

ABSORPTIVE TIP BRUSH BIOPSY DEVICE, KIT AND METHOD**FIELD OF THE INVENTION**

The present invention provides a system and method for performing a biopsy of the uterus. More particularly, it is a device that disrupts and samples cells from the endometrium, and simultaneously takes a sample with an abrasive brush, an aspirate, and an absorptive structure.

BACKGROUND OF THE INVENTION

The present technology represents improvements over US patent Nos. 9,351,712, 8,920,336, 8,517,956, 8,348,856, and 20180161021. Those patents, in turn, represent an improvement over the Cook Medical Tao Brush™ I.U.M.C. Endometrial Sampler, and the Pipelle endometrial biopsy device (See, Sierecki AR, Gudipudi DK, Montemarano N, Del Priore G., "Comparison of endometrial aspiration biopsy techniques: specimen adequacy." J Reprod Med. 53(10):760-4, 2008 Oct). As shown in Figs. 3 and 4, the Tao Brush™ has a bead at the tip, to reduce trauma when the brush reaches the fundus of the uterus. Fig. 4 shows the brush extended from the sheath, while Fig. 2 shows the brush retracted. Proximal to the brush, on the guidewire, is an inner sleeve provided to center the wire, but this does not provide an interference fit, and does not draw a vacuum when the guidewire is retracted. The sample taken by the Tao Brush™ represents the cells swept or abraded from the endometrium, by the bristles.

Sampling devices for cervical tissue are disclosed in US 20160331357 and 20020161313. Cervical sampling differs from endometrial sampling in that the cervix and the cervical os, are more accessible, and that to obtain a proper sample of endometrial tissue, the biopsy device must be protected as it passes through the cervix. Further, the diameter of the endometrial biopsy device is constrained by the cervical os.

Figs. 20A-20C and 7 show the use of the Tao Brush™. The manufacturer (Cook Medical) provides the following instructions for use:

1. Position screw-cap test tube containing 8 ml of CytoRich® Brush Cytology Preservative (AutoCyte, Inc., Elon College, NC) in a test-tube rack at the site of the procedure.
2. Place patient in lithotomy position.
3. Retract the brush sampler completely into the outer sheath.
4. Gently insert the device to the level of the fundus. (Fig. 20A)
5. Pull back the outer sheath all the way to the handle. Amply rotate the brush sampler. (Fig. 20B)
6. In order to trap endometrial material in situ, push the outer sheath over the brush to the tip and remove the device. (Fig. 20C). The normal endometrial cavity is in a collapsed state, so the brush will have direct contact with the entire endometrial surface.

7. Immediately immerse the device into 8 ml of CytoRich® Brush Cytology Preservative. (Fig. 7)
8. Retract the sheath to expose the brush to preservative solution.
9. Hold the sheath firmly and move the brush in and out of the sheath to clean it of adherent cells and tissue.

Collections are generally stable in preservative for periods of up to several weeks.

10. Remove the brush assembly from the test-tube, replace the screw cap, and submit the tube to the laboratory for processing.

Two alternate methods of obtaining the biopsy sample are suggested:

- 1) Rotate brush sampler in a clockwise manner until reference mark on the handle indicates completion of a 360°

turn, then rotate counterclockwise the (opposite direction) until the reference mark on the handle indicates completion of a 360° turn;

2) Rotate the brush sampler in only one direction by completing 4 or 5 360° rotations. Note: Reference mark on handle indicates completion of a 360° rotation.

5 To Obtain Uncontaminated Endometrial Cultures

1. After insertion of a sterile, nonlubricated vaginal speculum, swab the ectocervix and the endocervical canal with povidone iodine solution. NOTE: Insert the swab about 1.5 cm into the endocervical canal to ensure adequate swabbing of the endocervix with the povidone.

10 2. Insert the brush into the endometrial cavity following steps 3-6 from the section preceding these instructions. The reference mark on the handle indicates completion of a 360° turn.

3. Remove sampler.

4. Wipe the rounded tip of the brush with 95% alcohol gauze.

5. Pull back the sheath. Prepare morphologic evaluation (if required) by preparing a direct smear on a sterile glass slide and spray-fix immediately.

