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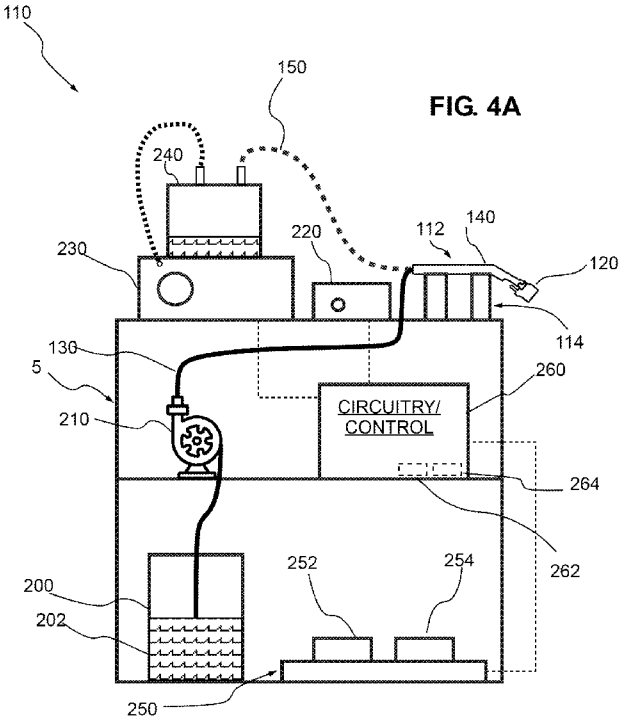
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(54) Title: DEVICES, SYSTEMS, AND METHODS FOR COLLECTING SAMPLES FOR ANALYSIS

FIG. 4A



(57) Abstract: A system includes a device including a handle and a sampling enclosure connected to the handle. The sampling enclosure includes an opening to place an internal volume of the sampling enclosure in fluid connection with tissue, a first port in fluid connection with the internal volume to deliver fluid under pressure to tissue via the opening, and a second port in fluid connection with the internal volume to draw a sample into the internal volume. The system further includes a source of the fluid, a pressurizing mechanism in connection with the source of fluid and with the first port, and a source of negative pressure in connection with the second port. A sample collection volume is placed in fluid connection with the source of negative pressure and with the second port.

[Continued on next page]

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DEVICES, SYSTEMS, AND METHODS FOR COLLECTING SAMPLES FOR ANALYSIS

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of U.S. Provisional Patent Application Serial No. 63/614,202, filed December 22, 2023, the disclosure of which is incorporated herein by reference.

BACKGROUND

[0002] The following information is provided to assist the reader in understanding technologies disclosed below and the environment in which such technologies may typically be used. The terms used herein are not intended to be limited to any particular narrow interpretation unless clearly stated otherwise in this document. References set forth herein may facilitate understanding of the technologies or the background thereof. The disclosure of all references cited herein are incorporated by reference.

[0003] Visual inspection (either in a physical exam or via imaging) of potentially cancerous lesions is typically followed by an invasive biopsy procedure in determining if the lesion is cancerous. However, in the case of certain cancers, the tissue in which the cancer forms prevents visualization of a lesion. For example, in the case of cancers related to HPV and other throat cancers, precancerous or cancerous lesions may arise deep within tonsillar crypts or at the base of tongue. The tissue at the base of the tongue is histologically identical to the tissue of the tonsillar crypts. Localization of such cancers requires invasive exploratory surgery because they are often not evident on imaging or in a physical exam. There is currently no technology for identification of microscopic cancers that may, for example, be located in the crypts of the tonsil and base of tongue, and patients often present with advanced metastasis because such lesions are not findable on physical exam or imaging.

SUMMARY

[0004] A system includes a device including a handle and a sampling enclosure connected to the handle. The sampling enclosure includes an opening configured to place an internal volume of the sampling enclosure in fluid connection with tissue, a first port in fluid connection with the internal volume, and a second port in fluid connection with the internal volume. The system

further includes a source of fluid, a pressurizing mechanism in connection with the source of fluid and with the first port, and a source of negative pressure in connection with the second port. A sample collection volume can be placed in fluid connection with the source of negative pressure and with the second port. The first port is configured (for example, positioned etc.) to deliver a flow of the fluid, under pressure via the pressurizing mechanism, to an area of the tissue through the opening of the sampling enclosure. The second port is configured to draw at least a portion of the fluid which has impacted the area of the tissue therethrough and thereby into the sample collection volume (under negative pressure or suction via the source of negative pressure).

[0005] In a number of embodiments, the system further includes a source of energy configured to apply energy to the area of the tissue. The source of energy may, for example, be a source of ultrasound energy, a source of mechanical energy, or a source of electromagnetic energy (for example, light energy).

[0006] The system further comprising electronic circuitry to control the pressurizing mechanism and to control the source of negative pressure in a number of embodiments. The system may further include one or more foot pedals in communicative connection with the electronic circuitry to control at least one of the pressurizing mechanism and the source of negative pressure.

[0007] In a number of embodiments, the sampling enclosure comprises a first connector in fluid connection with the first port, the first connector being configured to place the first port in connection with the pressurizing mechanism via a first conduit, and a second connector in fluid connection with the second port, the second connector being configured to place the second port in fluid connection with the sample collection volume via a second conduit.

[0008] The handle may, for example, include a passage therethrough configured to pass the first conduit therethrough to connect to the first port and to pass the second conduit therethrough to connect to the second connector. The first port may be placed in fluid connection with the first connector via a conduit passing through a housing of the sampling enclosure. In a number of embodiments, the first port is configured to provide a determined shape of flow of the fluid therefrom. The second connector may be placed in fluid connection with the second port via an extending conduit which extends into the internal volume of the

sampling enclosure. In a number of embodiments, the second port is positioned in the vicinity of the opening of the sampling enclosure.

[0009] The sampling enclosure may be removably connectable to the handle. In a number of embodiments, the sampling enclosure is flexible, at least in the vicinity of the opening. In a number of embodiments, the sampling enclosure includes a flexible sealing member in connection with the opening. The sampling enclosure may, for example, be configured for use in connection with specific tissue or in connection with a specific procedure (for example, in size, port characteristics, flexibility, adjustability in position, etc.).

[0010] A device includes a handle and a sampling enclosure connected to the handle. The sampling enclosure includes an opening configured to place an internal volume of the sampling enclosure in fluid connection with tissue, a first port in fluid connection with the internal volume, and a second port in fluid connection with the internal volume. The first port is configured to deliver a flow of a fluid, under pressure, to an area of the tissue through the opening of the sampling enclosure. The second port is configured to draw, under negative pressure, at least a portion of the fluid which has impacted the area of the tissue into the second port.

[0011] The sampling enclosure may include a first connector in fluid connection with the first port, which is configured to place the first port in connection with a pressurizing mechanism via a first conduit to deliver the fluid to the first port. A second connector may, for example, be configured to place the second port in fluid connection with a sample collection volume and a source of negative pressure via a second conduit.

[0012] In a number of embodiments, the handle includes a passage configured to pass the first conduit therethrough to connect to the first connector and to pass the second conduit therethrough to connect to the second connector. The first port may be in fluid connection with the first connector via a conduit passing through a housing of the sampling enclosure. The first port may, for example, be configured to provide a determined shape of flow of the fluid therefrom. The second connector may be in fluid connection with the second port via an extending conduit which extends into the internal volume. In a number of embodiments, the second port is positioned in the vicinity of the opening of the sampling enclosure.

[0013] The sampling enclosure may be removably connectable to the handle. The sampling enclosure may be flexible, at least in the vicinity of the opening. In a number of embodiments, the sampling enclosure includes a flexible sealing member in connection with the opening. The sampling enclosure may be configured for use in connection with specific tissue.

[0014] A method of collecting a sample from tissue of a patient includes impacting an area of the tissue with a flow of a fluid under pressure, collecting the sample from the fluid that has impacted the area of the tissue, and analyzing the sample. Analyzing the sample may, for example, include at least analysis of cell free DNA therein and cytology of cells therein. A plurality of areas of the tissue may be impacted with the flow of the fluid under pressure. A separate sample of fluid that has impacted each of the plurality of areas of the tissue may be collected, and each of the separate samples may be analyzed individually. Analysis data for each of the separate samples may be used to localize a lesion that has not been previously localized.

[0015] The tissue may, for example, include at least one of tissue from the base of the tongue of the patient or tissue from a tonsil of the patient. The area of the tissue may include a known lesion or a previously localized lesion. Analysis data from the sample or samples may be used to determine whether to proceed with a more invasive biopsy technique.

[0016] The method hereof may be performed after analysis of a molecular test on a body fluid has indicated presence of cancer. The body fluid may, for example, be blood or saliva. The cancer may, for example, be a cancer related to HPV.

[0017] The area of the tissue may be accessible without surgery. In a number of embodiments, the tissue is accessed surgically. The tissue may, for example, be accessed in an endoscopic procedure. The tissue may, for example, include at least one of lung tissue, tissue located in small bronchi, tissue in the abdomen, and hepatic tissue.

[0018] The method may further include application of energy to the area of the tissue. The energy may, for example, include at least one of ultrasound energy, mechanical energy, and electromagnetic energy.

[0019] The fluid may include at least one of a marker for cancer cells and an exfoliating agent. The fluid may include at least one of a liquid and a gas. In a number of embodiments, the fluid further comprises one or more exfoliating agents. The one or more exfoliating agents may

include at least one of a chemical exfoliating agent and a physical exfoliating agent. In a number of embodiments, the one or more exfoliating agents comprise solid particles.

[0020] The fluid may be delivered to the area of the tissue via a device including a handle and a sampling enclosure connected to the handle as described herein. As described above, the sampling enclosure includes an opening configured to place an internal volume of the sampling enclosure in fluid connection with the tissue, a first port in fluid connection with the internal volume, and a second port in fluid connection with the internal volume. The first port is configured to deliver the flow of the fluid, under pressure, to the area of the tissue through the opening of the sampling enclosure. The second port is configured to draw, under negative pressure, the sample of the fluid which has impacted the area of the tissue into the second port.

[0021] In a number of embodiments, the fluid is delivered to the area of tissue via a system including such a device, a source of the fluid, a pressurizing mechanism in connection with the source of the fluid and with the first port, a source of negative pressure, and a sample collection volume in fluid connection with the source of negative pressure and with the second port.

[0022] The devices, systems, and method hereof provide a significant advance in, for example, early detection of cancer, and particularly early detection of HPV positive or HPV+ cancers. The devices, systems, and methods hereof may, for example, be coupled with existing molecular tests for early detection of cancers in body fluids such as blood and saliva.

[0023] In a number of embodiments, if such a molecular test is positive, the devices, systems, and methods hereof may be used to find or localize microscopic, clinically occult cancer. After localization of the cancer, appropriate actions for treatment may be taken. Many molecular tests for cancer (such as HPV+ cancer), which are designed for early detection, have failed to gain traction because there is not an obvious intervention when such tests are positive. The device, systems, and methods hereof provide such an intervention.

[0024] Furthermore, the devices, system, and methods hereof provide a relatively noninvasive or less invasive option to provide diagnostic testing on a certain location or lesion either before or in lieu of a more invasive technique. Moreover, certain locations or lesions may not be readily accessible by certain invasive biopsy tools but may be accessed using the devices systems, and methods hereof.

[0025] The present devices, systems, and methods, along with the attributes and attendant advantages thereof, will best be appreciated and understood in view of the following detailed description taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0026] FIG. 1 illustrates schematically an open mouth showing the base of the tongue and tonsils and a plurality of representative sampling sites at which samples may be harvested or taken using a device or system hereof.

