of two or more capture reagents for selection using the user interface.

**[0007]** In other embodiments, the plurality of preprogrammed combinations are sorted by the disease profile. In yet other embodiments, the disease profile is an allergy disease profile, an infectious disease profile, or an autoimmune disease profile. In other embodiments, the plurality of preprogrammed combinations are sorted by type of immunogen. In other embodiments, the selection of the combination of two or more capture reagents is made by individually selecting each of the capture reagents in the combination. In some embodiments, the combination of two or more capture reagents is a combination of 2-10 capture reagents. In yet other embodiments, the logic implementer is configured to cause the automated immunochemistry analyzer to perform additional analyses using at least one of the two or more capture reagents if a test using the combination of two or more capture reagents returns a positive result.

**[0008]** Also disclosed herein is a method for *in situ* preparation of a plurality of analytical substrates customizable for a particular disease profile, the method comprising: providing an instrument configured to store a plurality of capture reagents, each capture reagent specific for an immunogen, wherein the instrument comprises; (a) a user interface configured to allow a selection of a capture reagent, or a combination of two or more capture reagents, from the plurality of capture reagents based on input by a user; and (b) a logic implementer configured to cause the instrument to (i) mix together each capture reagent of the combination of two or more capture reagents, and (ii) bind the capture reagent or the combination of two or more capture reagents to the paramagnetic particles; selecting at least one disease profile from a graphical user interface (GUI) associated with the instrument and wherein the instrument selects a combination of two or more capture reagents from the plurality of selectable capture reagents available; adding each capture reagent of the

combination of two or more capture reagents to a container containing paramagnetic particles; thereby forming at least one analytical substrate.

**[0009]** In other embodiments, the immunogens are selected from allergens, infectious disease antigens, and autoantigens. In yet other embodiments, the method includes narrowing the number of capture reagents that are available for selection. In other embodiments, the combination of two or more capture reagents comprises 2-10 capture reagents. In some embodiments, selecting from the plurality of selectable capture reagents includes selecting from a plurality of preprogrammed combinations of two or more capture reagents. In certain embodiments, selecting from the plurality of selectable capture reagents includes individually selecting each capture reagent from the plurality of selectable capture reagents. In yet other embodiments, the method includes preparing additional analytical substrates using at least one of the two or more capture reagents individually from the combination if a test using the combination of two or more capture reagents returns a positive result.

**[0010]** Also disclosed herein is a system for *in situ* preparation of a plurality of analytical substrates customizable for a particular disease profile, the system comprising: an instrument configured to store a plurality of capture reagents, each capture reagent specific for an immunogen, and a plurality of paramagnetic particles; wherein the instrument comprises (a) a graphical user interface which allows for the input of disease profile data by a user; (b) a selection module that allows a selection of a single capture reagent or a combination of two or more capture reagents from the plurality of capture reagents; (c) a mixing module that (i) mixes together each capture reagent of the combination of two or more capture reagents, and (ii) binds the single capture reagent or the mixture of the combination of two or more capture reagents to the paramagnetic particles; wherein at least one analytical substrate is formed by the instrument.

**[0011]** In other embodiments, the immunogens are selected from allergens, infectious disease antigens, and autoantigens. In yet other embodiments, the combination of two or more capture reagents comprise 2-10 capture reagents. In other embodiments, the system includes an inventory tracking module that stores locations of the plurality of capture reagents. In some embodiments, the inventory tracking module communicates the locations of the plurality of capture reagents to at least one of: (i) the selection module; (ii) the mixing module; and (iii) the analysis module.

**[0012]** In other embodiments, the system includes an inventory replenishment module that replenishes the plurality of capture reagents. In yet other embodiments, the analysis module instructs the mixing module to mix a second combination of two or more capture

reagents if a test of the combination of two or more capture reagents returns a positive result. In other embodiments, the selection module allows for individual selection of each capture reagent of the combination of two or more capture reagents. In some embodiments, the selection module allows for selection of the combination of two or more capture reagents from a plurality of preprogrammed combinations of two or more capture reagents.

#### BRIEF DESCRIPTION OF THE DRAWINGS

**[0013]** Embodiments of the present disclosure will now be explained in further detail by way of example only with reference to the accompanying figures, in which:

**[0014]** Fig. 1 is a top schematic view of an embodiment of an automated immunochemistry analyzer and reagent system according to the present disclosure;

**[0015]** Fig. 2 is a schematic illustration of an embodiment of a process for performing a diagnostic assay according to the present disclosure;

**[0016]** Fv. 3A to 3C illustrate an embodiment of a graphical user interface that can be used with the process of Fig. 2;

**[0017]** Figs. 4A and 4B are schematic illustrations of an embodiment of a process for performing a diagnostic assay according to the present disclosure;

**[0018]** Figs. 5A and 5B are schematic illustrations of an embodiment of a process for performing a diagnostic assay according to the present disclosure;

**[0019]** Fig. 6 is a schematic illustration of an embodiment of a process for performing a diagnostic assay according to the present disclosure;

**[0020]** Fig. 7 is a schematic illustration of an embodiment of a system that can be controlled to perform the processes of Figs. 2 to 6.

#### DETAILED DESCRIPTION

**[0021]** Before describing in detail the illustrative system and method of the present disclosure, it should be understood and appreciated herein that the present disclosure relates to methods and apparatus that prepare, *in situ*, analytical substrates by mix a plurality of individual capture reagents to form analytical substrates to optimize diagnostic assays for different types of analyte molecules of interest, specifically for molecules that bind to immunogens. In general, the system utilizes common paramagnetic particles, for example magnetic beads or microparticles, that are pulled to the wall of a reaction cuvette by magnets during a washing process so that liquid can be aspirated from the cuvette.

**[0022]** As used herein, the term “in situ” refers to the preparation of the analytical substrate by the system and apparatus disclosed herein and specifically excludes the preparation of analytical substrates manually.

**[0023]** As used herein, the term “immunogen” refers to an antigen to which an individual will make a detectable immune response. For the purposes of the present disclosure, immunogen-binding molecules present in the blood of patients are tested for binding to the immunogen. Exemplary immunogens include, but are not limited to, allergens, infectious disease antigens, and autoantigens. Immunogens can be proteins, glycoproteins, carbohydrates, lipids, glycolipids, or nucleic acids. Additionally the term immunogen can refer to a fragment of one of the autoantigens, allergens, or infectious agent antigens disclosed herein.

**[0024]** Exemplary allergens include, but are not limited to, food allergens (i.e., peanuts, soy, shellfish, etc.), plant allergens (i.e., pollen, poison oak, grasses, weeds, trees, etc.), insect allergens (i.e., bee venom, etc.), animal allergens (i.e., wool, fur, dander, etc.), drugs (i.e. penicillin, sulfonamides, salicylates, etc.), mold spores, fragrances, latex, metals, wood, etc.

**[0025]** Infectious agents include, but are not limited to, bacteria, virus, viroids, prions, nematodes (e.g., roundworms, pinworms), parasites (e.g., malaria, tapeworm), and fungi (e.g., yeast, ringworm). As used herein the terms “infectious agent,” “pathogen”, “pathogenic microorganism” and “microorganism” all refer to the infectious agents listed above. Antigens from infectious agents can be any isolated protein, glycoprotein, nucleic acid, enzyme, lipid, liposaccharide, or combination thereof, from an infectious agent. Antigens can also include extracts or homogenized preparations from infectious agents which include a plurality of different antigenic moieties.

**[0026]** Examples of autoantigens include, but are not limited to, nuclear antigens (target of antinuclear antibodies (ANA)), aggrecan, alanyl-tRNA synthetase (PL-12), alpha beta crystallin, alpha fodrin (Sptan 1), alpha-actinin,  $\alpha$ 1 antichymotrypsin,  $\alpha$ 1 antitrypsin,  $\alpha$ 1 microglobulin, alsolase, aminoacyl-tRNA synthetase, amyloid (e.g., amyloid beta, amyloid P), annexins (e.g., annexin II, annexin V), apolipoproteins (e.g., ApoB, ApoE, ApoE4, ApoJ), aquaporin (e.g., AQP1, AQP2, AQP3, AQP4), bactericidal/permeability-increasing protein (BPI),  $\beta$ -globin precursor BP1,  $\beta$ -actin,  $\beta$ -lactoglobulin A,  $\beta$ 2-glycoprotein I,  $\beta$ 2-microglobulin, blood group antigens (e.g., Rh blood group antigens, I blood group antigens, ABO blood group antigens), C reactive protein (CRP), calmodulin, calreticulin, cardiolipin, catalase, cathepsin B, centromere proteins (e.g., CENP-A, CENP-B), chondroitin sulfate, chromatin, collagen (e.g., types I, II, III, IV, V, VI collagen), complement components (e.g., C1q, C3,

C3a, C3b, C4, C5, C6, C7, C8, C9), cytochrome C, cytochrome P450 2D6, cytokeratins, decorin, dermatan sulfate, DNA (e.g., double stranded DNA, single stranded DNA), DNA topoisomerase I, elastin, Epstein-Barr nuclear antigen 1 (EBNA1), elastin, entactin, extractable nuclear antigens (Ro, La, Sm, RNP, Scl-70, Jo1), Factor I, Factor P, Factor B, Factor D, Factor H, Factor X, fibrinogen (e.g., fibrinogen IV, fibrinogen S), fibronectin, formiminotransferase cyclodeaminase (LC-1), gliadin and amidated gliadin peptides (DGPs), gp210 nuclear envelope protein, GP2 (major zymogen granule membrane glycoprotein), glycoprotein gp11b/IIIa, glial fibrillary acidic protein (GFAP), glycated albumin, glyceraldehyde 3-phosphate dehydrogenase (GAPDH), haptoglobin A2, heat shock proteins (e.g., Hsp60, HSP70), hemocyanin, heparin, histones (e.g., histones H1, H2A, H2B, H3, H4), histidyl-tRNA synthetase (Jo-1), hyaluronidase, immunoglobulins, insulin, insulin receptor, integrins (e.g., integrins  $\alpha_1\beta_1$ ,  $\alpha_2\beta_1$ ,  $\alpha_3\beta_1$ ,  $\alpha_4\beta_1$ ,  $\alpha_5\beta_1$ ,  $\alpha_6\beta_1$ ,  $\alpha_7\beta_1$ ,  $\alpha_L\beta_2$ ,  $\alpha_M\beta_2$ ,  $\alpha_{IIb}\beta_3$ ,  $\alpha_V\beta_1$ ,  $\alpha_V\beta_3$ ,  $\alpha_V\beta_5$ ,  $\alpha_V\beta_6$ ,  $\alpha_V\beta_8$ ,  $\alpha_6\beta_3$ ,  $\alpha_1\beta_1$ ), interstitial retinol-binding protein 3, intrinsic factor, Ku (p70/p80), lactate dehydrogenase, laminin, liver cytosol antigen type 1 (LC1), liver/kidney microsomal antigen 1 (LKM1), lysozyme, melanoma differentiation-associated protein 5 (MDA5), Mi-2 (chromodomain helicase DNA binding protein 4), mitochondrial proteins (e.g., M1, M2, M3, M4, M5, M6, M7, M8, M9, BCOADC-E2, OGDC-E2, PDC-E2), muscarinic receptors, myelin-associated glycoprotein, myosin, myelin basic protein, myelin oligodendrocyte glycoprotein, myeloperoxidase (MPO), rheumatoid factor (IgM anti-IgG), neuron-specific enolase, nicotinic acetylcholine receptor  $\alpha$  chain, nucleolin, nucleoporin (e.g., Nup62), nucleosome antigen, PM/Scl100, PM/Scl 75, pancreatic  $\beta$ -cell antigen, pepsinogen, peroxiredoxin 1, phosphoglucose isomerase, phospholipids, phosphatidyl inositol, platelet derived growth factors, polymerase beta (POLB), potassium channel KIR4.1, proliferating cell nuclear antigen (PCNA), proteinase-3, proteolipid protein, proteoglycan, prothrombin, recoverin, rhodopsin, ribonuclease, ribonucleoproteins (e.g., Ro, La, snRNP, scRNP), ribosomes, ribosomal phosphoproteins (e.g., P0, P1, P2), RNA (double stranded RNA, single stranded RNA), Sm proteins (e.g., SmB, SmB', SmD1, SmD2, SmD3, SmF, SmG, SmN), Sp100 nuclear protein, SRP54 (signal recognition particle 54 kDa), selectin, smooth muscle proteins, sphingomyelin, streptococcal antigens, superoxide dismutase, synovial joint proteins, T1F1 gamma collagen, threonyl-tRNA synthetase (PL-7), tissue transglutaminase, thyroid peroxidase, thyroglobulin, thyroid stimulating hormone receptor, transferrin, triosephosphate isomerase, tubulin, tumor necrosis alpha, topoisomerase, U1-dnRNP 68/70 kDa, U1-snRNP A, U1-snRNP C, U-snRNP B/B', ubiquitin, vascular endothelial growth factor, vimentin, and vitronectin.