15 6. For culture studies, place the brush into sterile Stuarts Transportation Medium and agitate for 5 seconds.

Figs. 8A (before sample) and 8B (after sample is drawn) show a Pipelle biopsy tool, which aspirates a sample into a sheath, but does not have an exposed brush.

20 Figs. 9 and 10A-10C show the design according to US patent Nos. 9,351,712, 8,920,336, 8,517,956, and 8,348,856, which improve the Tao Brush™ design by implementing an aspiration biopsy in addition to an abrasive tissue sampling biopsy. This is achieved by providing an interference fitting plunger 4 proximal to the biopsy brush 3, which draws in a fluid sample from the uterus as the brush is withdrawn into the sheath 1 by withdrawal of the wire 2. Fig 10A shows the brush in the initial state during insertion into the uterus. Fig. 10B shows the brush extended from the sheath. Fig. 10C shows the brush withdrawn into the sheath after a biopsy sample is taken. However, according to the Tao Brush™ design and that of US patent Nos. 9,351,712, 8,920,336, 8,517,956, and 8,348,856, the brush is inserted either an arbitrary or estimated distance, or until
25 resistance is encountered by the tip of the brush pushing against the fundus of the uterus, which risks unnecessary tissue damage, and in some cases, complications. US patent Nos. 9,351,712, 8,920,336, 8,517,956, and 8,348,856 discuss an intrauterine biopsy sampling device having a narrow cylindrical tube with a guidewire and biopsy sampling device at the end at the end of the guidewire, similar to a Cook Medical (Bloomington, IN) Tao Brush™ I.U.M.C. Endometrial Sampler, modified such that disposed within the sheath, is a piston-like structure which, when the wire is withdrawn through the sheath, draws a
30 vacuum and sucks fluid surrounding the guidewire into the sheath. A vacuum biopsy sampling device, such as the known Pipelle endometrial suction curette, produces a vacuum and draws it into the sheath by a similar principle, but lacks the brush or other biopsy sampling device at its distal end.

35 The device is a 1-3 mm diameter by 30-40 cm long coaxial "straw" 1 that can easily pass into the uterus endometrial cavity with little or no discomfort. It is malleable but rigid enough to apply sufficient force to pass through the cervix. In the center of the outer sheath, which is an impermeable tube, a thinner inner insert 2 can be extended beyond the end of the tube 3 into the uterus. Proximal from the biopsy brush is a suction element 4, which draws liquid into the sheath when the guidewire is withdrawn. The inner obturator disrupts the uterus to loosen and collect a biopsy sample of the uterus. The tissue sampling device includes a spirally twisted flexible wire with opposed proximal and distal ends. Also included is a plastic tube

covering a significant portion of the wire to provide additional rigidity without making the overall brush stiff.

Along the distal end portion of the wire is a brush that includes bristles that were used for collecting a tissue sample. The bristles are fixed within the spirally twisted wire near the distal end and are tapered from smaller to larger towards the distal end of the wire. Tapering of the bristles from the distal end of the device allows for more global tissue collection of the endometrium because of the shape of the endometrial cavity. An atraumatic bulb is located on the extreme distal end of the twisted wire. The plastic tube and twisted wire are contained within a sheath of shorter length than the twisted wire, such that the sheath can be moved along the plastic tube to the atraumatic bulb on the distal end of the twisted wire, thereby covering the brush during insertion and removal after tissue collection.

Before insertion, the sheath can be moved into position over the distal end of the twisted wire to protect the brush during insertion. Having the brush covered during insertion also increases comfort for the patient and protects the brush from collecting tissue from unintended areas. The sheath is moved back toward the proximal end of the twisted wire after the device has been inserted to the proper collection depth, exposing the brush and allowing for collection of a tissue sample. The sheath may be moved to completely uncover the brush or may be moved in gradients to uncover portions of the brush. This allows the practitioner to adjust the effective collection area of the brush based on the anatomy of the patient.