[0027] FIG. 2 illustrates schematically an embodiment of a system hereof in alignment with tissue (such as tissue of the tonsils or base of the tongue) to harvest a sample of a microscopic, early-stage cancerous lesion positioned deep within, for example, a tonsillar crypt.

[0028] FIG. 3 illustrates an embodiment of a system hereof in alignment with tissue of the tongue to harvest a sample of a visible, suspicious lesion on the surface of the tongue.

[0029] FIG. 4A illustrates schematically another embodiment of a system hereof used in a number of studies.

[0030] FIG. 4B illustrates a photograph of a prototype of the system of FIG. 4A used in studies hereof.

[0031] FIG. 5A illustrates a side, hidden-line view an embodiment of a sampling assembly including a handle and sampling housing, cup, or enclosure for use in connection with the system of FIG. 4A, wherein the handle and sampling enclosure are in a connected state.

[0032] FIG. 5B illustrates a side view of the assembly of FIG. 5A.

[0033] FIG. 6A illustrates a front, hidden-line view of the handle of FIG. 5A disconnected from the sampling enclosure.

[0034] FIG. 6B illustrates a side, hidden-line view of the handle of FIG. 5A.

[0035] FIG. 6C illustrates a top, hidden-line view of the handle of FIG. 5A.

[0036] FIG. 7A illustrates a top, hidden-line view of the sampling enclosure of FIG. 5A disconnected from the handle and having a first type of irrigation spray nozzle.

[0037] FIG. 7B illustrates a front, hidden-line view of the sampling enclosure of FIG. 7A.

[0038] FIG. 7C illustrates an isometric view of the sampling enclosure of FIG. 7A.

[0039] Fig. 7D illustrates a side, cross-sectional view of the sampling enclosure of FIG. 7A (section A-A of FIG. 7B).

[0040] FIG. 7E illustrates a detailed view of encircled section B of FIG. 7D.

[0041] FIG. 8A illustrates a top, hidden-line view of another embodiment of a sampling enclosure, which is connectible to the handle of FIG. 5A, and which includes a second type of spray nozzle.

[0042] FIG. 8B illustrates a front, hidden-line view of the sampling enclosure of FIG. 8A.

[0043] FIG. 8C illustrates an isometric view of the sampling enclosure of FIG. 8A.

[0044] Fig. 8D illustrates a side, cross-sectional view of the sampling enclosure of FIG. 8A (section A-A of FIG. 8B).

[0045] FIG. 8E illustrates a detailed view of encircled section B of FIG. 8D.

DETAILED DESCRIPTION

[0046] It will be readily understood that the components of the embodiments, as generally described and illustrated in the figures herein, may be arranged and designed in a wide variety of different configurations in addition to the described representative embodiments. Thus, the following more detailed description of the representative embodiments, as illustrated in the figures, is not intended to limit the scope of the embodiments, as claimed, but is merely illustrative of representative embodiments.

[0047] Reference throughout this specification to "one embodiment" or "an embodiment" (or the like) means that a particular feature, structure, or characteristic described in connection with the embodiment is included in at least one embodiment. Thus, the appearance of the phrases "in one embodiment" or "in an embodiment" or the like in various places throughout this specification are not necessarily all referring to the same embodiment.

[0048] Furthermore, described features, structures, or characteristics may be combined in any suitable manner in one or more embodiments. In the following description, numerous specific details are provided to give a thorough understanding of embodiments. One skilled in the relevant art will recognize, however, that the various embodiments can be practiced without one or more of the specific details, or with other methods, components, materials, et cetera. In other instances, well known structures, materials, or operations are not shown or described in detail to avoid obfuscation.

[0049] As used herein and in the appended claims, the singular forms "a," "an", and "the" include plural references unless the context clearly dictates otherwise. Thus, for example, reference to "a conduit" includes a plurality of such conduits and equivalents thereof known to those skilled in the art, and so forth, and reference to "the conduit" is a reference to one or more such conduits and equivalents thereof known to those skilled in the art, and so forth. Recitation of ranges of values herein are merely intended to serve as a shorthand method of referring individually to each separate value falling within the range. Unless otherwise indicated herein, each separate value, as well as intermediate ranges, are incorporated into the specification as if individually recited herein. As used herein, the term "approximately indicates a value within 10% of the indicated value(s). All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contraindicated by the text.

[0050] The terms "electronic circuitry", "circuitry" or "circuit," as used herein include, but are not limited to, hardware, firmware, software, or combinations of each to perform a function(s) or an action(s). For example, based on a desired feature or need, a circuit may include a software controlled microprocessor, discrete logic such as an application specific integrated circuit (ASIC), or other programmed logic device. Field programmable gate arrays (FPGAs) include integrated circuits that are "field programmable." In that regard, FPGAs may be reconfigured to meet specific use case requirements after the manufacturing process. A circuit may also be fully embodied as software. As used herein, "circuit" is considered synonymous with "logic." The term "logic", as used herein includes, but is not limited to, hardware, firmware, software, or combinations of each to perform a function(s) or an action(s), or to cause a function or action from another component. For example, based on a desired application or need, logic may include a software controlled microprocessor, discrete logic such as an application specific integrated circuit (ASIC), or other programmed logic device. Logic may also be fully embodied as software.

[0051] The term "processor," as used herein includes, but is not limited to, one or more of virtually any number of processor systems or stand-alone processors, such as microprocessors, microcontrollers, central processing units (CPUs), and digital signal processors (DSPs), in any combination. The processor may be associated with various other circuits that support operation of the processor, such as random access memory (RAM), read-only memory (ROM), programmable read-only memory (PROM), erasable programmable read only memory (EPROM), clocks, decoders, memory controllers, or interrupt controllers, etc. These support circuits may be internal or external to the processor or its associated electronic packaging. The support circuits are in operative communication with the processor. The support circuits are not necessarily shown separate from the processor in block diagrams or other drawings.

[0052] The term "memory system" refers to a collection of electronic components that store data and instructions. In computerized systems, a processor system can quickly access information stored in a memory system. Memory allows storage and retrieval of information and may, for example, include primary memory and secondary memory. Primary memory includes, for example, RAM, cache memory, etc. Secondary memory includes, for example, hard drives, hard disk drives etc.

[0053] The term "controller," as used herein includes, but is not limited to, any circuit or device that coordinates and controls the operation of one or more input and/or output devices. A controller may, for example, include a device having one or more processors, microprocessors, or central processing units capable of being programmed to perform functions.

[0054] The term "software," as used herein includes, but is not limited to, one or more computer readable or executable instructions that cause a computer or other electronic device to perform functions, actions, or behave in a desired manner. The instructions may be embodied in various forms such as routines, algorithms, modules, or programs including separate applications or code from dynamically linked libraries. Software may also be implemented in various forms such as a stand-alone program, a function call, a servlet, an applet, instructions stored in a memory, part of an operating system or other types of executable instructions. It will be appreciated by one of ordinary skill in the art that the form of software is dependent on, for example, requirements of a desired application, the environment it runs on, or the desires of a designer/programmer or the like.

[0055] FIG. 1 illustrates schematically a base 2 of tongue 4 and tonsils 6. As set forth above, the tissue of the base of the tongue and the tonsils is histologically identical. FIG. 2 illustrates schematically an embodiment of a system 10 hereof. System 10 includes a flexible enclosure, sampling housing, sampling enclosure (sometimes referred to herein as a sampling enclosure), which has a conical or frustoconical shape in the embodiment illustrated in FIG. 2. Sampling enclosure 20 may, for example, function in the manner of a suction cup as described below. Sampling enclosure 20 may be pressed against the tissue to be sampled. Sampling enclosure 20 may be articulatable or adjustable in position (for example, about connective section or connector C) to aid in positioning sampling enclosure 20 in suitable contact with tissue T to be sampled (for example, tonsil tissue 6 or base of tongue 2). The distal end of sampling enclosure 20 includes an opening 22 and may form a seal or a partial seal with an area of tissue T to be sampled. A sealing member 24 which may, for example, be formed from a softer material (that is, of lower Young's modulus) than the remainder of sampling enclosure 20 may be provided in connection with the distal end of sampling enclosure 20. Suitable materials for sampling enclosure 20 and sealing member 24 include, for example, flexible silicone materials, which may be readily formed to vary in modulus, as known in the polymer arts. The diameter of distal opening 22 of the flexible sampling enclosure 20 may, for example, differ for differing uses. In a number of representative embodiment, the diameter of sampling enclosure 20 is within the range of approximately 2 mm to approximately 5 cm or within the range of approximately 2 mm to approximately 2 cm. In FIG. 2, system 10 is illustrated with sampling enclosure 20 positioned in alignment with tissue T of the tonsils or base of the tongue to harvest a sample of a microscopic, early-stage cancerous lesion 7 which may, for example, be positioned deep within a tonsillar crypt 8. As described above, such lesions are not detectable on the mucosal surface of the tissue.

[0056] System 10 further includes a first tube or conduit 30, which may be flexible, in fluid connection with an interior volume of sampling enclosure 20 at one end thereof and in fluid connection with a source of a contact, impact or irrigation fluid (referred to generally herein as an irrigation fluid) at the other end thereof. Conduit 30 may, for example, pass through a sleeve or outer sleeve 40 connected to sampling enclosure 20 (via connector C in the illustrated embodiment) which may, for example, be more rigid than conduit 30 and function in the manner of a handle (that is, an extending section that can be held, attached to, and/or controlled). The irrigation fluid can include a liquid, a gas, or a mixture thereof. Examples of irrigation fluids include water and water-based fluids. In a number of embodiments, the

irrigation fluid is water or saline. The irrigation fluid may, for example, include an exfoliating agent to disrupt cell surfaces and/or detach cells from tissue which may, for example, be a chemical and/or a physical exfoliating agent. For example, acetic acid may be included in the irrigation fluid as a chemical exfoliating agent. Examples of physical exfoliating agents (which function to exfoliate via physical contact) include nanoparticles (that is, solid nanoparticles), microparticles, or gasses within a liquid irritation fluid. Irrigation fluids hereof can also include markers or tags that can mark cancer cells (for example, in crypts), providing for easier detection. An example of such markers include, for example, fluorescent proteins such as antibodies and other cancer-specific proteins or molecular markers that function as target specific probes.

[0057] In addition to use of an irrigation fluid, energy can be applied to the area of tissue being irrigated to, for example, facilitate in disrupting cell surfaces and/or detaching cells. An embodiment of an energy application system 38 is illustrated schematically in FIG. 3. The energy application system may, for example, deliver the energy from within sampling enclosure 20 in some embodiments or be positioned external to sampling enclosure 20. For example, ultrasound energy can be applied to the area to cause ultrasonic vibration and/or ultrasonic cavitation. Other types of energy such as mechanical (for example, contact, vibratory etc.) energy or electromagnetic (for example, light/laser) energy may be applied. Similarly to brush biopsies, brushing may be applied to, for example, assist in disrupting cells and improving sampling (via, for example, a brush or brushing mechanism).

[0058] A second tube or conduit 50, which may be flexible, is in fluid connection with an interior volume of sampling enclosure 20 at one end thereof and in fluid connection with a source of negative pressure/suction (for example, a vacuum pump or suction pump) at the other end thereof. Through appropriate contemporaneous adjustment of flow rate of the irrigation fluid and negative pressure applied to remove irrigation fluid/cells/DNA (using known engineering principles), the system hereof can be operated in a generally self-contained manner in which relatively little fluid escapes the system.