**[0027]** As used herein, the term “analytical substrate” refers to a complex of one or more capture reagents and paramagnetic particles. The analytical substrate is substantially free of unbound capture reagent.

**[0028]** As used herein, the term “disease profile” refers to a symptom, a group of symptoms, a disease diagnosis, or other information regarding a patient which will allow the selection of capture reagents. For example, a subject with allergy symptoms will have an allergy disease profile requiring the testing for one or more environmental allergens, food allergens, plant allergens, etc.

**[0029]** As used herein, the term “simultaneously” refers to the ability of the system and instrument to generate a plurality of analytical substrates at the same time, without waiting for one analytical substrate to be completed before the next analytical substrate can be generated.

**[0030]** In the beginning of the process, the paramagnetic particles are coated with one or more capture reagent that will eventually bind analyte molecules of interest in the patient's blood sample. In exemplary embodiments, the capture molecule is an immunogen which binds an immunogen-binding molecule (analyte), such as an antibody, in the patients' blood sample. After the capture reagents bind to the paramagnetic particles and the cuvettes undergo a washing process, the patient sample, and optionally a diluent if needed, is added to the particles in the reaction cuvette and incubated. This allows analytes of interest in the patient's blood sample to bind to the one or more capture reagent that have in turn been bound to the surface of a paramagnetic particle.

**[0031]** After the patient sample incubation period, another washing process is performed to remove any excess or unbound sample, and then a conjugate and a luminescent label are added to the cuvette. When added to the cuvette, it can be expected that some portion of the conjugate will bind to the capture reagent/sample complex on the paramagnetic particles after an incubation period. The particles then undergo another wash process to remove any unbound conjugate, and then the luminescent label is added to the reaction cuvette and incubated for a short period of time to allow the chemiluminescent glow reaction to reach equilibrium. After equilibrium is reached, luminescence and fluorescence readings of the sample can be taken.

**[0032]** Fig. 1 illustrates various components of an embodiment of an automated immunochemistry analyzer 1 according to the present disclosure. Automated immunochemistry analyzer 1 can take an analyte sample, create an environment that will allow it to bind to a paramagnetic particle, perform a number of washing steps, and then quantify and normalize the luminescence signal of the analyte sample. This can be



accomplished through an automated process that utilizes a vortexer 2, an R1 pipettor 4, a reaction rotor 6, an optics pipettor 8, an optics box 10, a multi rinse pipettor 12, a reagent rotor 14, a single rinse pipettor 16, a sample rotor 18, a sample pipettor 20, an R2 pipettor 22, and a mixed substrate container 24.

**[0033]** In one embodiment disclosed herein, the apparatus can quantify and normalize the luminescence signal of an analyte sample before reaction of the analyte with the capture reagent. In an embodiment, automated immunochemistry analyzer 1 begins by first dispensing fluorescently labelled paramagnetic particles, or fluo-beads, into a cuvette located within the reaction rotor 6. The fluo-beads can be initially located in vortexer 2 and transferred to reaction rotor 6 by R1 pipettor 4. R1 pipettor 4 can aspirate a desired quantity of the fluo-bead mixture and transfer the aspirated quantity to reaction rotor 6 where it is injected into the cuvette of reaction rotor 6. Optics pipettor 8 can then aspirate a test sample from the cuvette of reaction rotor 6 and transfer the test sample to optics box 10, where fluorescence and luminescence measurements can be recorded. The initial recording of the fluorescence and luminescence signal can be used as a baseline measurement for the fluorescence signal that can correspond to the initial concentration of fluo-beads in a sample. After recording the measurements, multi rinse pipettor 12 can rinse the cuvettes using a wash buffer.

**[0034]** In order to prepare the analytical substrates, fluo-beads can be transferred from vortexer 2 to a cuvette in reaction rotor 6 via R1 pipettor 4. R1 pipettor 4 can aspirate one or more capture reagent from the reagent rotor 14 and inject the one or more capture reagents into the cuvette located in reaction rotor 6. After an incubation period, single rinse pipettor 16 can inject a rinse buffer to stop the capture reagent binding reaction with precise timing. A substantial amount of the suspended fluo-bead can then be localized by magnets within the reaction rotor 6 over a period of time. After the magnets have substantially localized the fluo-beads within the cuvette, multi rinse pipettor 12 can aspirate and dispose of a portion of the rinse buffer, leaving a portion of the fluo-beads localized within the cuvette. Multi rinse pipettor 12 can proceed to inject a wash buffer into the cuvette of reaction rotor 6, resuspending the fluo-beads. The fluo-beads can again be localized by the magnets within reaction rotor 6 to be followed by multi rinse pipettor 12 aspirating and discarding a portion of the sample that was not localized from the cuvette in the reaction rotor 6. Thus, any unbound capture reagent is removed from the cuvette.

**[0035]** A patient sample can be contained in a sample tube in sample rotor 18. The patient sample can further be partially diluted with a sample diluent. At this point, sample pipettor 20 can aspirate a portion of the patient sample and inject the patient sample into the cuvette of reaction rotor 6 to resuspend the fluo-beads. The cuvette containing the patient

sample within the reaction rotor 6 can then incubate the patient sample. In one embodiment, the incubation temperature can be about 37°C +/-about 0.2°C while the incubation time can be about 37.75 minutes +/-about 2 minutes. After incubation, multi rinse pipettor 12 can inject the rinse buffer to again resuspend the fluo-beads. Another localization process is performed by reaction rotor 6 by allowing the fluo-beads to substantially collect within the cuvette near the magnets in reaction rotor 6. After the localization of the fluo-beads, multi rinse pipettor 12 can aspirate and discard a portion of the fluid within the cuvette of reaction rotor 6 that was not localized during the localization process.

**[0036]** Multiple rinse cycles can then be performed on the sample within the cuvette of reaction rotor 6. The rinse cycles can be performed using multi rinse pipettor 12 to inject a wash buffer into the cuvette to resuspend the fluo-beads. Another localization step can allow the fluo-beads to collect within the cuvette by the magnets within reaction rotor 6. After about a 90 second fluo-beads collection period, multi rinse pipettor 12 can aspirate and discard a portion of the wash buffer, leaving a substantial portion of the fluo-beads within the cuvette of the reaction rotor 6. Another rinse cycle can then occur using multi rinse pipettor 12 to again inject wash buffer into the cuvette and allow the fluo-beads to resuspend. Another fluo-bead localization process can utilize the magnets within the reaction rotor 6 to localize the fluo-beads from the rest of the sample. Finally, the multi rinse pipettor 12 can aspirate a portion of the sample that was not localized by the localization process.

**[0037]** At this point, R1 pipettor 4 can aspirate a conjugate contained in a conjugate cuvette within reagent rotor 14. R1 pipettor 4 can then inject the previously aspirated conjugate into the cuvette of the reaction rotor 6. After incubating the cuvette under controlled time and temperature in reaction rotor 6, multi rinse pipettor 12 can inject a rinse buffer into the cuvette in reaction rotor 6. Another fluo-bead localization cycle can be performed by allowing magnets within reaction rotor 6 to substantially localize the fluo-beads within the cuvette. Multi rinse pipettor 12 can aspirate and discard a portion of the sample within the cuvette that has not been localized during the localization cycle.

**[0038]** Multiple rinse cycles can be performed on the sample within the cuvette of reaction rotor 6. Multi rinse pipettor 12 can inject a wash buffer to resuspend the fluo-beads within the cuvette. Another fluo-bead localization cycle can localize the fluo-beads by locating the cuvette within close proximity to the magnets in reaction rotor 6 over an adequate period of time. After the localization cycle, multi rinse pipettor 12 can aspirate and discard a portion of the sample that was not localized during the localization cycle. Another wash cycle can then occur by using multi rinse pipettor 12 to inject the wash buffer to resuspend the fluo-beads. Another localization cycle can utilize the magnets within reaction rotor 6 to localize the fluo-beads within the cuvette. After the localization process, multi rinse

pipettor 12 can again aspirate and discard a portion of the sample that was not localized during the localization cycle.

**[0039]** At this point, R2 pipettor 22 can aspirate a portion of a first substrate and a second substrate from reagent rotor 14 and inject the substrates into the mixed substrate container 24 creating a mixed substrate sample. R2 pipettor 22 can then aspirate the mixed substrate sample from the mixed substrate container 24 and inject the mixed substrate sample into the cuvette of the reaction rotor 6, resuspending the fluo-bead with the mixed substrate sample. The sample is then incubated for a period of time. The sample in the cuvette of reaction rotor 6 can then be aspirated by optics pipettor 8 and placed in optics box 10. After optics box 10 makes fluorescence and luminescence optical observations, the sample is discarded and the multi rinse pipettor rinses the cuvettes of reaction rotor 6 in preparation for the next test.

**[0040]** For the above steps to be possible, a capture reagent must be bound to the fluo-beads within a cuvette in reaction rotor 6 to create a single solid phase that is then combined with a patient sample. In an embodiment of the present disclosure, a user of automated immunochemistry analyzer 1 can customize a solid phase on the fly with several different capture reagents of the user's choosing. This customizable feature is advantageous because it improves the efficiency and timing to test a patient sample for reactivity to multiple immunogens.

**[0041]** In an embodiment depicted in Fig. 2, automated immunochemistry analyzer 1 can include a graphical user interface ("GUI") 30 and a logic implementer 32 that work together to allow a user to customize a solid phase. GUI 30 and logic implementer 32 can accompany or be a part of automated immunochemistry analyzer 1, or can be located remotely from automated immunochemistry analyzer 1 and communicate with automated immunochemistry analyzer 1 via a wireless or wired data connection.