The plastic tube covering the wire is scored in centimeter gradations along the plastic tube with markings indicating the exact length of the brush inserted into the uterus, starting from the distal tip of the brush to the proximal end of the plastic tube. This allows the clinician to know how deeply the brush is inserted into the uterus. The sheath is approximately the same length as the plastic tube and in position to cover the brush bristles prior to insertion. The sheath may be formed of a clear material such that the gradations on the plastic tube may be viewed through the sheath. The ability to measure insertion depth increases the certainty that the tissue sample collected is from the correct area. After a tissue sample is collected from the proper area, while the tissue sampling device remains inserted, the sheath can be moved back along the distal end of the twisted wire to cover the brush bristles before removing the brush. This allows for the tissue sample to be protected on the brush within the sheath during removal.

Additionally, the gradations along the flexible tube allow the practitioner to measure the length of bristles exposed. As the practitioner pulls the sheath from its insertion position towards the handle, the further the sheath is pulled the more bristles are exposed. The gradations (ruler) provide a visual confirmation of this measurement and allow the practitioner to be precise in exposing only a certain length of the brush bristles. This measurement allows the practitioner to have better control of where the tissue is sampled and allows the practitioner to adjust the length of brush based on patient specific parameters; such as uterine size measured during previous tests or inferred based on patient history. Control of brush exposure increases sampling precision and patient comfort.

Simultaneously with withdrawal of the inner obturator back into the narrow cylindrical tube, the device creates a weak suction to collect the disrupted sample into the outer tube. The entire apparatus is then withdrawn from the uterus and the sample is collected by reversing the process outside the body.

Combining two or more biopsy methods into one device eliminates pain, discomfort, and inconvenience, e.g., a second procedure to obtain an adequate and accurate specimen. The multiple methods of specimen collection, e.g., disruption by physical means, and suction, used together, allows a gentler application of the individual methods, e.g. a gentle disruption and gentle suction applied simultaneously can replace a vigorous disruption, e.g. D&C, and a powerful suction. The combination of multiple gentler methods in one device is safer and more effective than any method alone.

SUMMARY OF THE INVENTION

The present invention provides multiple sampling modalities for intrauterine tissue biopsy. First, there is a brush or tissue surface disruptive modality. Second, there is a bulk fluid and suspended cellular material sampling modality. Third, there is a fluid absorptive modality. These features may be provided in combination or subcombination.

5 A preferred embodiment of the present invention provides a narrow cylindrical tube with a guidewire and biopsy sampling device at the end, similar to a Cook Medical (Bloomington, IN) Tao Brush™ I.U.M.C. Endometrial Sampler, modified such that the distal tip of the biopsy sampling device has an absorptive structure which draws in cellular material. Further, proximal to the biopsy sampling device on the guidewire is a flange or piston structure, that draws a vacuum in the tube as the guidewire is withdrawn at the conclusion of sampling.

10 Surrounding the cylindrical tube, a cervical stop may be provided that limits insertion of the cylindrical tube beyond a fixed distance past the external os of the uterus. The cervical stop may be adjustable along the cylindrical tube to control depth. Optionally, the movement of the cervical stop on the cylindrical tube may be limited in range, to be positioned at the cervix at initial insertion, and then provide tactile feedback when the cylindrical tube is fully inserted. Therefore, the user can control both the extension of the biopsy sampling device from the end of the cylindrical tube, and the depth of insertion of the
15 cylindrical tube into the uterus. This additional parameter is meaningful since the sample drawn by the brush, and especially by the flange or piston, will depend on where the opening of the cylindrical tube is when the biopsy sampling device is withdrawn into it. See, US patent Nos. 9,351,712, 8,920,336, 8,517,956, and 8,348,856.

For example, the cervical stop may have a frictional fit with the cylindrical tube to provide damped but smooth axial movement. At the ends of the range, a proximal and distal protrusion or O-ring may be provided, to limit the sliding
20 movement. Alternately, the smoothness or frictional coefficient of the cervical stop against the cylindrical tube may abruptly change, especially in the distal case. Indeed, sequential zones of frictional variation (e.g., every centimeter) may be provided to provide haptic/sensory feedback to the user to permit counting of the depth of insertion. When the cervical stop reaches the proximal stop, that will limit further insertion to help avoid puncturing the uterus with the end of the biopsy sampling device.