[0059] Through forceful delivery or delivery under pressure of the irrigation fluid (which may be delivered in a continuous or discontinuous/pulsed flow), one or both of cells and DNA may be detached from a targeted lesion via contact or impact of the irrigation fluid with the lesion. In a number of representative embodiments, the fluid or irrigation fluid may, for example, be delivered at a pressure in the range 10 to 140 pounds per square inch (PSI) in a focused

collimated flow or jet, similar to the flow in a water-based flossing system. Lower or higher pressure than the one discussed above may be used in certain embodiments.

[0060] In the illustrated embodiments of FIGS. 2 and 3, second or suction conduit 50 is in fluid connection with a reservoir, trap or sampling volume positioned between the first end of the second conduit 50 (which is in fluid connection with sampling enclosure 20) and the source of suction/negative pressure. The sampling volume may, for example, include one or more cell/DNA collection units therein to collect cells and cell free DNA (cfDNA) removed, detached or freed from a lesion through disruption of the tumor or lesion surface via the impact of fluid from system 10 hereof. Cell free DNA include small fragments of DNA that circulate in body fluids, such as blood, urine, cerebrospinal fluid, saliva etc. Such collection units may, for example, use filtration, physiochemical interaction, etc. to collect cells and/or DNA. Fluid from which cells and/or cell free DNA has been removed/recovered may, for example, be removed from the system via an evacuation port in fluid connection with the reservoir, trap or sampling volume. Collected cells and cfDNA (as well as any other collected materials for diagnostic testing) harvested from one or more collection units may, for example, be separated or purified and analyzed via various analytical techniques including liquid biopsy techniques (for example, cfDNA, cytology, etc.).

[0061] FIG. 4A illustrates another representative embodiment of a system 110 hereof positioned on a cart or mobile cart 5. A photograph of a prototype of the system of FIG. 4A is provided in FIG. 4B. In the illustrated embodiment, a device or sampling assembly 112 (see, for example, FIGS. 5A and 5B) includes a sampling enclosure 120 and a handle 140. Sampling assembly or device 112 is supported by a support or cradle 114 in the illustrated embodiment of system 110. Handle 140 may, for example, be formed from a relatively rigid polymeric material. Handle 140 connects to sampling enclosure 120 via a connective section 141 on a distal end thereof. The connection between handle 140 and sampling enclosure 120 can readily be made articulatable or adjustable in relative position. Likewise, handle 140 can readily be made articulatable or adjustable in one or more positions thereon. Handle 140 may readily be adapted for use in connection with integrated with a robotic system. Such a robotic system may, for example, include a robotic arm to which handle 140 may be attached or the robotic arm may from at least a portion of a handle hereof. Handle 140 is further illustrated in FIGS. 6A through 6C, and sampling enclosure 120 is further illustrated in FIGS. 7A through 7E. An irrigation line or tube 130 and a negative/pressure or suction line or tube 150 may be routed or

passed through passage 142 in handle 140 to be placed in fluid connection with sampling enclosure 120 (see, for example, FIG. 5A).

[0062] Irrigation tube 130 is in fluid connection with an irrigation fluid reservoir 200 (containing a volume of irrigation fluid 202) via an irrigation pump system 210 (for example, a pressurizing mechanism or system such as a diaphragm pump), which pressurizes irrigation fluid or, simply, fluid 202. Electronic circuity can be provided for operation and control of various elements of system 110. The electronic circuitry may, for example, be centralized or distributed. A controller 220, for example, may provide for control over the pressure of irrigation fluid 202 from pump system 210. An adjustable vacuum or suction unit 230 provides controlled negative pressure via suction line or tube 150 in the illustrated embodiment. A sample collection volume or reservoir 240 may, for example, be placed in fluid connection between suction unit 230 and sampling enclosure 120. In the illustrated embodiment, a foot pedal system 250 is provided which includes foot pedals 252 and 254 for control of irrigation pump system 210 and suction unit 230, respectively. Food pedal system 250 may, for example, be in communicative connection with controller 220 for irrigation pump system 210 and suction system 230 via circuitry 260. Electronic circuitry hereof may, for example, include a processor system in communicative connection with a memory system. The memory system may include one or more software algorithms stored therein which are executable by the processor system to operate and control various aspects of system 110. Circuitry 260 of the electronic circuitry is, for example, illustrated as including a processor system 262 and a memory system in communicative connection with processor system 262.

[0063] Referring, for example, to FIGS. 5A, 5B and 7A through 7E, in the illustrated embodiment, sampling enclosure 120 includes a first connector 121‘ (for example, a Luer lock connector) to connect to a cooperating connector on a conduit or irrigation tube 130. Sampling enclosure 120 also includes a second connector 121” (for example, a barbed connector) for connection of a conduit or suction tube 150 thereto. Irrigation tube 130 and suction tube 150 are illustrated schematically (in broken lines) passing through passage 142 of handle 140 in FIG. 5A to connect with first connector 121’ and second connector 121”, respectively.

[0064] First connector 121’ is in fluid connection with a passage 122’ which terminates in a port or nozzle 123’. Port or nozzle 123’ is illustrated in further detail in, for example, FIGS. 7D and 7E. Opening 124 on a distal end of sampling enclosure 120 is configured or adapted to place sampling enclosure 120 in fluid connection with tissue to be sampled (as, for example,

discussed in connection with sampling enclosure 20). Irrigation fluid is delivered to the tissue to be sampled via port 123' and opening 124.

[0065] Second connector 121" is in fluid connection with a conduit 122", which is in fluid connection with one or more extending conduits or passages (two in the illustrated embodiment) which extend through or along an interior of housing 120' of sampling enclosure 120 into the interior volume of sampling enclosure 120 to terminate in port(s) or suction port(s) 123" positioned at a point near opening 124 in the illustrated embodiment.

[0066] A proximal section of sampling enclosure 120 may include a connective section 126 (for example, including a flange and/or seating to cooperate with a cooperating flange and/or seating of connective section 141) which is configured to form a connection (for example, a removable connection) with connective section 141 of handle 140.

[0067] Handles and/or sampling enclosures hereof may be modified for use in connection with specific procedures. Handles and/or sampling enclosures may differ in, for example, one more of configuration, dimension, flexibility, fluid delivery methodology, etc. For example, FIGS. 8A through 8E illustrate another embodiment of a sampling enclosure 120a. Sampling enclosure 120a is similar in many respects to sampling enclosure 120. In that regard, sampling enclosure 120a includes a first connector 121a' which may be used to connect to a cooperating connector on irrigation tube 130. A second connector 121a" may be used for connecting to suction tube 150. First connector 121a' is in fluid connection with a passage 122a', which terminates in a first port or nozzle 123a'. Second connector 121a" is in fluid connection with one or more conduits 122a" which extend through housing 120a' into the interior volume of sampling enclosure 120a and terminate in one or more ports or suction ports 123a". Sampling enclosure 120a further includes an opening 124a on a distal end thereof to place sampling enclosure 120a in fluid connection with tissue to be sampled. A proximal section of sampling enclosure 120a may include a connective section 126a which is configured to form a connection with connective section 141 of handle 140. Sampling enclosure 120a differs from sampling enclosure 120 in the nature of first port or nozzle 123a' compared to first port or nozzle 123'. In that regard, nozzle 123a' has a configuration to result in a fan or conical spray, while nozzle 123' has a configuration to result in a focused jet or collimated flow. Jet-like sprays may, for example, be used in connection with smaller, point lesions or to create more concentrated force (over a smaller area), while broader, fan-like sprays may, for example, be

used in connection with plaque-like lesions. As clear to one skilled in the art, may types of ports or nozzles may be used in systems hereof depending upon the requirement of a procedure.

[0068] Genetic and epigenetic alterations in plasma circulating cfDNA have, for example, shown potential for early detection of cancers. Such cfDNA may be shed from tumors into the bloodstream. Cell free DNA testing of plasma may, for example, indicate that an HPV related cancer or other throat cancer may be present in a patient. Such cancers arise in the lymphoid tissue of the base of the tongue and the tonsils. However, as described above, such cancers may not be detectible via physical examination and imaging in the early stages thereof. The devices, systems, and methods hereof provide an avenue for localization of such early-stage cancer. As, for example, illustrated in **FIG. 1**, multiple sites may be sampled over a tissue surface (for example, the tissue surface(s) of base of the tongue or the tonsils) using devices, systems and methods hereof, and samples from each site may be individually analyzed to localize an early-stage cancer. Components of the devices or systems hereof such as the sampling enclosure and the reservoir/trap (and/or a collection system thereof) may be removable and replaceable between uses or movement of collection location. Various removable connection systems or methods such as Luer lock systems/methods may be used to provide removable connectivity. Components which are not replaced between uses and/or locations may be rinsed or otherwise cleaned/sterilized. The entirety of devices or systems hereof may, for example, be disposable and used in connection with only a single use or patient.

[0069] Once again, there is currently no technology for identification of microscopic cancers located in the crypts of the tonsil and base of tongue, and patients very often present cancers with advanced metastasis. The localization of early-stage cancers provided by the devices, systems, and methods hereof thus provides the potential for a significant improvement in the art. Once such cancer is determined and localized via the devices, systems, and methods hereof (without an invasive biopsy), more invasive biopsy technique may be used for further analysis.

[0070] In addition to the localization or detection of difficult-to-find, early-stage cancers, the devices, systems, and methods hereof may also be used in initial characterization of a detected or previously localized lesion. In the representative embodiment of **FIG. 3**, the system hereof is used to take one or more samples from a suspicious lesion that has already been localized (for example, visually during a physical exam) on the tongue. Analysis of the one or more samples can, for example, be used to provide information as to whether an invasive biopsy is

needed or if one is not necessary. Previously localized lesions to be sampled may be located on tissue other than oral tissues (for example, on the skin).

[0071] Currently liquid biopsy techniques are simple and non-invasive alternatives to surgical biopsies which enables doctors to discover a range of information about a tumor through analysis of a blood sample. Small amounts or traces of DNA of a cancer in a body fluid such as the blood may provide information about which treatments are most likely to beneficial a patient. In general, the devices, systems, and methods hereof may be considered to create a liquid biopsy environment wherein such an environment did not previously exist.

[0072] In the representative examples discussed above, the tissue to be sampled is accessible for impact with the flow of the irrigation fluid from a device or system hereof without surgery. As used herein, surgery or surgical procedures are procedures that are typically done under anesthesia and typically require an incision or the use of an endoscopic device which can be inserted via a body orifice. The devices, system, and methods hereof may be used in a surgical environment. An example use of a device, system, or method hereof in a surgical environment is the use thereof in diagnostic testing of pulmonary lesions. Such a lesion may be located distally, for example, in small bronchi, which cannot be accessed with currently available biopsy devices. A flexible device or system hereof may be inserted in an endoscopic procedure to reach such a lesion. The cells, DNA, etc. recovered in the procedure may serve to diagnose the type of cancer. Small bronchi lesions may thus be diagnosed in a transbronchial procedure hereof without open surgery Devices, systems, and method hereof may also, for example, be use in abdominal surgical procedures (for example, in diagnosing liver/hepatic lesions).

[0073] The devices, systems, and methods hereof can be readily combined with existing endoscopic procedures such as GI upper endoscopy or colonoscopy. These procedures often employ low pressure irrigation or lavage. Employing higher pressure irrigation and tumor cell exfoliation hereof with endoscopy can, for example, aid in collecting cells or DNA for diagnosis or localization of a tumor. A representative example of an endoscopic procedure is endoscopy for diagnosis of Barrett's esophagus. The relatively high-pressure irrigation and collection systems hereof could be used to disrupt cells and collect for diagnosis in a less invasive fashion that current procedures, and could be more representative than a single biopsy at a single site in the esophagus.