**[0042]** Fig. 2 illustrates a flow chart of a process that uses GUI 30 and logic implementer 32 to allow a user to create a single solid phase that tests a patient sample for reactivity to multiple immunogens. Beginning at step 40, a user initiates the process by instructing GUI 30 that the user wishes to customize a single solid phase with multiple capture reagents. The user can instruct GUI 30 to create a single solid phase for a single patient sample or for multiple patient samples. If the user has previously customized solid phases and saved those solid phases to logic implementer 32, the user can also be presented with the option of recalling a previously customized solid phase from a library of preprogrammed customized solid phases that automated immunochemistry analyzer 1 is capable of creating on the fly based on the capture reagents available to automated immunochemistry analyzer 1. If the

user wishes to create a newly customized solid phase, logic implementer 32 proceeds to steps 42 and 44. If the user wishes to access a library of preprogrammed customized solid phases, then the logic implementer 32 proceeds to steps 46 and 48.

**[0043]** At step 42, GUI 30 presents the user with a series of options based on the capture reagents that are available for use within reagent rotor 14. The series of options are provided to GUI 30 by logic implementer 32, which stores information on each of the capture reagents that are available for use within reagent rotor 14. The stored information can include, for example, the name of the capture reagent, the amount of capture reagent currently held by reagent rotor 14, and cross-reactivity interference information on each capture reagent. The stored information can also include a class (e.g., allergy immunogen) and subclass (e.g., grass, mold, food, etc.) for each capture reagent. Using the stored information, logic implementer 32 can determine every combination of capture reagents that can be created by automated immunochemistry analyzer 1.

**[0044]** Using the class and subclass of each capture reagent, GUI 30 can present the user with suggested combinations of capture reagents to test. In an embodiment, GUI 30 presents the user with a list of symptoms, from which the user can select one or more symptoms. Based on the selected symptom, GUI 30 can then present the user with a suggested combination of capture reagents. For example, one symptom could be that of an allergic reaction when drinking wine. If the user selected this symptom, GUI 30 could suggest a combination of capture reagents that test for allergic reactions to grapes, yeast, tartaric acid, and other wine ingredients. Other symptoms could include, for example, symptoms related to different autoimmune disorders.

**[0045]** The series of options provided to GUI 30 by logic implementer 32 can be narrowed by logic implementer 32 for a variety of reasons. For example, if the user wishes to create a solid phase to test with multiple patient samples, but reagent rotor 14 does not have enough of a capture reagent stored to create enough solid phase to test each of the samples, logic implementer 32 can either remove that capture reagent as an option, instruct the user as to the deficiency with the capture reagent, or add more of the capture reagent to reagent rotor 14.

**[0046]** The logic implementer can also determine whether certain capture reagents cannot be combined with other capture reagents, or can place a limit on the total number of capture reagents that can be combined. Figs. 3A to 3C illustrate an example embodiment of GUI 30, in which the user is presented with five possible capture reagents that are stored in reagent rotor 14. Those of ordinary skill in the art will recognize that more than five capture reagents will be stored in reagent rotor 14 in most instances, but the number has been

reduced in the present example for simplicity. In Fig. 3A, the user can click on any one of the five individual capture reagents to add the capture reagent to a combination solid phase. In Fig. 3B, the user has chosen to add Capture Reagent A to the solid phase. When the user makes the selection of Capture Reagent A, however, logic implementer 32 determines that Capture Reagent A and Capture Reagent C cannot be combined, so logic implementer 32 removes Capture Reagent C from the list of remaining options, and Capture Reagent C remains removed from the remaining options unless the user deselects Capture Reagent A. In Fig. 3C, the user has chosen to mix Capture Reagent D with Capture Reagent A. As before, logic implementer 32 then determines that Capture Reagent B is not compatible with Capture Reagent D, so logic implementer 32 removes Capture Reagent B from the list of remaining options, and Capture Reagent B remains removed from the remaining options unless the user deselects Capture Reagent D. In an alternative embodiment, logic implementer 32 removes Capture Reagent B in Fig. 3C because although Capture Reagent B can be compatible with Capture Reagent D, Capture Reagent B is not compatible with the combination of Capture Reagent A and Capture Reagent D.

**[0047]** Logic implementer 32 can therefore continuously reassess the potential options available to the user as the user makes selections, and update GUI 30 with new information. In an alternative embodiment to Figs. 3A to 3C, the user can be presented with all five options and the logic implementer can wait until after the user has selected the desired capture reagents to determine if the selected capture reagents are compatible. Logic implementer 32 can also be programmed to suggest alternative capture reagents to the user if the user chooses a combination that cannot be created by automated immunochemistry analyzer 1.

**[0048]** In step 44 of Fig. 2, the user has individually selected each capture reagent to be added to a combination. The user therefore finalizes the selected combination, and logic implementer 32 then determines where each of the selected capture reagents is located within reagent rotor 14. Logic implementer 32 can then dispense the appropriate amount of fluo-beads into a cuvette located within the reaction rotor 6, and then control R1 pipettor 4 and reagent rotor 14 to cause R1 pipettor 4 to aspirate each of the individually selected capture reagents from reagent rotor 14 and inject the capture reagents into the cuvette located in reaction rotor 6.

**[0049]** If the user selects at step 40 to access a library of preprogrammed customized solid phases, then the process proceeds from step 40 to step 46, where logic implementer 32 provides GUI 30 with a list of previously stored combinations. In an embodiment, the user at step 44 can save a selected combination to the library for later access by the logic implementer. Alternatively, the stored combinations can be programmed before the user

initiates automated immunochemistry analyzer 1, or can be downloaded to automated immunochemistry analyzer 1 via a wireless or wired data connection. Logic implementer 32 can also narrow the selections from the library that are available for selection by the user based on, for example, whether the user exhibits a particular symptom, whether a capture reagent of a combination is available to add to a mixture at the time of selection, or whether an amount of an available capture reagent is enough for the selected test. At step 48, the user makes a selection from the list provided by logic implementer 32, so that logic implementer 32 can then dispense the appropriate amount of fluo-beads into a cuvette located within the reaction rotor 6, and then control R1 pipettor 4 and reagent rotor 14 to cause R1 pipettor 4 to aspirate each capture reagent of the selected combination from reagent rotor 14 and inject the capture reagents into the cuvette located in reaction rotor 6.

**[0050]** In step 50 of Fig. 2, the combination solid phase is combined with a patient sample and incubated, bound and tested as described above by performing several wash steps, adding the conjugate and substrate, and then aspirating the patient sample into optics pipettor 8 so that optics box 10 can take fluorescence and luminescence measurements. As understood by those of skill in the art, a positive result determined by optics box 10 for a mixture of capture reagents indicates a positive result for at least one of the capture reagents in the mixture. For example, a positive test with respect to a mixture containing Capture Reagent A, Capture Reagent B, and Capture Reagent C would indicate a positive test for at least one of Capture Reagent A, Capture Reagent B, and Capture Reagent C. In this case, however, it may not be possible to determine which one or more of Capture Reagent A, Capture Reagent B, and Capture Reagent C caused the positive test. On the other hand, a negative result for a mixture of Capture Reagent A, Capture Reagent B, and Capture Reagent C conclusively indicates that the patient sample did not test positive for any one of Capture Reagent A, Capture Reagent B, and Capture Reagent C.

**[0051]** Logic implementer 32 can therefore end the test if there is a negative result for the optical analysis of the patient sample at step 50. That is, if logic implementer 32 has determined that the mixture of capture reagents yielded a negative result at step 50, logic implementer 32 can then proceed to step 56 and report to the user via GUI 30 or another mechanism that the patient sample tested negative for each of the capture reagents in the selected mixture.

**[0052]** If the mixture tested positive at step 50, however, logic implementer 32 can proceed to step 52. At step 52, logic implementer attempts to determine whether the positive result can be attributed to a particular capture reagent within the mixture, or whether any particular capture reagent in the mixture can be ruled out as causing the positive result as shown for example at Fig. 6 below. If logic implementer 32 can conclusively determine

that each capture reagent of the combination either caused the positive result or could not have caused the positive result, logic implementer 32 can then proceed to step 56 and report to the user via GUI 30 or another reporting mechanism the results for each capture reagent of the combination.

**[0053]** If logic implementer 32 cannot conclusively determine that any one capture reagent in the mixture caused the positive result and that the rest of the capture reagents in the mixture can be eliminated, logic implementer 32 proceeds to step 54. At step 54, logic implementer can either break down the capture reagents into subgroups, or test each individual capture reagent separately, depending on how many capture reagents are in the combination or how many capture reagents could have yielded the positive result. Once logic implementer performs additional testing of the capture reagents and determines whether each capture reagent results in a positive or negative test, logic implementer 32 can then proceed to step 56 and report to the user via GUI 30 or another reporting mechanism the results for each capture reagent of the combination. In an alternative embodiment, logic implementer can skip steps 52 and 54 and simply report to the user via GUI 30 or another reporting mechanism that the patient sample tested positive for at least one of the capture reagents in the mixture.

**[0054]** Fig. 4A is a flow chart illustrating a simple example of how logic implementer 32 can perform a test of Capture Reagent A, Capture Reagent B, and Capture Reagent C. As illustrated, logic implementer 32 begins at step 60a by testing a mixture of Capture Reagent A, Capture Reagent B, and Capture Reagent C. If the mixture yields a negative result, then logic implementer can conclusively report at step 62a that the patient sample tested negative for each of Capture Reagent A, Capture Reagent B, and Capture Reagent C. If the initial test yields a negative result, only one test is required to report on three different reagents.

**[0055]** If the mixture yields a positive result, then logic implementer at steps 64a, 66a and 68a separately tests each of Capture Reagent A, Capture Reagent B, and Capture Reagent C. Logic implementer can then report at steps 70a, 72a and 74a the results for each of Capture Reagent A, Capture Reagent B, and Capture Reagent C.

**[0056]** Fig. 4B shows an example of how the testing of Fig. 4A would proceed if only Capture Reagent C tested positive for a particular patient sample. At step 60b, the test yields a positive result for the mixture of Capture Reagent A, Capture Reagent B, and Capture Reagent C. Logic implementer 32 therefore separately tests each of Capture Reagent A, Capture Reagent B, and Capture Reagent C at steps 64b, 66b and 68b, respectively. At steps 64b and 66b, logic implementer 32 determines that Capture Reagent A and Capture Reagent B yield negative results, which are reported to the user at steps 70b

and 72b. At step 68b, logic implementer 32 determines that Capture Reagent C yields a positive result, which is reported to the user at step 74b.

**[0057]** It should be apparent from Fig. 4B that logic implementer 32 ran four separate tests (60b, 64b, 66b, 68b) to determine that the sample tested positive for Capture Reagent C, whereas only three tests would be necessary if each of Capture Reagent A, Capture Reagent B, and Capture Reagent C was tested separately from the beginning. It should be understood, however, that the tests are being run for hundreds or thousands of samples, and that every negative test of a three reagent mixture requires only one test (versus three individual tests) to determine that the patient sample tests negatively for each of the three capture reagents. As the number of patient samples increases, the number of total tests decreases significantly. For example, if one hundred patient samples are tested for three different reagents using the example in Fig. 4A, and half of those tests yield a negative result for all three reagents, then the average number of tests per sample would decrease to 2.5 (as opposed to 3 tests per sample if each capture reagent is tested separately) ( $50 \times 1 + 50 \times 4 = 250$ ;  $250/100 = 2.5$ ). Thus, in this example, the total number of tests run for the one hundred patient samples is cut from 300 (with individual testing) to 250 (with mixture testing according to the present disclosure).