For sampling, the biopsy sampling device (e.g., brush) is withdrawn into the cylindrical tube by retracting the
25 guidewire while maintaining the insertion depth of the cylindrical tube, which then samples fluid surrounding the biopsy sampling device at that position by drawing a vacuum from the retraction of the flange or piston structure. Therefore, the cylindrical tube should be inserted to the desired depth from where the fluid surrounding the biopsy sampling device is desired to be sampled. Unless a restraining force is applied to the cervical stopper, when the cylindrical tube is withdrawn from the uterus, the cervical stopper will no longer contact the cervix.

30 The biopsy sampling device may extend a few centimeters beyond the end of the cylindrical tube during the procedure, before being withdrawn back into the cylindrical tube and withdrawal from the cervical os.

The distal protrusion or O-ring is inserted into the cervical os, and must therefore not cause tissue trauma. The proximal protrusion or O-ring is not inserted into the cervical os, and remains proximal to the larger cervical stop.

The distal protrusion or O-ring may be fixed or displaceable, and in some cases, the user may wish to adjust the initial
35 depth of insertion.

As mentioned above, the distal tip of the biopsy sampling device includes a porous absorptive structure, that can draw a cellular fluid sample from the endometrium. The tip also includes an atraumatic function which caps the end of the guidewire (if it extends that far) and prevents puncture of the endometrium by the biopsy sampling device. The porous

absorptive structure is preferably frictional or textured, to provide abrasive quality to shear off cells from the surface, while the biopsy sampling device is being manipulated. For example, a polymeric foam bulb may be formed over a cap on the end of the guidewire, distal to a set of bristles that extend from the guidewire, which in turn is distal to the flange or piston structure. The foam bulb in this case is adhered to the cap, and is sized and configured to be withdrawn into the cylindrical tube so that the porous absorptive structure is isolated from the cervix during insertion and withdrawal. Likewise, this protects the porous absorptive structure from compression and consequent loss of sample during withdrawal.

The sample(s) obtained by the device are preferably suitable for genetic material analysis, i.e., PCR or RT-PCT for DNA and RNA, respectively. In order to avoid contamination, it is preferable that the materials, especially the foam or other absorptive material, be synthetic and sterile.

The device is intended to collect tissue samples from the lining of the uterus (endometrium). The device has a brush at the distal end of the catheter. The brush is intended to gently sample the endometrium by brushing off surface mucous and cells. The proximal end of the device has a handle for ease of physician handling. The device has a relatively rigid, outer sheath, that can be move along the length of the device (with respect to the handle), to cover or expose the brush at the distal end.

The device preferably has a skirt stopper, i.e., the cervical stop, around the distal end of the outer sheath. A skirt stopper is preferably an annular flange which extends radially from a hub around the cylindrical sheath. The skirt stopper may be formed of a flexible silicone or polyurethane rubber.

The skirt is intended to locate the device in relation to the cervix. The cervical stop may be fixed in position, i.e., displaced from the tip a sufficient amount to permit the end of the cylindrical tube to be inserted past the cervical epithelial cells, or manually slidable along the outer sheath. In general, the cervical stop, if slidable, should have a sufficiently frictional coefficient with respect to the outer surface of the cylindrical tube, to remain axially fixed in position after placement except where intentionally repositioned, such that when the cervical stop abuts the cervix, manipulation of the guidewire and the sheath will not unintentionally reposition the cervical stop.

A series of axial markings are preferably provided to allow quantitative alignment of the cervical stop along the sheath. As noted above, a marking may also be provided showing the user a degree of rotation of the guidewire with respect to the cylindrical tube.

In some cases, portions of the biopsy process may be automated. For example, one or more electrical motors may control the rotation and extension of the guidewire. For example, a coreless DC motor (e.g., type 0408, 0412, or 612) motor may drive guidewire rotation through e.g., a reducing gear transmission, while a similar motor may be operated as a servo to control extension and retraction from the sheath. For example, the worm gear and follower (screw and nut) may be used. The control may be an ARM M0 or M4-based microcontroller, executing Arduino or other operating system, or directly microcoded. Advantageously, the processor is included within an RFID device, to provide both identification and information processing functions, and control functions, e.g., NXP PN7462, NTAG203; NTA53321G0F, etc.