[0074] Anywhere it is desirable to avoid a more invasive procedure or in which it is not possible to use a more invasive procedure, the devices, systems, and methods hereof may be used. Irrigation with a relatively high volume/relatively high pressure stream of irrigation fluid accompanied by immediate or contemporaneous collection of post-impact fluid which includes cells separated from the tissue, DNA, etc. provides a very flexible avenue for localization and characterization/diagnoses of lesions.

[0075] The devices and system hereof may be manufactured from individual components hereof to create a new device or may be formed by retrofitting existing devices. In that regards, devices such a dental devices, medical devices, and powered water flossing devices may be retrofitted to form embodiments of the devices and systems hereof.

[0076] The foregoing description and accompanying drawings set forth a number of representative embodiments at the present time. Various modifications, additions and alternative designs will, of course, become apparent to those skilled in the art in light of the foregoing teachings without departing from the scope hereof, which is indicated by the following claims rather than by the foregoing description. All changes and variations that fall within the meaning and range of equivalency of the claims are to be embraced within their scope.

WHAT IS CLAIMED IS:

1. A system, comprising:

a device comprising a handle and a sampling enclosure connected to the handle, the sampling enclosure comprising an opening configured to place an internal volume of the sampling enclosure in fluid connection with tissue, a first port in fluid connection with the internal volume, and a second port in fluid connection with the internal volume;

a source of fluid;

a pressurizing mechanism in connection with the source of fluid and with the first port;

a source of negative pressure;

a sample collection volume in fluid connection with the source of negative pressure and with the second port;

wherein the first port is configured to deliver a flow of the fluid, under pressure via the pressurizing mechanism, to an area of the tissue through the opening of the sampling enclosure and the second port is configured to draw at least a portion of the fluid which has impacted the area of the tissue therethrough and thereby into the sample collection volume.

2. The system of claim 1 further comprising a source of energy configured to apply energy to the area of the tissue.

3. The system of claim 2 wherein the source of energy comprises at least one of a source of ultrasound energy, a source of mechanical energy, and a source of electromagnetic energy.

4. The system of any one of claims 1 through 3 further comprising electronic circuitry to control the pressurizing mechanism and to control the source of negative pressure.

5. The system of claim 4 further comprising one or more foot pedals in communicative connection with the electronic circuitry to control at least one of the pressurizing mechanism and the source of negative pressure.

6. The system of any one of claims 1 through 3 wherein the sampling enclosure comprises a first connector in fluid connection with the first port, the first connector being configured to place the first port in connection with the pressurizing mechanism via a first conduit, and a second connector in fluid connection with the second port, the second

connector being configured to place the second port in fluid connection with the sample collection volume via a second conduit.

7. The system of claim 6 wherein the handle comprises a passage therethrough configured to pass the first conduit therethrough to connect to the first port and to pass the second conduit therethrough to connect to the second connector.

8. The system of 6 wherein the first port is in fluid connection with the first connector via a conduit passing through a housing of the sampling enclosure.

9. The system of 8 wherein the first port is configured to provide a determined shape of flow of the fluid therefrom.

10. The system of 6 wherein the second connector is in fluid connection with the second port via an extending conduit which extends into the internal volume of the sampling enclosure.

11. The system of 10 wherein the second port is positioned in the vicinity of the opening of the sampling enclosure.

12. The system of 6 wherein the sampling enclosure is removably connectable to the handle.

13. The system of claim 1 wherein the sampling enclosure is flexible, at least in the vicinity of the opening.

14. The system of claim 1 wherein the sampling enclosure comprises a flexible sealing member in connection with the opening.

15. The system of claim 1 wherein the sampling enclosure is configured for use in connection with specific tissue or in connection with a specific procedure.

16. A device comprising a handle and a sampling enclosure connected to the handle, the sampling enclosure comprising an opening configured to place an internal volume of the sampling enclosure in fluid connection with tissue, a first port in fluid connection with the internal volume, and a second port in fluid connection with the internal volume, wherein the first port is configured to deliver a flow of a fluid, under pressure, to an area of the tissue through the opening of the sampling enclosure and the second port is configured to draw, under negative pressure, at least a portion of the fluid which has impacted the area of the tissue into the second port.

17. The device of claim 16 wherein the sampling enclosure comprises a first connector in fluid connection with the first port, the first connector being configured to place the first port in connection with a pressurizing mechanism via a first conduit to deliver the fluid to the first port, and a second connector configured to place the second port in fluid connection with a sample collection volume and a source of negative pressure via a second conduit.

18. The device of claim 17 wherein the handle comprises a passage configured to pass the first conduit therethrough to connect to the first connector and to pass the second conduit therethrough to connect to the second connector.

19. The device of 17 wherein the first port is in fluid connection with the first connector via a conduit passing through a housing of the sampling enclosure.

20. The device of 19 wherein the first port is configured to provide a determined shape of flow of the fluid therefrom.

21. The device of 17 wherein the second connector is in fluid connection with the second port via an extending conduit which extends into the internal volume.

22. The device of 21 wherein the second port is positioned in the vicinity of the opening of the sampling enclosure.

23. The device of 17 wherein the sampling enclosure is removably connectable to the handle.

24. The device of claim 16 wherein the sampling enclosure is flexible, at least in the vicinity of the opening.

25. The device of claim 16 wherein the sampling enclosure comprises a flexible sealing member in connection with the opening.

26. The device of claim 16 wherein the sampling enclosure is configured for use in connection with specific tissue or in connection with a specific procedure.

27. A method of collecting a sample from tissue of a patient, comprising:

impacting an area of the tissue with a flow of a fluid under pressure;

collecting the sample from the fluid that has impacted the area of the tissue; and

analyzing the sample.

28. The method of claim 27 wherein analyzing the sample comprises at least analysis of cell free DNA therein and cytology of cells therein.

29. The method of claim 27 wherein a plurality of areas of the tissue are impacted with the flow of the fluid under pressure, a separate sample of fluid that has impacted each of the plurality of areas of the tissue is collected, and each of the separate samples is analyzed individually.

30. The method of claim 29 where analysis data for each of the separate samples are used to localize a lesion that has not been previously localized.

31. The method of claim 30 wherein the tissue comprises at least one of tissue from the base of the tongue of the patient or tissue from a tonsil of the patient.

32. The method of claim 27 wherein the area of the tissue includes a known lesion or a previously localized lesion.

33. The method of claim 32 wherein analysis data from the sample is used to determine whether to proceed with a more invasive biopsy technique.

34. The method of any one of claims 27 through 33 wherein the method is performed after analysis of a molecular test on a body fluid has indicated presence of cancer.

35. The method of claim 34 wherein the body fluid is blood or saliva.

36. The method of claim 34 wherein the cancer is a cancer related to HPV.

37. The method of any one of claims 27 through 33 wherein the area of the tissue is accessible without surgery.

38. The method of any one of claims 27 through 33 wherein the tissue is accessed surgically.

39. The method of claim 38 wherein the tissue is accessed in an endoscopic procedure.

40. The method of claim 39 wherein the tissue is lung tissue.

41. The method of claim 39 wherein the tissue is located in small bronchi.

42. The method of claim 38 wherein the tissue is in the abdomen.

43. The method of claim 42 wherein the tissue is hepatic tissue.

44. The method of any one of claims 27 through 33 further comprising application of energy to the area of the tissue.

45. The method of claim 44 wherein the energy comprises at least one of ultrasound energy, mechanical energy, and electromagnetic energy.

46. The method of any one of claims 27 through 33 wherein the fluid comprises at least one of a marker for cancer cells and an exfoliating agent.

47. The method of any one of claims 27 through 33 wherein the fluid comprises at least one of a liquid and a gas.

48. The method of claim 47 wherein the fluid further comprises one or more exfoliating agents.

49. The method of claim 48 wherein the one or more exfoliating agents comprises at least one of a chemical exfoliating agent and a physical exfoliating agent.

50. The method of claim 49 wherein the one or more exfoliating agents comprise solid particles.

51. The method of any one of claims 27 through 33 wherein the fluid is delivered to the area of the tissue via a device comprising a handle and a sampling enclosure connected to the handle, the sampling enclosure comprising an opening configured to place an internal volume of the sampling enclosure in fluid connection with the tissue, a first port in fluid connection with the internal volume, and a second port in fluid connection with the internal volume, wherein the first port is configured to deliver the flow of the fluid, under pressure, to the area of the tissue through the opening of the sampling enclosure and the second port is configured to draw, under negative pressure, the sample of the fluid which has impacted the area of the tissue into the second port.

52. The method of any one of claims 27 through 33 wherein the fluid is delivered to the area of tissue via a system comprising:

a device comprising a handle and a sampling enclosure connected to the handle, the sampling enclosure comprising an opening configured to place an internal volume of the sampling enclosure in fluid connection with the tissue, a first port in fluid connection with the internal volume, and a second port in fluid connection with the internal volume;

a source of the fluid;

a pressurizing mechanism in connection with the source of the fluid and with the first port;

a source of negative pressure; and

a sample collection volume in fluid connection with the source of negative pressure and with the second port;

wherein the first port is positioned to deliver a flow of the fluid, under pressure via the pressurizing mechanism, to the area of the tissue through the opening of the sampling enclosure, and the second port is configured to draw the sample of the fluid which has impacted the area of the tissue therethrough and thereby into the sample collection volume.

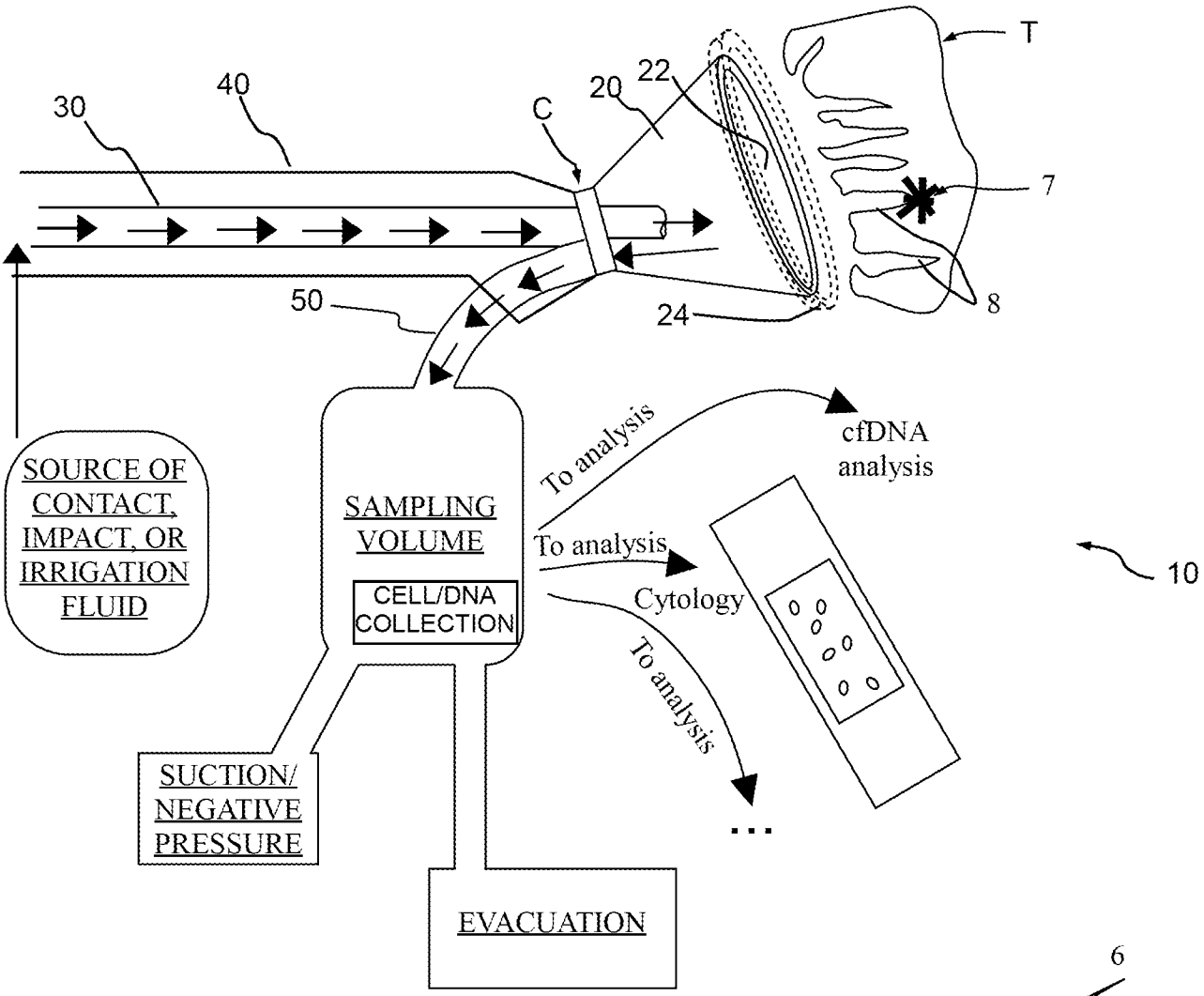

T
40
30
C
20
22
7
50
24
8
SOURCE OF CONTACT, IMPACT, OR IRRIGATION FLUID
SAMPLING VOLUME
CELL/DNA COLLECTION
To analysis
cfDNA analysis
To analysis
Cytology
To analysis
10
SUCTION/ NEGATIVE PRESSURE
EVACUATION