**[0058]** The reduction of the total number of tests is even more significant as the number of capture reagents tested is increased. Fig. 5A shows another example of a more complicated scheme in which logic implementer 32 breaks down a ten reagent mixture into subgroups to determine the cause of a positive result. Similar to above, if the ten reagent mixture yields a negative result, then logic implementer 32 can conclusively report that the patient sample tested negative for each of Capture Reagents A-J. If the ten reagent mixture yields a positive result, then logic implementer 32 proceeds to further testing.

**[0059]** In Fig. 5A, logic implementer 32 begins at step 80a by testing a mixture of Capture Reagents A-J. If the mixture yields a negative result, then logic implementer 32 can conclusively report at step 82a that the patient sample tested negative for each of Capture Reagents A-J. If the initial test yields a negative result, only one test is required to report on ten different reagents.

**[0060]** If the test at step 80 yields a positive result, logic implementer 32 moves on to steps 84a and 86a, where the logic implementer 32 breaks the ten capture reagents into two subgroups with five reagents in each group. Logic implementer 32 then tests each of the two subgroups, and if either subgroup yields a negative test result, logic implementer 32 can report that the five capture reagents in the subgroup each yield a negative result. If one or both of the two subgroups yields a positive result, logic implementer 32 can move on to



steps 90a-99a, where the capture reagents are separately tested. Logic implementer 32 can then report the results at steps 100a-109a.

**[0061]** Fig. 5B shows an example of how the testing of Fig. 5A would proceed if only Capture Reagent C tested positive for a particular patient sample. At step 80b, the test yields a positive result for the mixture of Capture Reagents A-J. Logic implementer 32 therefore separates Capture Reagents A-J into a first subgroup with Capture Reagents A-E and a second subgroup with Capture Reagents F-J, and separately tests the first subgroup and the second subgroup at steps 84b and 86b, respectively.

**[0062]** At step 86b, logic implementer 32 determines that the second subgroup with Capture Reagents F-J yields a negative result. Logic implementer 32 can therefore conclusively determine that none of Capture Reagents F-J caused the positive result at step 80b, and logic implementer 32 can report the negative result for each of Capture Reagents F-J at step 89b.

**[0063]** At step 84b, logic implementer 32 determines that the first subgroup with Capture Reagents A-E yields a positive result. Logic implementer 32 can then break the first subgroup into additional subgroups or test each of the capture reagents separately. In the example shown, logic implementer 32 has tested each the capture reagents in the first subgroup separately, and has determined at step 92b that Capture Reagent C caused the initial positive result at step 80b. The positive result for Capture Reagent C, as well as the negative results for each of the other capture reagents, are then reported to the user at steps 89b and 100b-104b.

**[0064]** In the example of Fig. 5B, logic implementer 32 runs a total of eight tests (80b, 84b, 86b, 90b, 91b, 92b, 93b, 94b) to determine that the sample tested positive for Capture Reagent C, whereas ten tests would be necessary if each of Capture Reagents A-J was tested separately from the beginning. In comparison with the example of Fig. 4, Fig. 5 demonstrates that as the number of capture reagents in the initial mixture increases, the relative number of tests performed decreases. In the example of Fig. 5B, if one hundred patient sample were tested for ten different reagents, and half of those tests yielded a positive result for one reagent, then the average number of tests per sample would decrease to 4.5 (as opposed to 10 tests per sample if each capture reagent is tested separately) ( $50 \times 1 + 50 \times 8 = 450$ ;  $450/100 = 4.5$ ). Thus, in this example, the total number of tests run for the one hundred patient samples is cut from 1000 (with individual testing) to 450 (with mixture testing according to the present disclosure).

**[0065]** In certain embodiments, an initial test mixture of capture reagents will have a mixture of 2-10 capture reagents. Subsequent rounds of testing may have a mixture of 1, 2,

3, 4, 5, 6, 7, 8, 9, or ten capture reagents per test. Thus, in certain embodiments, testing with single capture reagents, and not a mixture of test reagents is within the scope of the present disclosure.

**[0066]** In exemplary embodiments, immunogens can be grouped in tests according to type of allergen, type of infectious disease antigen, or type of autoantigen. Exemplary groups of allergens include, but are not limited to food allergens, animal allergens, plant allergens, etc. Exemplary groups of infectious disease immunogens include, but are not limited to, Gram-positive bacteria, Gram-negative bacteria, viruses, fungi, etc. Additionally, autoantigens can be grouped in similar ways, such as by cellular antigens, nuclear antigens, organ-specific antigens, etc.

**[0067]** Fig. 6 shows one example embodiment of how logic implementer 32 can eliminate a capture reagent as having caused a positive test result, without having to retest the particular capture reagent. In Fig. 6, logic implementer 32 initiates two separate tests. At step 120, logic implementer 32 initiates a test for Symptom A by testing a mixture of Capture Reagents A and B, and at step 122 logic implementer 32 initiates a test for Symptom B by testing a mixture of Capture Reagents B, C, and D. At step 124, logic implementer determines that the mixture of Capture Reagents A and B yielded a positive result, which could be attributed to Capture Reagent A, Capture Reagent B, or both of Capture Reagents A and B. At step 126, however, logic implementer determines that the mixture of Capture Reagents B, C, and D yielded a negative result, meaning that the patient sample tested negative for each of Capture Reagents B, C, and D, which logic implementer can report to the user via GUI 30 or another mechanism at step 128. At step 130, logic implementer combines the tests for Symptom A and Symptom B, and determines that Capture Reagent B could not have caused the positive result for the mixture of Capture Reagents A and B because the patient sample tested negative for Capture Reagent B and step 126. Logic implementer 32 can therefore report to the user at step 132 that Capture Reagent A caused the positive result of the test of the mixture of Capture Reagents A and B.

**[0068]** Fig. 7 illustrates an embodiment of a system 210 with a plurality of optimization modules that are controlled by logic implementer 32 to perform the above process. In the illustrated embodiment, system 210 includes a selection module 220, an inventory tracking module 230, a mixing module 240, and analysis module 250, a reporting module 260, a communications module 270, and an inventory replenishment module 280. Those of ordinary skill in the art will recognize that more or less modules can be utilized according to the present disclosure.

**[0069]** Selection module 220 initiates the process illustrated at Figs. 2 to 5, for example, when a user turns on automated immunochemistry analyzer 1 or indicates via GUI 30 that a new test is to be run using automated immunochemistry analyzer 1. In an embodiment, selection module 220 allows the user to select via GUI 30 one or more patient samples to use for one or more new tests. The selection of one or more patient samples can be performed at the initiation or later in the process. In an alternative embodiment, patient data can be downloaded to selection module 220 via communications module 270, which can include a wireless network or a wired connection. In another embodiment, the selection of one or more patient samples can occur via the downloaded data.

**[0070]** Once the process has been initiated, selection module 220 communicates to inventory tracking module 230 via communications module 270 that a new test is to be run. Inventory tracking module 230 keeps track of the reagents and/or patient samples that are available for use by automated immunochemistry analyzer 1, for example, by accessing stored information on each of the capture reagents that are available within reagent rotor 14 and/or each of the patient samples that are stored in sample rotor 18. The stored information can be programmed by a user when new reagents and/or patient samples are added to automated immunochemistry analyzer 1, can be scanned into the system prior to initiation of the test using, for example, a machine-readable data scanner such as a barcode scanner, or can be generated by the inventory tracking module 230 via the machine-readable data scanner at the time that a new test is initiated by selection module 220. The stored information can include, for example, the name of the capture reagent, the amount of capture reagent currently held by reagent rotor 14, cross-reactivity interference information on each capture reagent and/or patient identification or blood sample information. The stored information can also include a class (e.g., allergy) and subclass (e.g., grass, mold, environmentals, etc.) for each capture reagent.

**[0071]** Inventory tracking module 230 can also communicate with an inventory replenishment module 280 if one or more reagents are not available within the reagent rotor 14 but are available for use by automated immunochemistry analyzer 1. In an embodiment, spare capture reagent can be stored outside of reagent rotor 14 and accessed or added to reagent rotor 14 when needed.

**[0072]** Once inventory tracking module 230 has surveyed the available inventory, inventory tracking module 230 communicates the available inventory to selection module 220 via communications module 270. Selection module 220 then organizes the available inventory and presents the available inventory to the user via GUI 30. In an embodiment, selection module 220 presents the user with a series of options based on the capture reagents that are available within reagent rotor 14. The series of options can be a list of

available reagents for individual selection. Alternatively, the series of options can be preprogrammed combinations that are available to the user based on the individual reagents that are available. In an embodiment, the preprogrammed combinations are based on a particular symptom exhibited by the patient. For example, if the user has previously customized solid phases and saved those solid phases, the user can be presented with the option of recalling a previously customized solid phase from a library of preprogrammed customized solid phases that the automated immunochemistry analyzer 1 is capable of creating on the fly based on the available inventory.

**[0073]** Selection module 220 then allows the user to individually select capture reagents to combine, to select a combination of capture reagents, and/or to select patient samples for testing via GUI 30. The user can also be presented with the option of saving a selected combination of capture reagents that can be recalled for subsequent tests.

**[0074]** Once a selection of a combination of capture reagents has been made, selection module 220 communicates the selected combination to mixing module 240 via communications module 270. Mixing module 140 then accesses reagent rotor 14 via R1 pipettor 4 and causes each selected capture reagent to be added to a cuvette within reaction rotor 6.

**[0075]** In an embodiment, mixing module 240 communicates with inventory tracking module 230 via communications module 270, before the capture reagents are mixed, to communicate the selected combination to inventory tracking module 230. Inventory tracking module 230 then confirms that each of the selected capture reagents is available for use and sends mixing module 240 the exact location of each of the selected capture reagents within reagent rotor 14. If the capture reagents need replenishment by inventory replenishment module 280, then inventory tracking module 230 communicates with inventory replenishment module 280 so that the needed capture reagents are added to reagent rotor 14, and then communicates the location of the newly added capture reagents to mixing module 240. Once mixing module 240 knows the location of each individual capture reagent of the selected combination, mixing module 240 can cause R1 pipettor 4 to separately aspirate each capture reagent and inject each capture reagent into a cuvette in reaction rotor 6. In an alternative embodiment, the location of each capture reagent of the selected combination in reagent rotor 14 can be communicated to mixing module 240 by selection module 220 without mixing module 240 having to communicate with inventory tracking module 230.

**[0076]** Once the selected capture reagents have been mixed and incubated so that the analytes of interest in the patient's blood sample are bound to the capture reagent that has in turn been bound to the surface of a paramagnetic particle, analysis module 250 causes

the patient sample to be tested through the addition of conjugates and substrates for fluorescence and luminescence within optics box 10, and then analyzes the results to determine whether the test yielded a positive or negative result. As described above, a positive result determined by optics box 10 for a mixture of capture reagents indicates a positive result for at least one of the capture reagents in the mixture, whereas a negative result determined by optics box 10 for a mixture of capture reagents conclusively indicates that the patient sample did not test positive for any one of the capture reagents in the mixture. Analysis module 250 therefore analyzes the results of the test to determine whether it can conclusively determine the results of the test with respect to each capture reagent in the mixture.