The control is preferably reusable, while the biopsy catheter is preferably single use, and transported to the pathology lab for analysis. The control is preferably autoclavable, or gas sterilizable, though it may also be waterproof and sterilized and/or cleaned by immersion into a sterilization/antiseptic solution. The microcontroller and power supply may be wirelessly coupled to the motor/actuator unit, for example coupled through a Qi or other wireless standard inductive coupling. As discussed below, other automated functions are possible using electronic assistance, and the basic sampling functions for a single biopsy device are reasonably performed manually by a skilled user without electronics.

The skirt stopper is preferably made of an elastomer with rounded edges, such as rubber, silicone, or plastic, having sufficient elasticity to provide the desired characteristics and avoid unintended traumatic injury even when a user applies excess pressure.

5 The device is intended to be advanced into the patient with the brush covered by the outer sheath until the skirt encounters the cervix and can advance no further. After the skirt is stopped against the cervix, the brush is advanced past the end of the sheath by moving the guidewire with respect to the sheath, to expose the brush inside the uterus, to allow tissue sampling. The skirt provides a force on the sheath when pressed against the cervix.

10 The device also has an O-ring, flange or piston secured to the main shaft, i.e., guidewire, of the catheter. The outer sheath, i.e., the cylindrical tube and O-ring, flange or piston create a seal against each other, and create suction (vacuum) at the distal end of the catheter for securing tissue samples when the guidewire and brush are withdrawn into the sheath.

The device is removed from the patient with the brush covered by the outer sheath. A stop may be provided to limit withdrawal of the guidewire into the sheath. For example, a toroidal or cylindrical member attached in fixed position inside the sheath may interfere with the O-ring (or flange or piston), and thus limit retraction.

15 The device preferably sterile, and intended for single-use only. Advantageously, the guidewire and sheath may be readily cut with a scissors (shears) or wire cutter, to reduce the material that need be transported for analysis. A cut point may be provided, which is more easily severed than the remainder. Typically, a twisted or braider stainless steel guidewire will be difficult to cut, or will scar a fine scissor. However, a weak portion of the wire may be provided, either by modifying the wire in a weak region, or providing an insert.

20 While a bar code or 2D bar code may also be used for identification, a writable RFID device has the advantage of being readable without being visible (e.g., cloaked or sheathed), being readily updatable during use (writable tags), avoids requirement of a line of sight, and permits cryptographic authentication and access limitations (depending on selected integrated circuit). In some cases, identity and associated information may be stored on a blockchain or distributed blockchain, which avoids need for centralized access on one hand, and avoids single point of failure and implicit trust on the other. Thus, using cryptographic handshaking, an RFID device associated with the biopsy device, for example, embedded in the
25 manipulation handle or cervical stop, can store identifying information, which may be a mere index number, or programmed with specific patient identification, as well as ad hoc or structured information, such as procedure and reporting details. In some cases, the preferred standard for the RFID may be according to ISO 11784 and ISO 11785, which operate at lower frequencies than ISO 14443, and thus may use a ferrite antenna with a coil wrapped around it, facilitating a cylindrical form factor and placement in, or molding within, the handle.

30 In some cases, the handle is severed (cut) from the handle to facilitate transport to the lab for analysis, and analysis. In that case, if the RFID is in the handle, it will be separated from the associated sample. In that case, the RFID may be provided on the sheath. An RFID semiconductor device is typically less than 2 mm, and potentially less than 1 mm, and so may be mounted on the sheath. However, the RFID antenna is generally configured as a coil around an area. In this case, the antenna may be long and thin, and wrapped around the sheath. For example, the antenna may be embedded in the sheath, or
35 additively printed on its surface.

The identification may also be a linear bar code on the sheath, or a QR code on the handle or tag associated with the handle end of the device. This may be printed or laser inscribed.

According to another embodiment, the identification is provided on a sample collecting chamber (cup) into which

the collected sample, i.e., the brush, sponge tip, and fluid withdrawn into the sheath, is placed after biopsy. In that case, the RFID may be a module inside the sample collecting container, outside the sample collecting container, or embedded in the wall or top of the sample collecting container. The sample collecting container may have a pocket for retaining the brush inside it. The sample collecting container may be prefilled with a preservative and/or fixative solution. Typically, the tip of the biopsy device is severed before placement into the sample collection container. The pocket may be securely closed about the tip, to prevent reopening outside of the pathology lab without evidence of tampering. Alternately, the pocket may have a reopenable flap closure.