FIG. 2

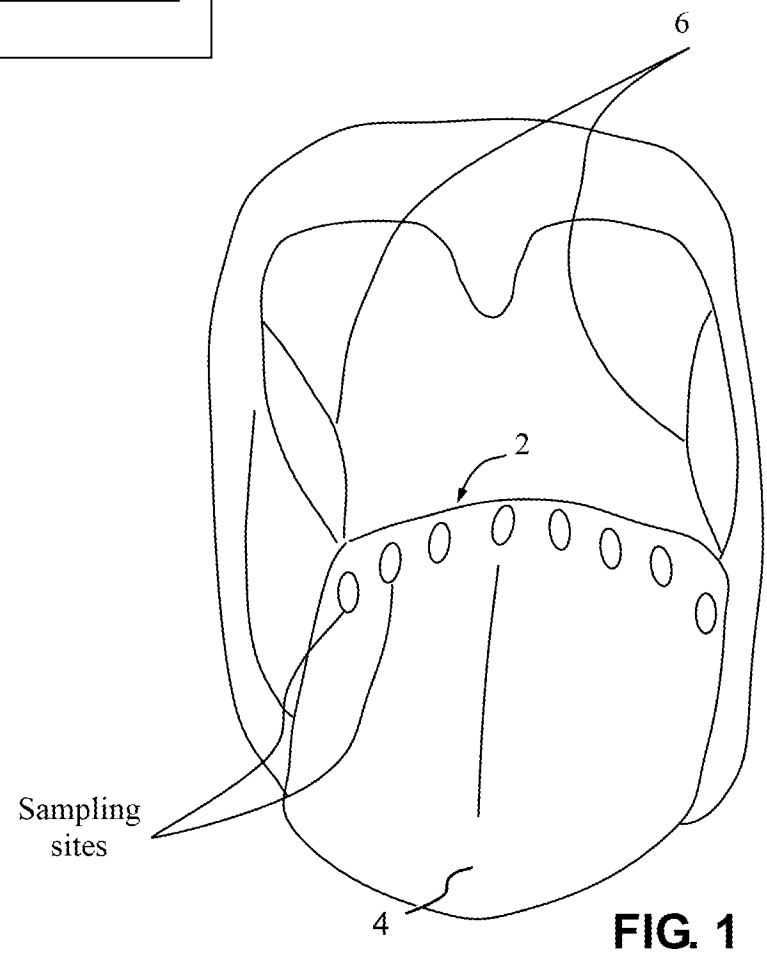

6
2
Sampling sites
4

FIG. 1

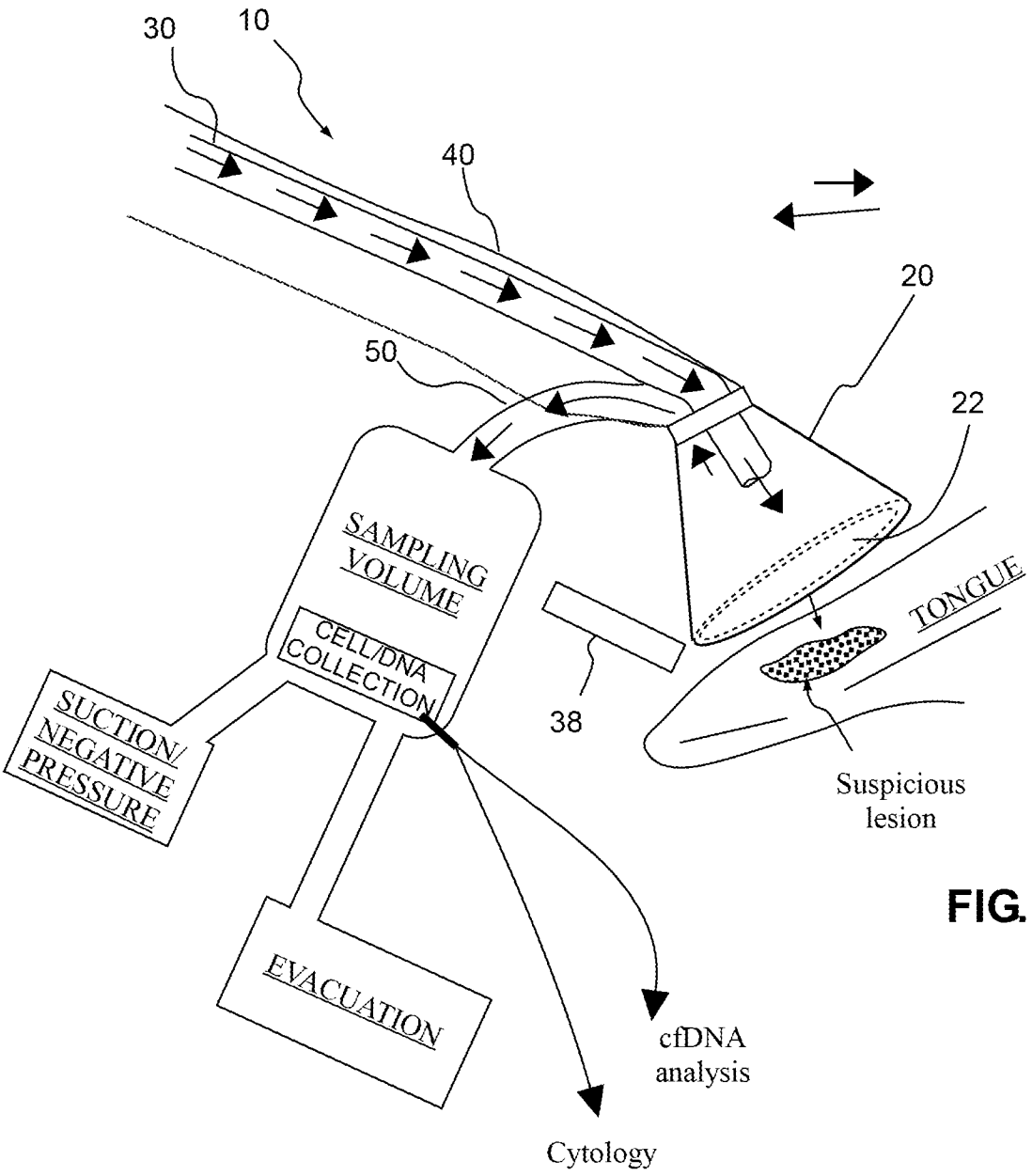

30
10
40
20
50
22
SAMPLING VOLUME
CELL/DNA COLLECTION
SUCTION/ NEGATIVE PRESSURE
38
TONGUE
Suspicious lesion
EVACUATION
cfDNA analysis
Cytology