**[0077]** If the test result is negative for the mixture, analysis module 250 determines that the patient sample tested negative for each capture reagent in the mixture, and communicates with reporting module 260 via communications module 270 so that reporting module 260 can process the results and report the results to the user via GUI 30 or another reporting mechanism. If the test result is positive for the mixture, analysis module 250 determines whether the positive result can be attributed to a particular capture reagent within the mixture, or whether any particular capture reagent in the mixture can be ruled out as causing the positive result. If analysis module 250 can conclusively determine that each capture reagent of the combination either caused the positive result or could not have caused the positive result, analysis module 250 communicates with reporting module 260 via communications module 270 so that reporting module 260 can process the results and report the results to the user via GUI 30 or another reporting mechanism.

**[0078]** If analysis module 250 cannot conclusively determine that each capture reagent of the combination either caused the positive result or could not have caused the positive result, then analysis module 250 can either break down the mixture of capture reagents into subgroups, or test each individual capture reagent separately, depending on how many capture reagents are in the combination or how many capture reagents could have yielded the positive result. In an embodiment, analysis module 250 communicates with inventory tracking module 230 while breaking down the mixture into subgroups or individual capture reagents to ensure that there is enough inventory for the further testing. In another embodiment, analysis module 250 breaks down the mixture of capture reagents based on the remaining inventory. For example, if there is only enough of a capture reagent to run one more test, analysis module 250 may choose to test that capture reagent individually rather than risk another inconclusive test.

**[0079]** Once analysis module 250 has determined how the subsequent testing is to be performed, analysis module 250 communicates the subsequent testing to mixing module

240 via communications module 270 so that mixing module 240 can prepare a new mixture or new individual samples. Mixing module 240 can again communicate with inventory tracking module 230 via communications module 270 to communicate the subsequent testing to inventory tracking module 230, confirm that each of the necessary capture reagents is available for use, and receive the exact location of each of the selected capture reagents for aspiration by R1 pipettor 4. Once the selected capture reagents have been mixed and incubated so that the analytes of interest in the patient's blood sample are bound to the capture reagent that has in turn been bound to the surface of a paramagnetic particle, analysis module 250 again causes the patient sample to be tested through the addition of conjugates and substrates for fluorescence and luminescence within optics box 10, and then analyzes the results to determine whether the test yielded a positive or negative result. Analysis module 250 then either determines that additional testing should take place or that reporting module 260 can process the final results and report the results to the user via GUI 30 or another reporting mechanism.

**[0080]** Disclosed herein are methods and systems for testing of patient samples with combinations of capture reagents. In alternative embodiments, the combination includes two to twelve capture reagents. In other embodiments, the combination includes three or more capture reagents, four or more capture reagents, five or more capture reagents, six or more capture reagents. In yet other embodiments, the combination includes three capture reagents, four capture reagents, five capture reagents, six capture reagents, seven capture reagents, eight capture reagents, nine capture reagents, or ten capture reagents.

**[0081]** It should be understood that various changes and modifications to the presently preferred embodiments described herein will be apparent to those skilled in the art. Such changes and modifications can be made without departing from the spirit and scope of the present subject matter and without diminishing its intended advantages. It is therefore intended that such changes and modifications be covered by the appended claims.

**[0082]** Unless otherwise indicated, all numbers expressing quantities of ingredients, properties such as molecular weight, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term "about." Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present disclosure. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques. Notwithstanding that the numerical ranges and parameters setting forth the broad scope of the disclosure are

approximations, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors necessarily resulting from the standard deviation found in their respective testing measurements.

**[0083]** The terms "a" and "an" and "the" and similar referents used in the context of the disclosure (especially in the context of the following claims) are to be construed to cover both the singular and the plural, unless otherwise indicated herein or clearly contradicted by context. Recitation of ranges of values herein is merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each individual value is incorporated into the specification as if it were individually recited herein. All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illuminate the disclosure and does not pose a limitation on the scope of the disclosure otherwise claimed. No language in the specification should be construed as indicating any non-claimed element essential to the practice of the disclosure.

**[0084]** The use of the term "or" in the claims is used to mean "and/or" unless explicitly indicated to refer to alternatives only or the alternatives are mutually exclusive, although the disclosure supports a definition that refers to only alternatives and "and/or."

**[0085]** Groupings of alternative elements or embodiments of the disclosure disclosed herein are not to be construed as limitations. Each group member may be referred to and claimed individually or in any combination with other members of the group or other elements found herein. It is anticipated that one or more members of a group may be included in, or deleted from, a group for reasons of convenience and/or patentability. When any such inclusion or deletion occurs, the specification is herein deemed to contain the group as modified thus fulfilling the written description of all Markush groups used in the appended claims.

**[0086]** Preferred embodiments of the disclosure are described herein, including the best mode known to the inventors for carrying out the disclosure. Of course, variations on those preferred embodiments will become apparent to those of ordinary skill in the art upon reading the foregoing description. The inventor expects those of ordinary skill in the art to employ such variations as appropriate, and the inventors intend for the disclosure to be practiced otherwise than specifically described herein. Accordingly, this disclosure includes all modifications and equivalents of the subject matter recited in the claims appended hereto as permitted by applicable law. Moreover, any combination of the above-described

elements in all possible variations thereof is encompassed by the disclosure unless otherwise indicated herein or otherwise clearly contradicted by context.

**[0087]** Specific embodiments disclosed herein may be further limited in the claims using consisting of or consisting essentially of language. When used in the claims, whether as filed or added per amendment, the transition term “consisting of” excludes any element, step, or ingredient not specified in the claims. The transition term “consisting essentially of” limits the scope of a claim to the specified materials or steps and those that do not materially affect the basic and novel characteristic(s). Embodiments of the disclosure so claimed are inherently or expressly described and enabled herein.

**[0088]** Further, it is to be understood that the embodiments of the disclosure disclosed herein are illustrative of the principles of the present disclosure. Other modifications that may be employed are within the scope of the disclosure. Thus, by way of example, but not of limitation, alternative configurations of the present disclosure may be utilized in accordance with the teachings herein. Accordingly, the present disclosure is not limited to that precisely as shown and described.



## CLAIMS

The invention is claimed as follows:

1. A system for *in situ* preparation of a plurality of analytical substrates customizable for a particular disease profile, the system comprising:

an instrument configured to store a plurality of capture reagents, each capture reagent specific for an immunogen, and a plurality of paramagnetic particles, wherein the instrument comprises;

(a) a user interface configured to allow a selection of a capture reagent, or a combination of two or more capture reagents, from the plurality of capture reagents based on input by a user; and

(b) a logic implementer configured to cause the instrument to (i) mix together each capture reagent of the combination of two or more capture reagents, and (ii) bind the capture reagent or the combination of two or more capture reagents to the paramagnetic particles, such that the analytical substrate does not have any unbound capture reagent associated therewith;

wherein at least one analytical substrate is formed by the instrument.

2. The system of Claim 1, wherein the instrument is adapted to prepare a plurality of custom analytical substrates simultaneously.

3. The system of Claim 2, wherein the plurality of custom analytical substrates are simultaneously prepared for the same disease profile.

4. The system of Claim 3, wherein the plurality of custom analytical substrates are simultaneously prepared for different disease profiles.

5. The system of Claim 1, wherein the immunogens are selected from allergens, infectious disease antigens, and autoantigens.

6. The system of Claim 1, wherein the instrument is an automated immunochemistry analyzer.

7. The system of Claim 1, wherein the logic implementer is configured to limit the number of capture reagents that the user interface allows for selection.

8. The system of Claim 7, wherein the logic implementer is configured to limit the number of capture reagents that the user interface allows for selection based on the availability of the capture reagents within the automated immunochemistry analyzer.

9. The system of Claim 1, wherein the logic implementer is configured to adjust the number of capture reagents that the user interface allows for selection as the selection is being made.

10. The system of Claim 1, wherein the logic implementer is configured to store a plurality of preprogrammed combinations of two or more capture reagents for selection using the user interface.

11. The system of Claim 10, wherein the plurality of preprogrammed combinations are sorted by the disease profile.

12. The system of claim 1, wherein the disease profile is an allergy disease profile, an infectious disease profile, or an autoimmune disease profile.

13. The system of Claim 10, wherein the plurality of preprogrammed combinations are sorted by type of immunogen.

14. The system of Claim 1, wherein the selection of the combination of two or more capture reagents is made by individually selecting each of the capture reagents in the combination.

15. The system of Claim 1, wherein the combination of two or more capture reagents is a combination of 2-10 capture reagents.

16. The system of Claim 15, wherein the combination of two or more capture reagents is a combination of three or more capture reagents.

17. The system of Claim 15, wherein the combination of two or more capture reagents is a combination of four or more capture reagents.

18. The system of Claim 1, wherein the logic implementer is configured to cause the automated immunochemistry analyzer to perform additional analysis using at least one of the two or more capture reagents if a test using the combination of two or more capture reagents returns a positive result.

19. A method for *in situ* preparation of a plurality of analytical substrates customizable for a particular disease profile, the method comprising:

providing an instrument configured to store a plurality of capture reagents, each capture reagent specific for an immunogen, wherein the instrument comprises;

(a) a user interface configured to allow a selection of a capture reagent, or a combination of two or more capture reagents, from the plurality of capture reagents based on input by a user; and

(b) a logic implementer configured to cause the instrument to (i) mix together each capture reagent of the combination of two or more capture reagents, and (ii) bind the capture reagent or the combination of two or more capture reagents to the paramagnetic particles,;

selecting at least one disease profile from a graphical user interface (GUI) associated with the instrument and wherein the instrument selects a combination of two or more capture reagents from the plurality of selectable capture reagents available;

adding each capture reagent of the combination of two or more capture reagents to a container containing paramagnetic particles; and

washing the complex of capture reagents and paramagnetic particles such that unbound capture reagent is removed;

thereby forming at least one analytical substrate.

20. The method of Claim 19, wherein the immunogens are selected from allergens, infectious disease antigens, and autoantigens.

21. The method of Claim 19, which includes narrowing the number of capture reagents that are available for selection.

22. The method of Claim 19, wherein the combination of two or more capture reagents comprise a combination of 2-10 capture reagents.

23. The method of Claim 22, wherein the combination of two or more capture reagents is a combination of three or more capture reagents.

24. The method of Claim 22, wherein the combination of two or more capture reagents is a combination of four or more capture reagents.

25. The method of Claim 19, wherein selecting from the plurality of selectable capture reagents includes selecting from a plurality of preprogrammed combinations of two or more capture reagents.

26. The method of Claim 19, wherein selecting from the plurality of selectable capture reagents includes individually selecting each capture reagent from the plurality of selectable capture reagents.

27. The method of Claim 19, which includes preparing additional analytical substrates using at least one of the two or more capture reagents individually from the combination if a test using the combination of two or more capture reagents returns a positive result.

28. A system for *in situ* preparation of a plurality of analytical substrates customizable for a particular disease profile, the system comprising:

an instrument configured to store a plurality of capture reagents, each capture reagent specific for an immunogen, and  
a plurality of paramagnetic particles;  
wherein the instrument comprises  
a graphical user interface which allows for the input of disease profile data by a user;  
a selection module that allows a selection of a single capture reagent or a combination of two or more capture reagents from the plurality of capture reagents; and  
a mixing module that (i) mixes together each capture reagent of the combination of two or more capture reagents, and (ii) binds the single capture reagent or the mixture of the combination of two or more capture reagents to the paramagnetic particles, such that the analytical substrate does not have any unbound capture reagent associated therewith;

wherein at least one analytical substrate is formed by the instrument.