FIG. 3

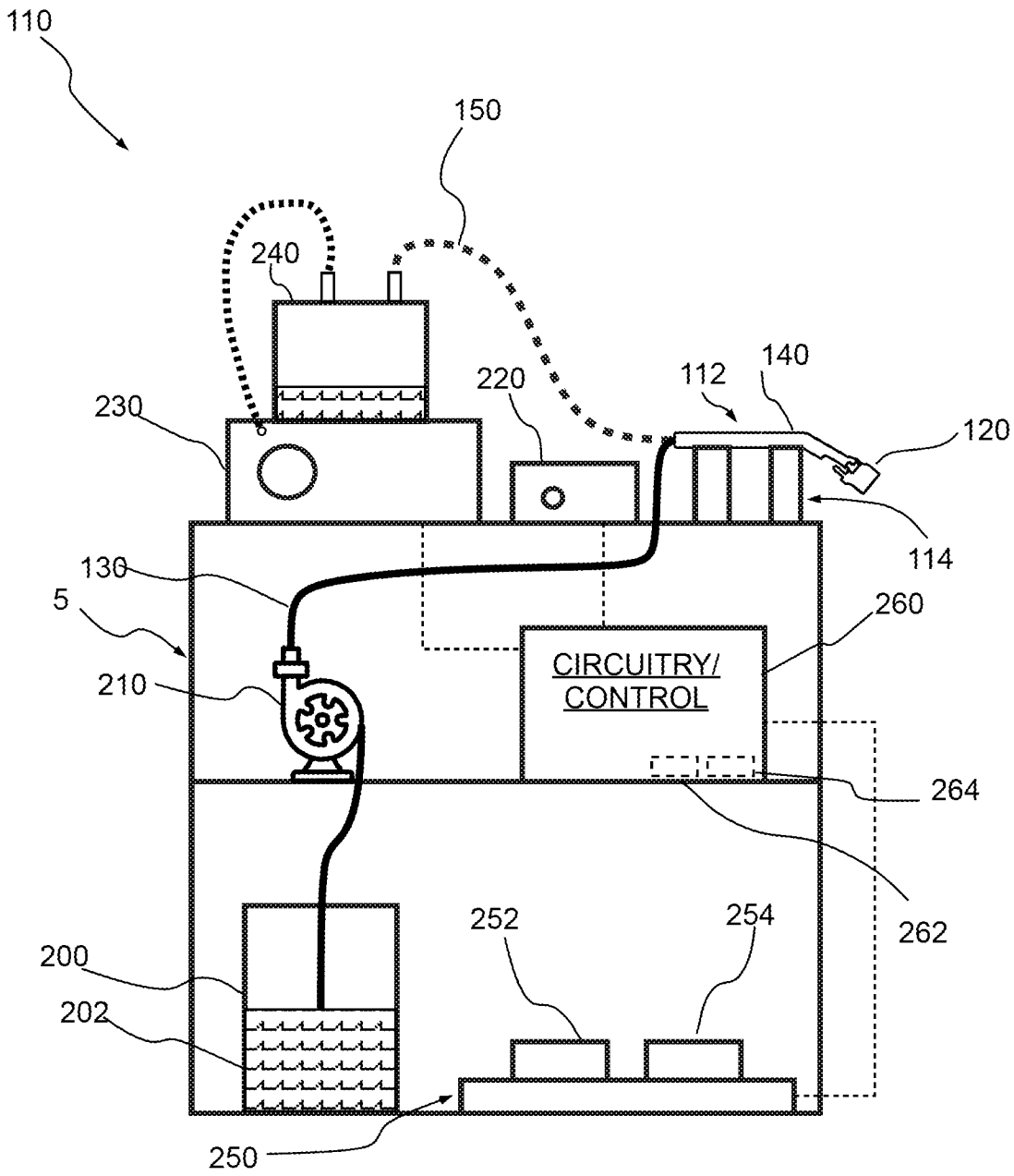

110
150
240
220
112
140
230
120
114
130
5
260
210
CIRCUITRY/
CONTROL
264
262
252
254
200
202
250

FIG. 4A

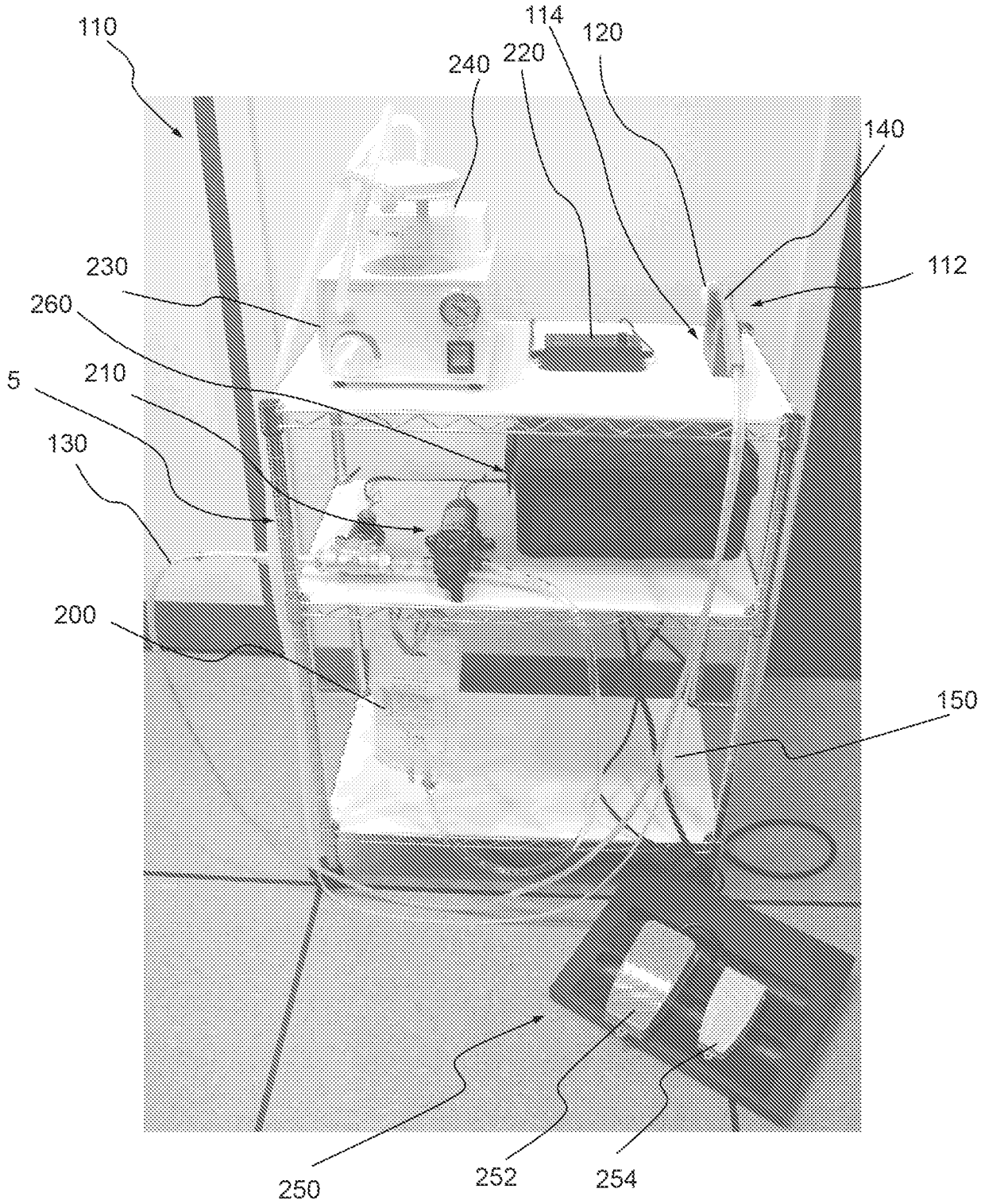


FIG. 4B

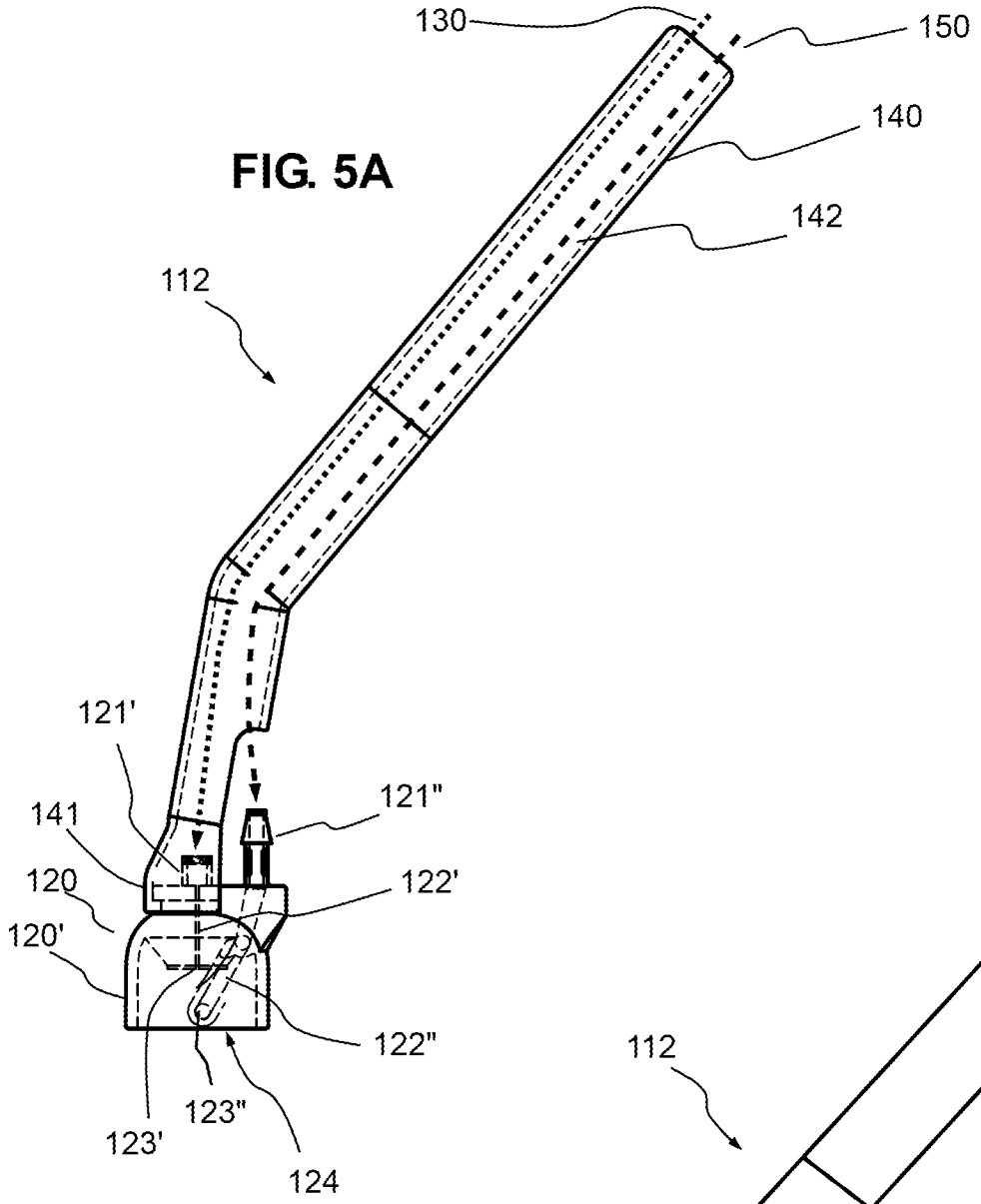

130
150
140
142
112
121'
121"
141
120
122'
120'
122"
123"
123'
124

FIG. 5A

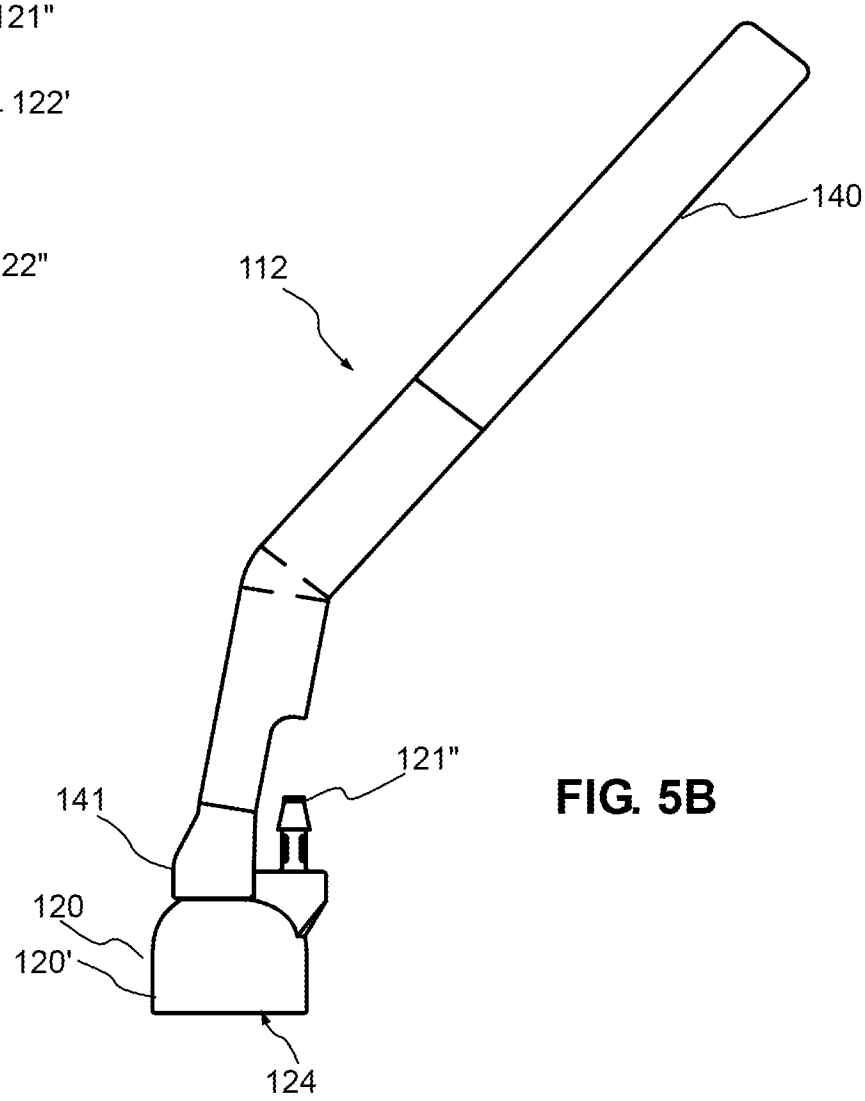

140
112
121"
141
120
120'
124

FIG. 5B

FIG. 6A

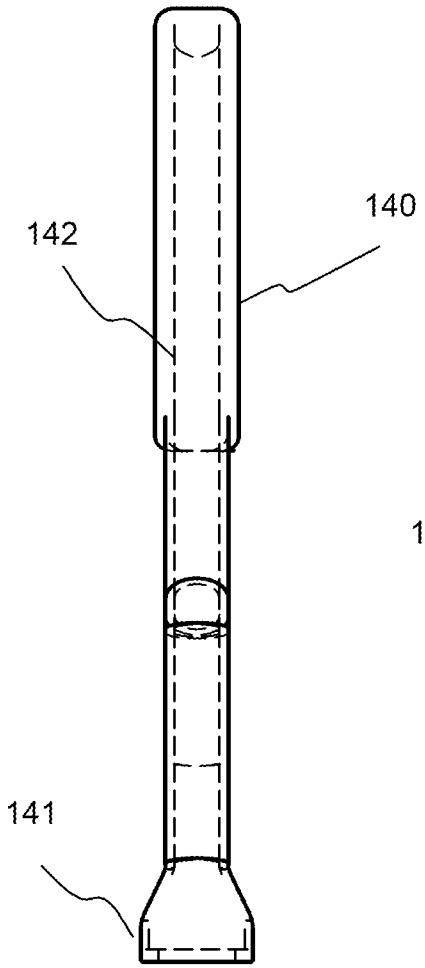


FIG. 6B

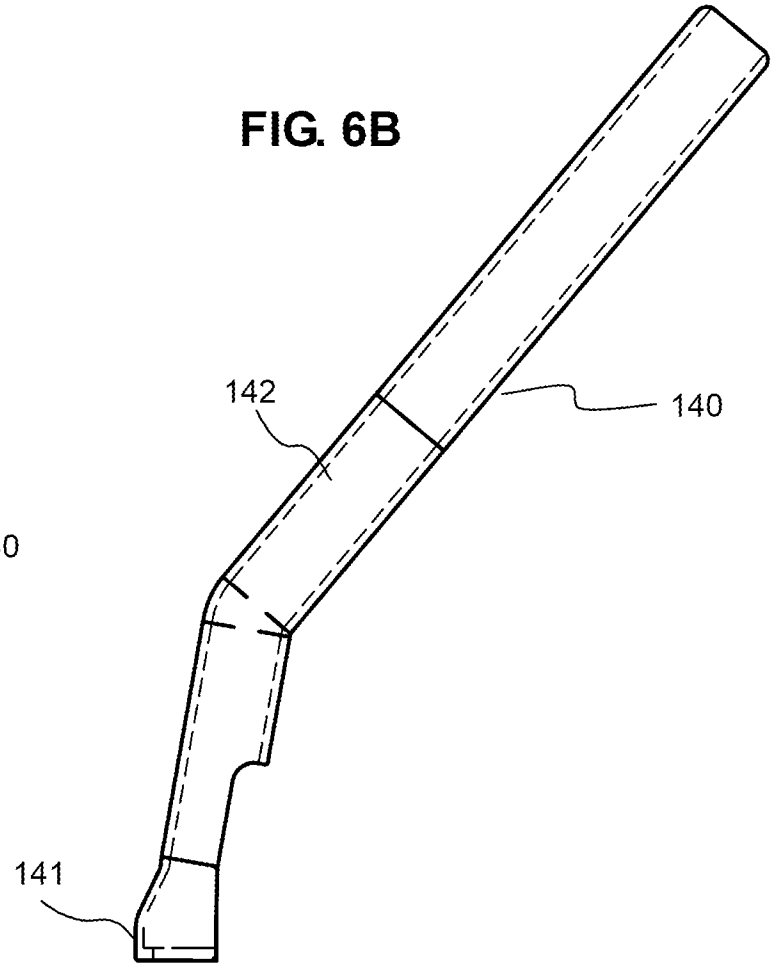


FIG. 6C

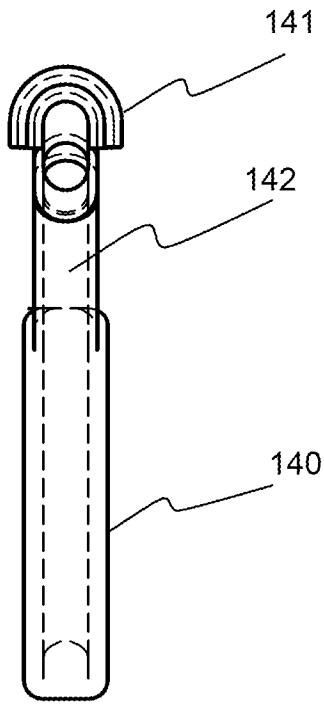


FIG. 7A

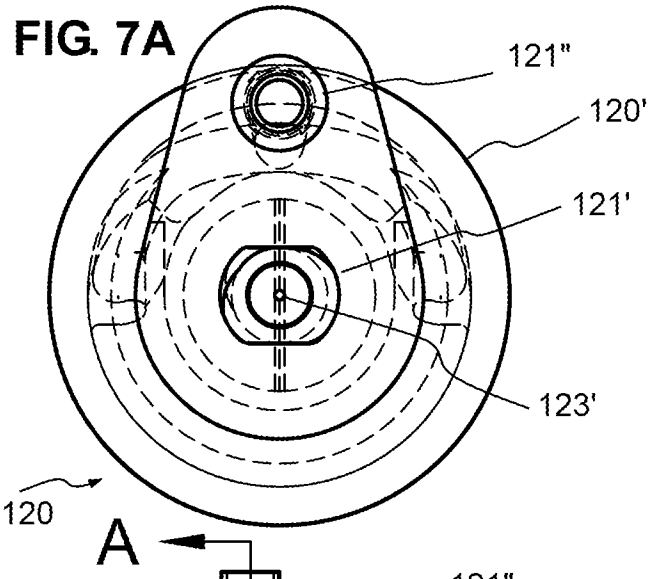


FIG. 7B

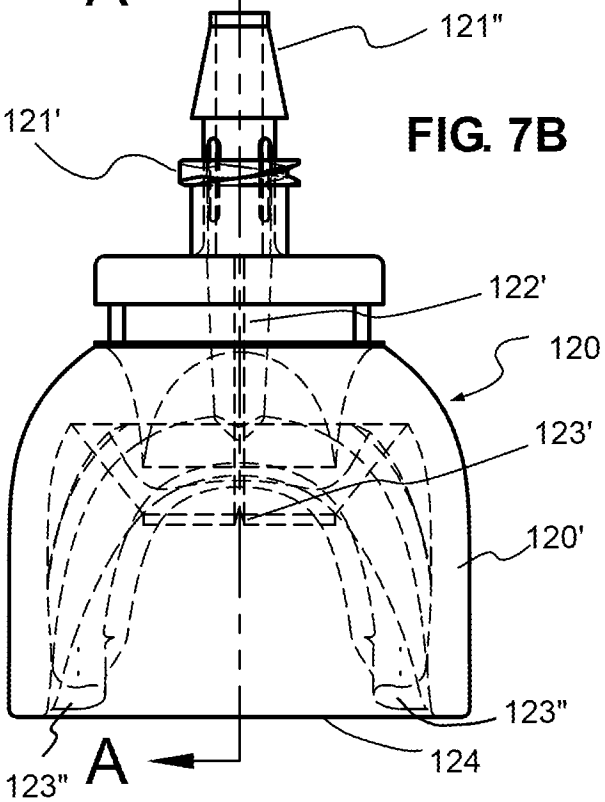


FIG. 7C

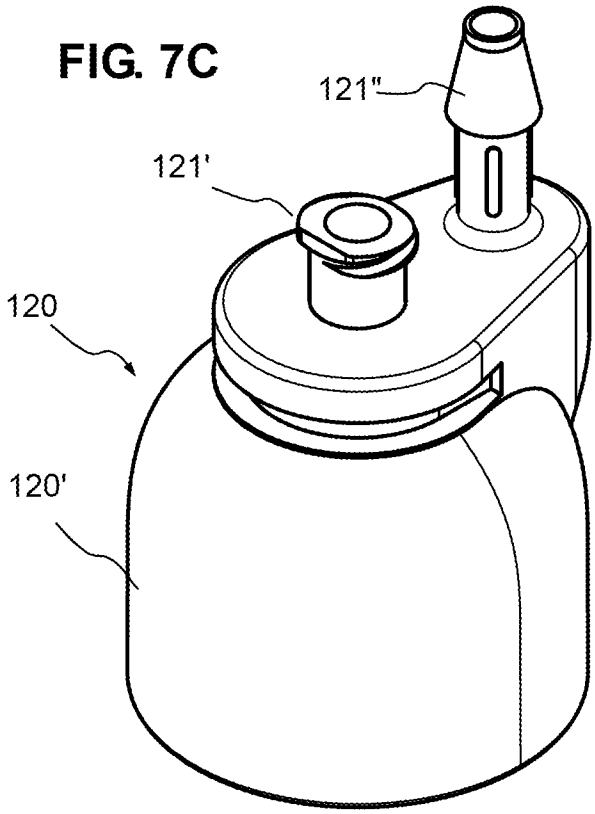
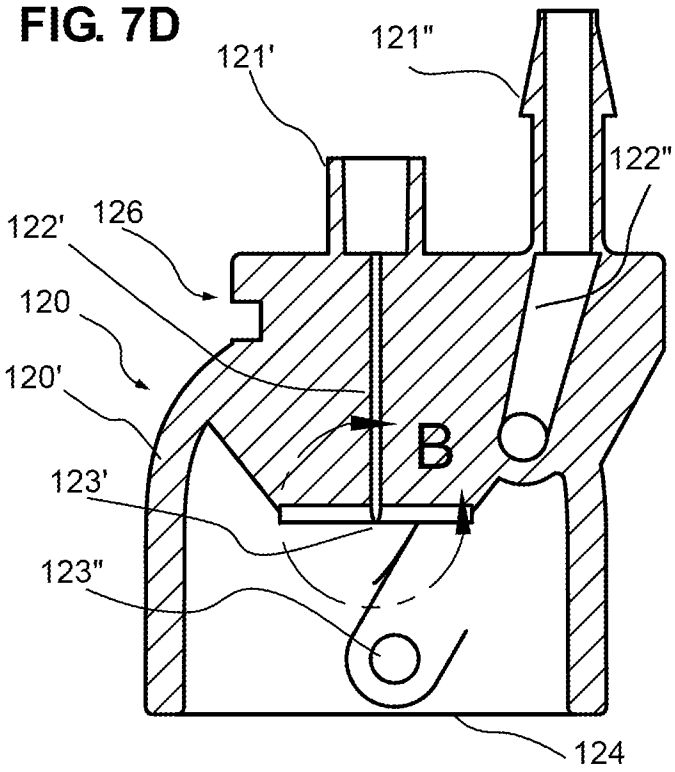