29. The system of Claim 28, wherein the immunogens are selected from allergens, infectious disease antigens, and autoantigens.

30. The system of Claim 28, wherein the combination of two or more capture reagents comprise a combination of 2-10 capture reagents.

31. The system of Claim 30, wherein the combination of two or more capture reagents is a combination of three or more capture reagents.

32. The system of Claim 30, wherein the combination of two or more capture reagents is a combination of four or more capture reagents.

33. The system of Claim 28, which includes an inventory tracking module that stores locations of the plurality of capture reagents.

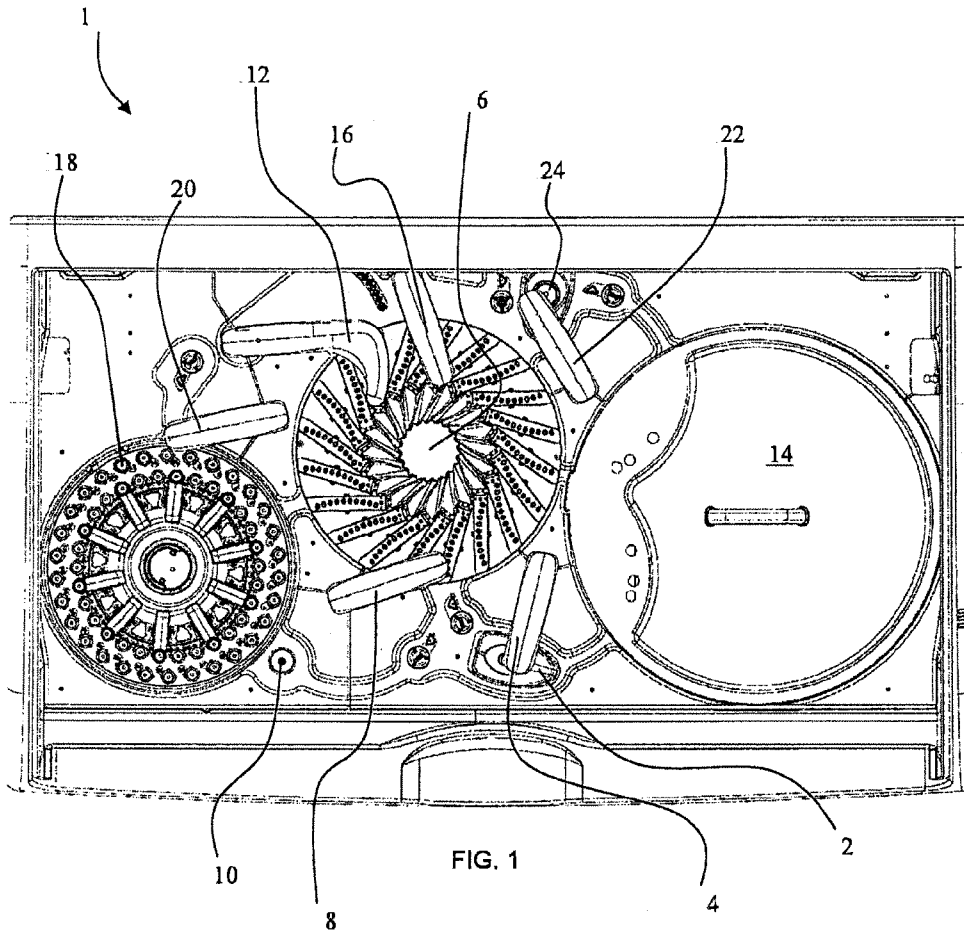
34. The system of Claim 33, wherein the inventory tracking module communicates the locations of the plurality of capture reagents to at least one of: (i) the selection module; (ii) the mixing module; and (iii) the analysis module.

35. The system of Claim 28, which includes an inventory replenishment module that replenishes the plurality of capture reagents.

36. The system of Claim 28, wherein the analysis module instructs the mixing module to mix a second combination of two or more capture reagents if a test of the combination of two or more capture reagents returns a positive result.

37. The system of Claim 28, wherein the selection module allows for individual selection of each capture reagent of the combination of two or more capture reagents.

38. The system of Claim 28, wherein the selection module allows for selection of the combination of two or more capture reagents from a plurality of preprogrammed combinations of two or more capture reagents.



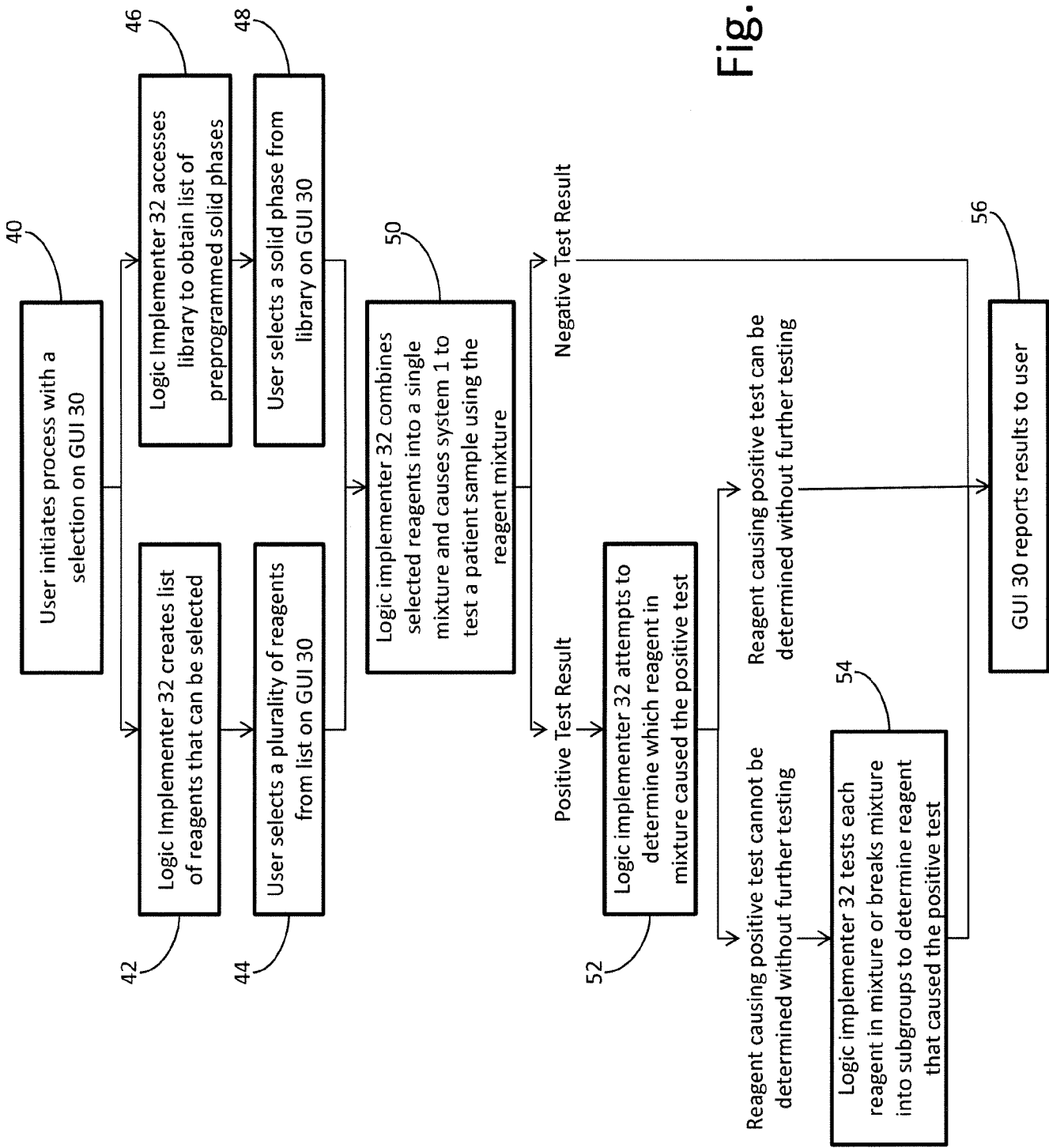


Fig. 2

30

Select Combination:

☐ Capture Reagent A

☐ Capture Reagent B

☐ Capture Reagent C

☐ Capture Reagent D

☐ Capture Reagent E

Fig. 3A

30

Select Combination:

☒ Capture Reagent A

☐ Capture Reagent B

☐ Capture Reagent D

☐ Capture Reagent E

Fig. 3B

30

Select Combination:

☒ Capture Reagent A

☒ Capture Reagent D

☐ Capture Reagent E

Fig. 3C



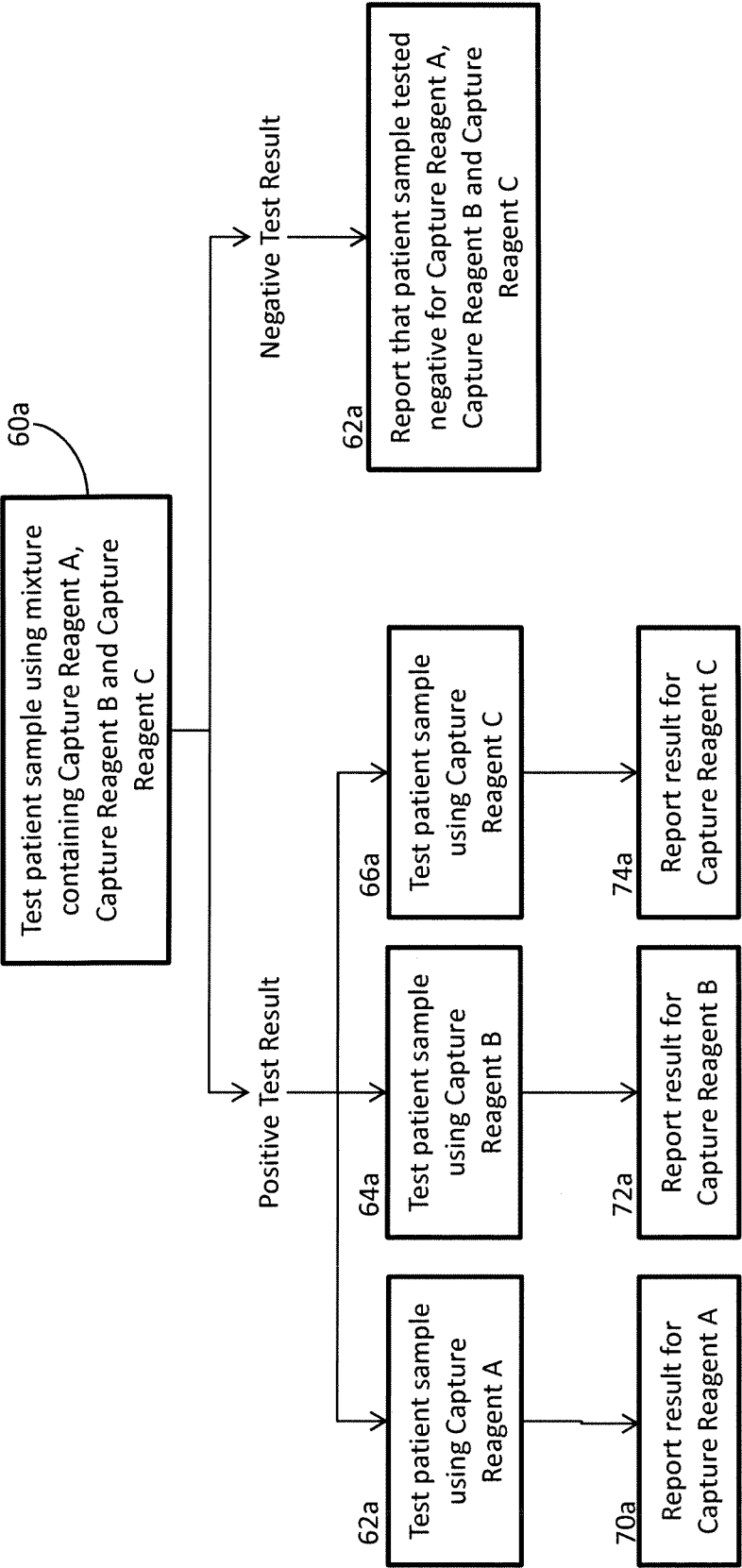


Fig. 4A

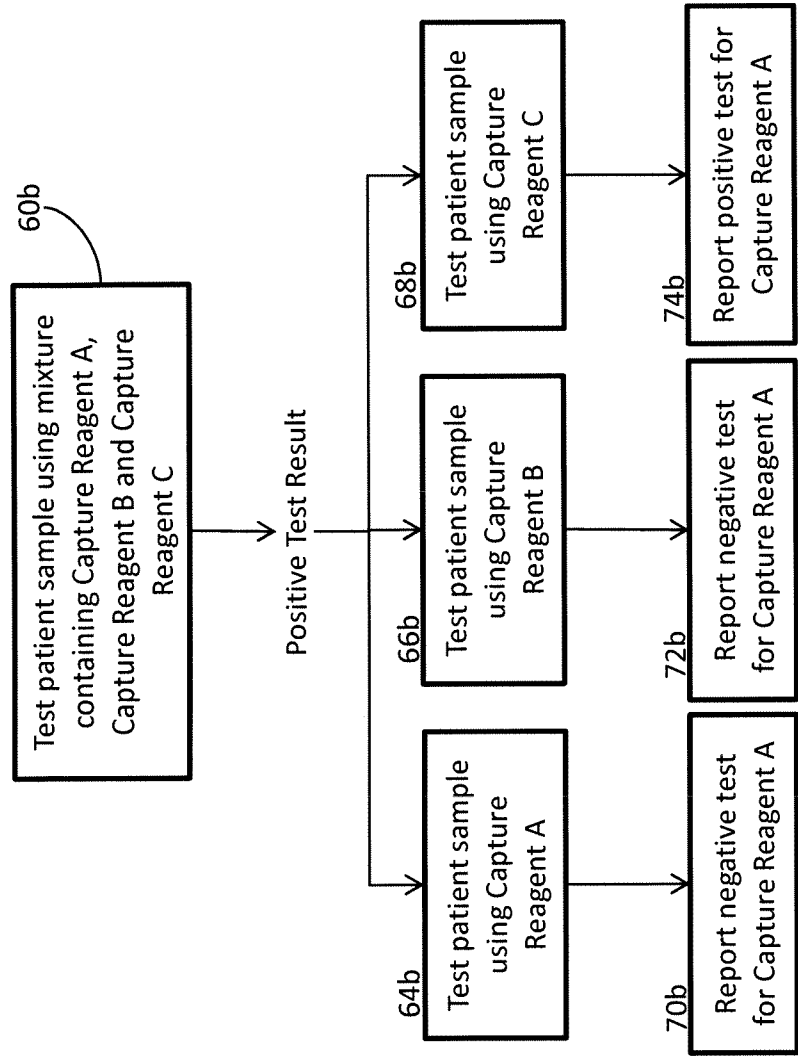
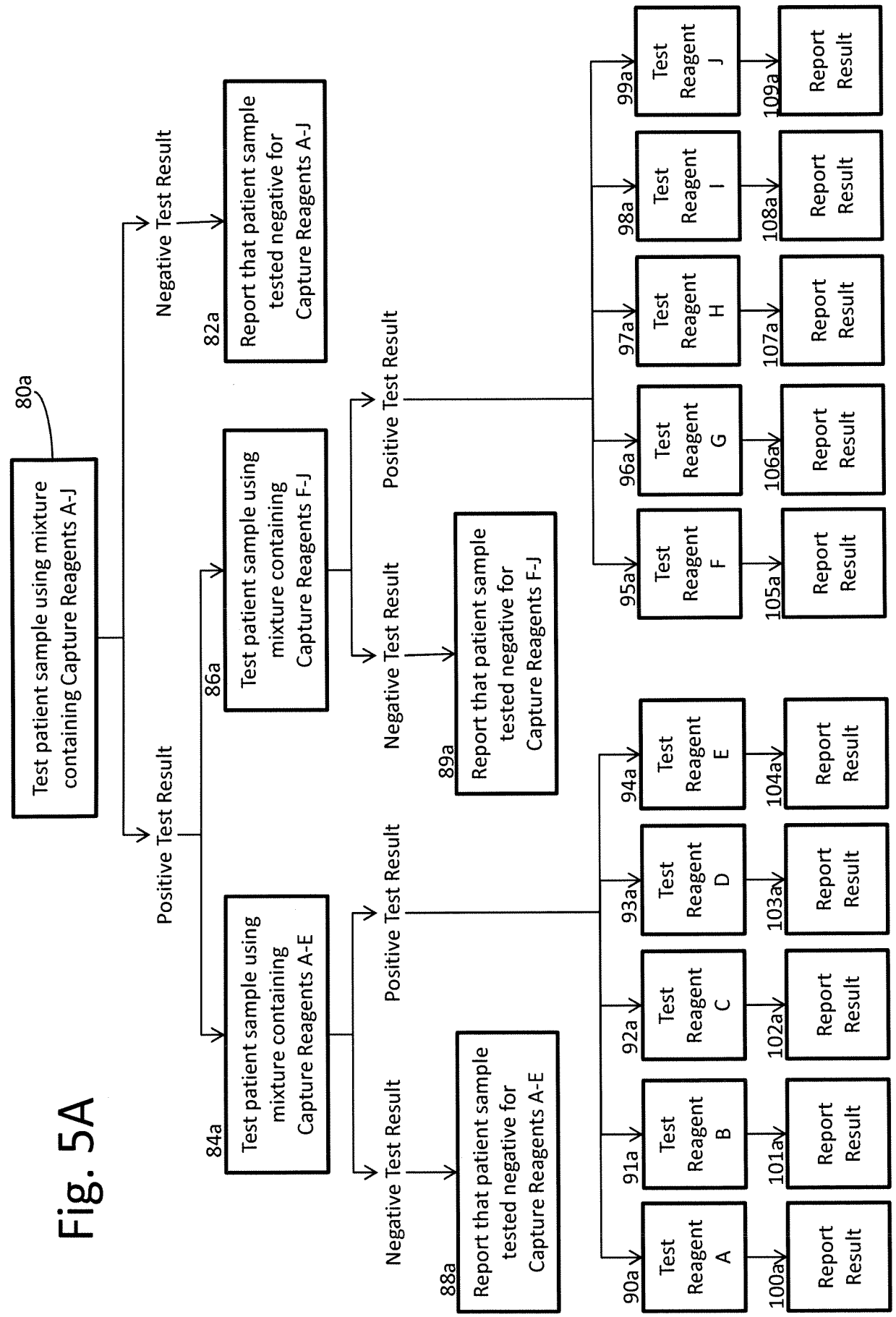