FIG. 7D



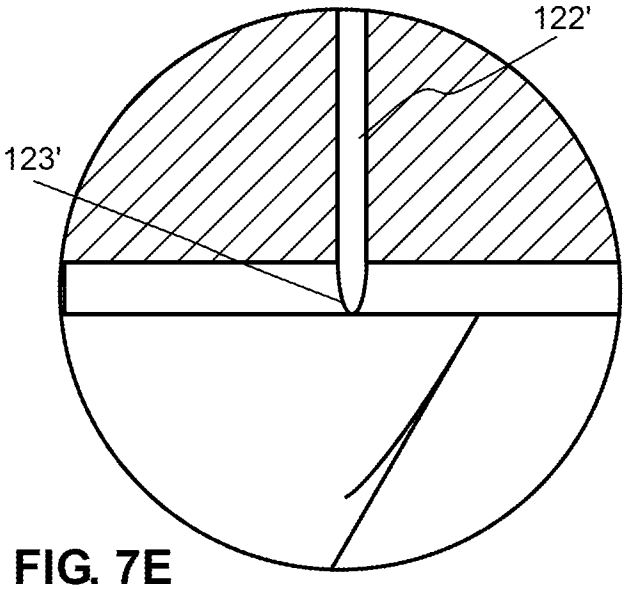


FIG. 7E

FIG. 8A

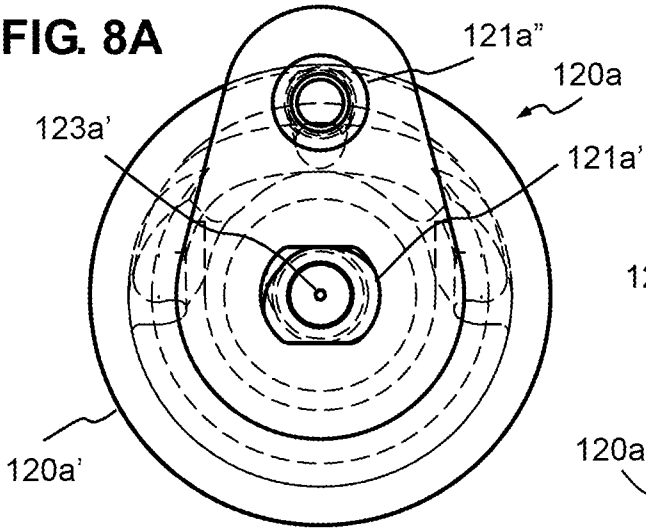


FIG. 8C

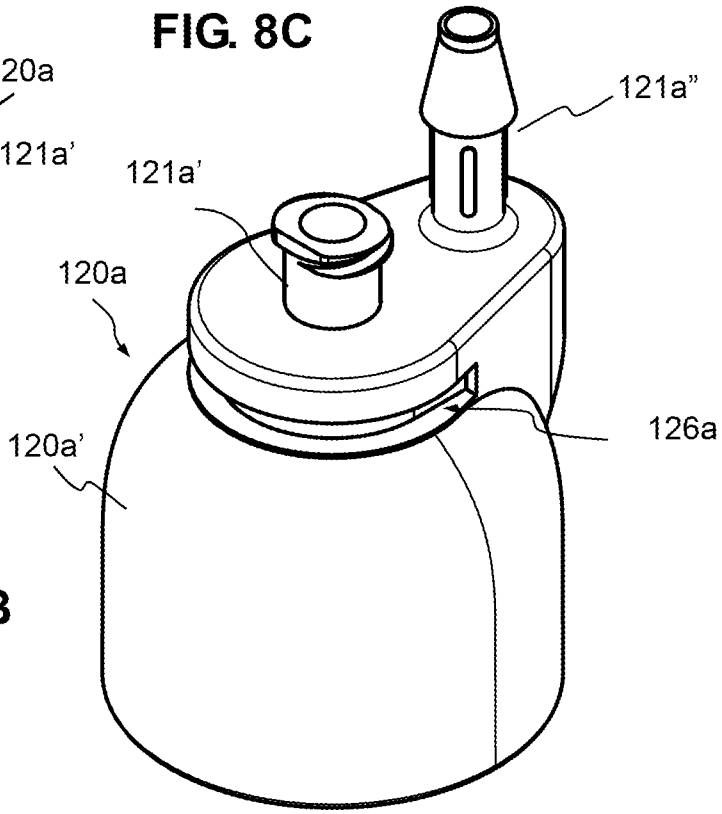


FIG. 8B

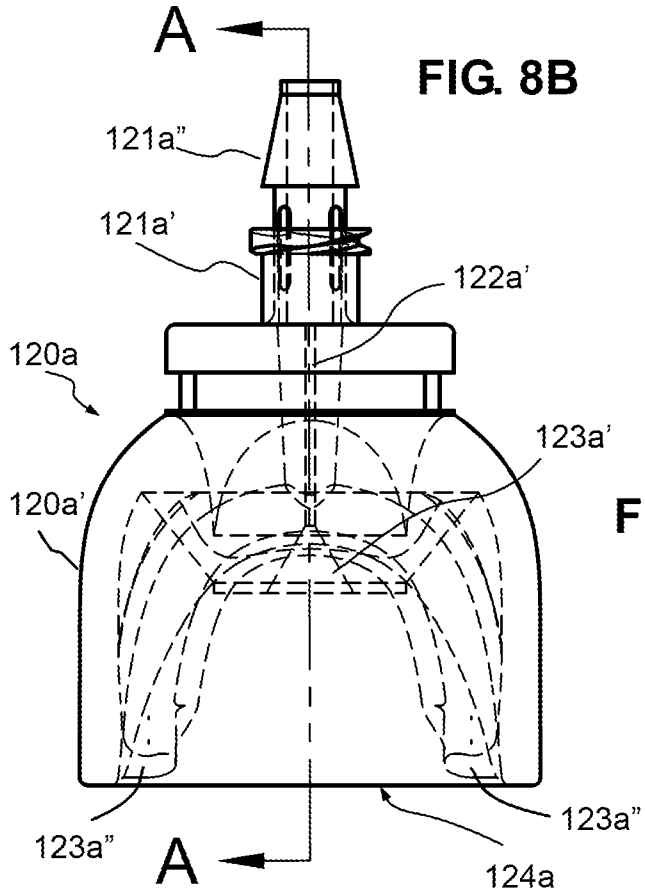


FIG. 8D

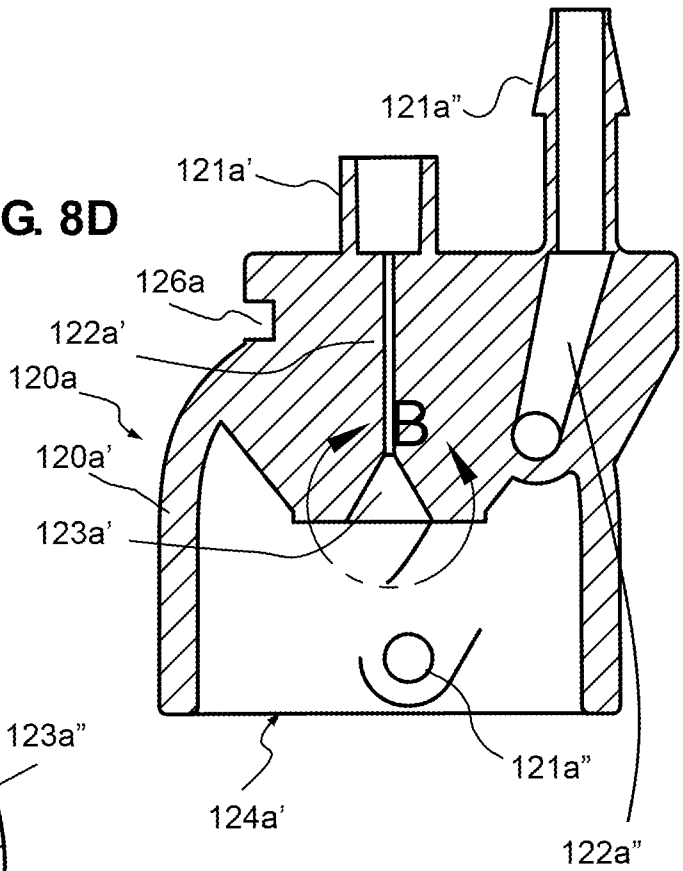
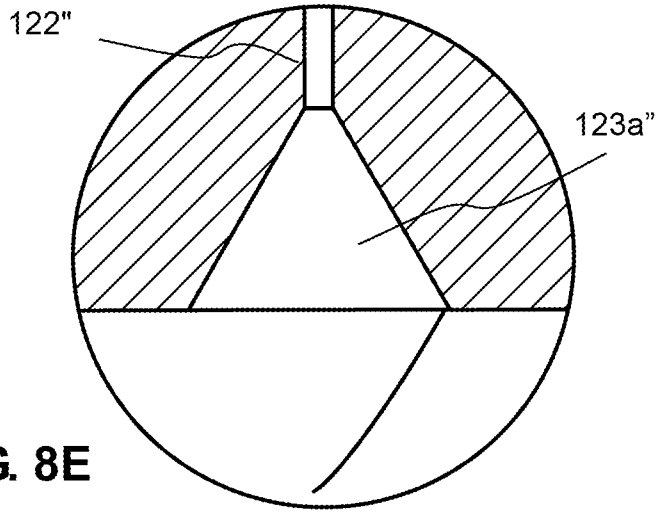


FIG. 8E



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/061618

A. CLASSIFICATION OF SUBJECT MATTER

IPC: ***A61B 10/02*** (2025.01); ***A61B 5/15*** (2025.01); ***A61M 3/02*** (2025.01)

CPC: ***A61B10/0045; A61B5/15; A61B10/02;*** *A61B5/150755*

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)

See Search History Document

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

See Search History Document

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

See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2016/0331356 A1 (JOHNSON & JOHNSON CONSUMER INC.) 17 November 2016 (17.11.2016) fig.17a, fig.17b; par [0101], [0147], [0173], [0183], [0244], [0246], [0255], [0258], [0268]-[0269], [0273]-[0274]	1, 4, 6-10, 12, 15-21, 23, 26
Y		2-3, 5, 11, 13-14, 22, 24-25
Y	US 2020/0000387 A1 (KONINKLIJKE PHILIPS N.V.) 02 January 2020 (02.01.2020) par [0025]	2-3
Y	US 2018/0221003 A1 (DEVICOR MEDICAL PRODUCTS INC.) 09 August 2018 (09.08.2018) par [0089]	5
Y	US 2018/0133064 A1 (SMITH & NEPHEW INC.) 17 May 2018 (17.05.2018) par [0063]	11, 22
Y	US 2014/0296806 A1 (BRACCO DIAGNOSTICS INC.) 02 October 2014 (02.10.2014) par [0065]	13, 24

☑ 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
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"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
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 March 2025 (19.03.2025)	**31 March 2025 (31.03.2025)**

Name and mailing address of the ISA/US	Authorized officer
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/061618

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2014/0112844 A1 (UVERA DIAGNOSTICS INC.) 24 April 2014 (24.04.2014) par [0044]	14, 25

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2024/061618

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fee must be paid.

Group I: Claims 1-26 are directed towards a device for sampling fluid.

Group II: Claims 27-52 are directed towards a method of collecting a sample from tissue of a patient.

The inventions listed as Groups I-II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons:

The special technical features of Group I include at least device comprising a handle and a sampling enclosure connected to the handle, the sampling enclosure comprising an opening configured to place an internal volume of the sampling enclosure in fluid connection with tissue, a first port in fluid connection with the internal volume, and a second port in fluid connection with the internal volume, wherein the first port is configured to deliver a flow of a fluid through the opening of the sampling enclosure and the second port is configured to draw at least a portion of the fluid under negative pressure, which are not present in Group II.

The special technical features of Group II include at least analyzing the sample, which are not present in Group I.

The common technical features shared by Groups I-II are impacting an area of the tissue with a flow of a fluid under pressure; collecting the sample from the fluid that has impacted the area of the tissue.

However, these common features are previously disclosed by US 6,866,994 B2 to Morton ("MORTON"). MORTON discloses impacting an area of the tissue with a flow of a fluid under pressure (introduce a carrier fluid retrograde into the duct, Such as through the use of a pressurized Stream directed to the external opening of the duct; col 13, ln 34-36); collecting the sample from the fluid that has impacted the area of the tissue (aspiration may occur either immediately following introduction of the carrier fluid; col 13, ln 42-44).

Since the common technical features are previously disclosed by the MORTON reference, these common features are not special and so Groups I-II lack unity.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☑ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: **1-26**

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.