Fig. 4B

Fig. 5A



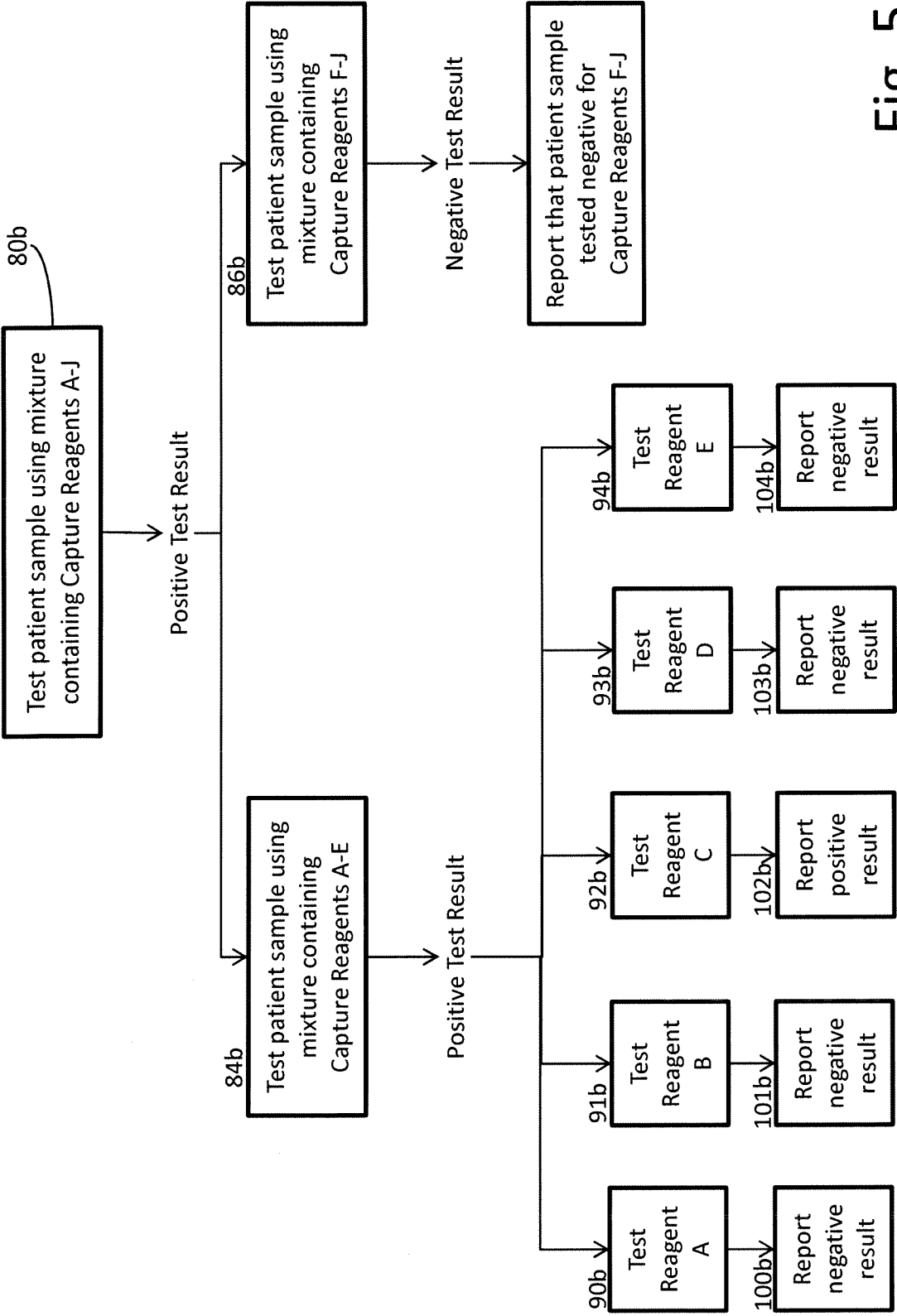


Fig. 5B

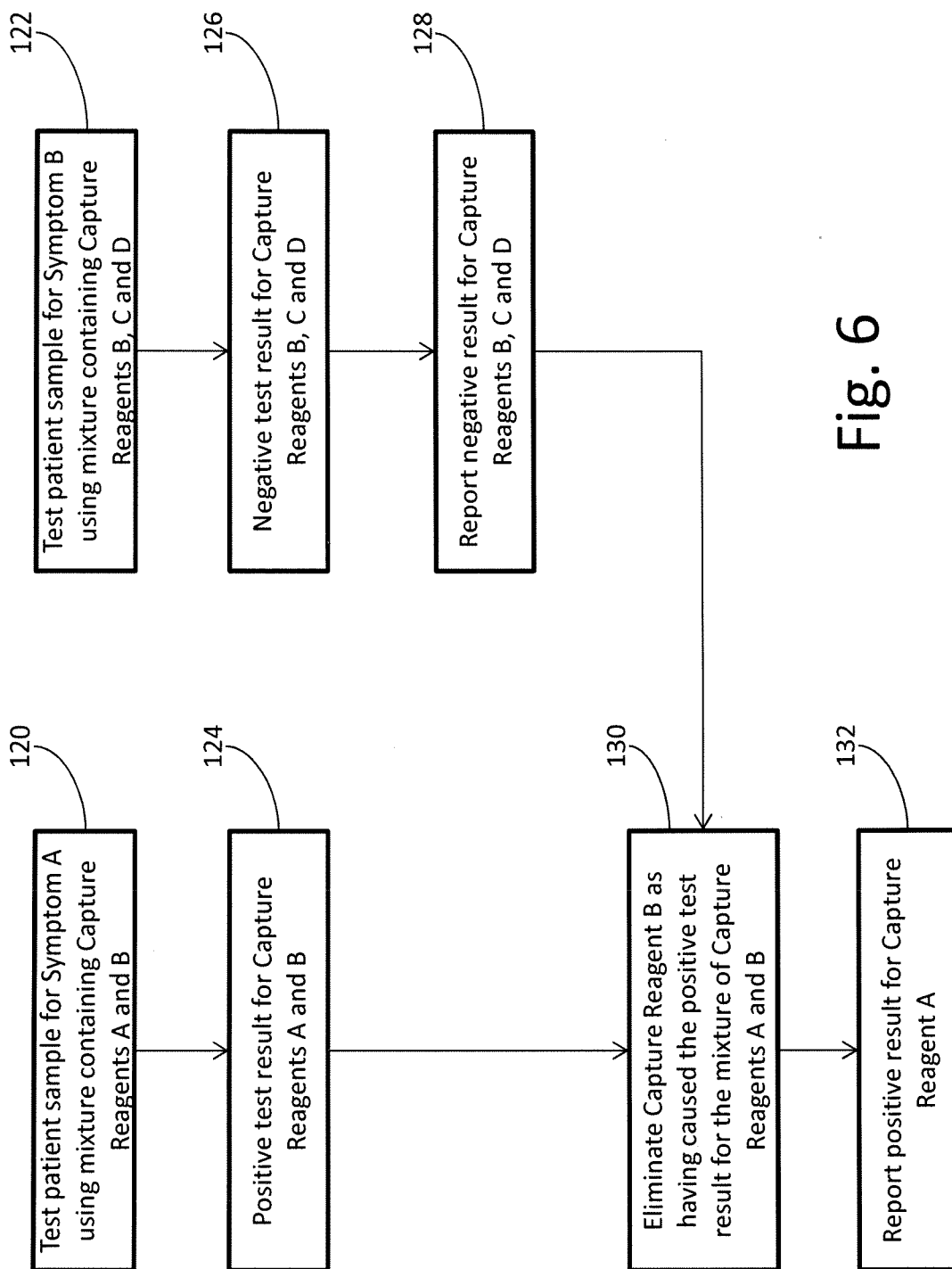


Fig. 6

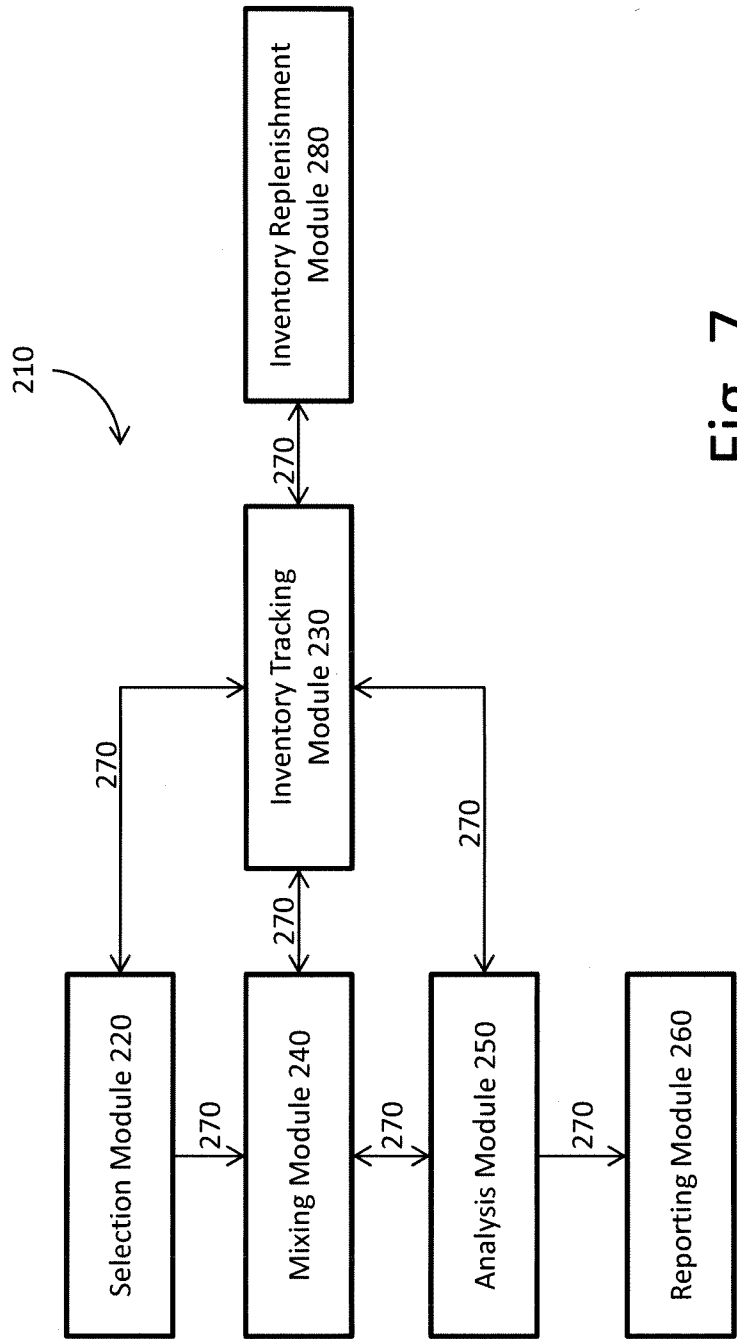


Fig. 7

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US16/43873

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - G01N 33/53, 33/564, 33/543, 33/68 (2016.01)

CPC - G01N 33/5306, 33/54326, 33/6893, 33/543

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC(8): G01N 33/564, 33/543, 33/569, 33/68, 21/76; C12Q 1/68 (2016.01)

CPC: G01N 35/0098, 33/5306, 33/543, 33/54326, 33/564, 33/68, 33/6854, 33/6893; Y10T 436/11, 436/119163; C12Q 1/68, 1/6804

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

PatSeer (US, EP, WO, JP, DE, GB, CN, FR, KR, ES, AU, IN, CA, RU, AT, CH, TH, BR, PH, CN, SE, NO, DK, FI, BE, NL, LU, MX, INPADOC Data); EBSCO; PubMed; Google Scholar; Google Patents; Lens; KEYWORDS: detection, analyzer, kit, assay, disease, allergen, autoantigen, immunogen, capture reagent, antibody, antigen, analyte, paramagnetic particles, magnetic beads, interface, GUI

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages                                                                                                        | Relevant to claim No.                       |
|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------|
| X         | US 2008/0241937 A1 (WAKAMIYA, Y et al.) October 02, 2008; figures 1, 5-6, 27, 33-36; abstract; paragraphs [0048, 0054, 0068-0069, 0079, 0112-113, 0117, 0121, 0162-0164, 0166-0167, 0198] | 1-4, 6-11, 13-19, 21-26, 28, 30-35, & 37-38 |
| ---       |                                                                                                                                                                                           | ---                                         |
| Y         |                                                                                                                                                                                           | 5, 12, 20, 27, 29, 36                       |
| Y         | US 2014/0274784 A1 (HYCOR BIOMEDICAL, INC) September 18, 2014; paragraph [0038]                                                                                                           | 5, 12, 20, 29                               |
| Y         | US 5,308,775 A (DONOVAN, J et al.) May 03, 1994; column 9, lines 21-42                                                                                                                    | 27                                          |
| Y         | US 5,637,275 A (CAREY, G et al.) June 10, 1997; column 9, lines 32-36; column 15, lines 57-62                                                                                             | 36                                          |

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

## \* Special categories of cited documents.

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

27 September 2016 (27.09.2016)

Date of mailing of the international search report

07 OCT 2016

Name and mailing address of the ISA/

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|                |                                                                                              |         |            |
|----------------|----------------------------------------------------------------------------------------------|---------|------------|
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| [标]申请(专利权)人(译) | HYCOR生物医学公司                                                                                  |         |            |
| 申请(专利权)人(译)    | HYCOR生物医学，INC.                                                                               |         |            |
| 当前申请(专利权)人(译)  | HYCOR生物医学，INC.                                                                               |         |            |
| [标]发明人         | VAN CLEVE MARK DAVID                                                                         |         |            |
| 发明人            | VAN CLEVE, MARK, DAVID                                                                       |         |            |
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| CPC分类号         | B01J2219/00479 B01J2219/005 B01J2219/00695 G01N33/5302 G01N35/0098 G01N35/1002 G01N2035/0094 |         |            |
| 代理机构(译)        | 绿色，MARK CHARLES                                                                              |         |            |
| 优先权            | 62/195878 2015-07-23 US<br>62/214773 2015-09-04 US                                           |         |            |
| 其他公开文献         | EP3325965A1                                                                                  |         |            |
| 外部链接           | <a href="#">Espacenet</a>                                                                    |         |            |

#### 摘要(译)

本文描述了混合多种单独捕获试剂用于诊断测定的方法和装置。在一个实施方案中，用于光学分析患者样品的系统包括存储多种捕获试剂和多个顺磁颗粒的自动化免疫化学分析仪，用户界面配置成允许选择两种或更多种捕获试剂的组合，和逻辑实施器，其被配置为使自动免疫化学分析仪（i）将两种或更多种捕获试剂的组的每种捕获试剂混合在一起；（ii）将两种或多种捕获试剂的组的混合物与顺磁性颗粒结合；（iii）将患者样品与两种或多种捕获试剂的组的结合混合物结合；（iv）光学分析患者样本。