The sponge tip has limited fluid absorption and therefore when withdrawn into the sheath, is not squeezed to discharge its fluid payload. For example, expansion of the sponge when absorbing fluid may be 0-30%. For example, absorption may be largely by capillary action rather than expansion.

In some cases, the RFID is separable from the biopsy device, and is manually transferred with the tip to (or in conjunction with) the sample collecting container.

Alternately, the RFID device may act similarly to a contactless RF credit card, e.g., according to NFC (en.wikipedia.org/wiki/Near-field_communication) or other standard, such as ISO/IEC 14443. Instead of storing the information in the device, the device provides secure authentication for itself, which links to a record which then is access based on proof of authenticity of the device, based on a cryptographic handshake. Access to confidential information may then require that the subsequent user, which is e.g., at the pathology lab, have verified credentials. For example, a physician who takes a sample may program the patient record for a specific lab. Alternately, a lab may provide its biopsy devices to physicians, and only it can then read and use the electronically stored information using a private key or PIN.

The biopsy device may have a writable RFID device, and the information written may be encrypted or cryptographically protected. The need for RFID arises from avoidance of contact, which in the case of biopsy specimens, may be associated with biohazards and contamination. On the other hand, RFID allows reading and writing of tags without breaching a sanitary or sealed enclosure. The writable RFID device may include various relevant parts of the procedure record and/or the patient record, though prudence dictates that the information stored should be curtailed to that required or reasonably relevant for the analysis and reporting of the biopsy device. In some cases, the biopsy device is stored after receipt, for example it may include forensic evidence, and in that case, it may be advantageous for the tag to include chain of custody, storage conditions, and the like, which can be updated or automatically updated after initial sampling.

In accordance with another embodiment of the invention, a multiple sample biopsy device is provided, capable of obtaining and segregating a plurality of biopsy samples taken in a single session. In accordance with this embodiment, the biopsy instrument is placed at an anatomical orifice, such as a cervical os or anus. Advantageously, a protrusion provides a positional reference with respect to the outer portion of the orifice, similar to the aforementioned cervical stop. This protrusion may be part of the design, or an added element to achieve the desired depth-of-insertion reference function.

The multiple sample biopsy device may advantageously be automatically controlled with an electronic microcontroller. In this case, the selection and actuation of the multiple sample components may be automatic, controlled by a microcontroller. Similarly, in some cases, the biopsy sampling may benefit from automated control. For example, the collection of different isolated liquid specimens during a procedure may entail a controlled vacuum source, and sample isolation. The samples may also be electronically labelled and identity managed based on an electronic or RFID tag.

The biopsy device according to the multiple sample embodiment provides a plurality of biopsy sampling tools, which

may each be the same or different, e.g., an endocervical sampler, an endometrial sampler, a punch sampler, and an endometrial sampler with suction. Each tool is provided as a device inside a sheath, such as a 1.5-4mm tube, which is operable by a guidewire to extend the tool sampling head beyond the end of the sheath, twist with respect to the sheath, and retract the tool sampling head back within the sheath.

- 5 In addition to providing control over advancing the biopsy tool with respect to the sheath, each sheath is controllable to be selectively inserted into the orifice, and advance into the organ with the biopsy tool retracted into the sheath, and to be removed from the organ with the biopsy tool retracted into the sheath.

- In some cases, the sheath itself may be articulable or angularly guidable to direct the biopsy tool to a desired region. The articulable sheath may be a single axis, i.e., a curvature of the end of the sheath, typically as a result of a tension on a
10 tensile element such as cable, guidewire or filament attached to the wall of the sheath. A shape memory alloy (SMA), such as titanium-nickel alloy, may be used as a thermally-controlled actuator. The temperature may be controlled ohmic heating with a control current. By controlling the angle of curvature, and the rotational angle of the sheath with respect to the organ, a reasonable range of control is provided. The SMA elements may be selectively provided at positions along the length of the sheath, and actuated by a signal along a serial control line, which is received by an addressable serial receiver integrated circuit
15 embedded in the sheath. Multiple receivers may be provided, thus providing possibility of complex motions.

 Similarly, a punch, or snare, or encapsulating biopsy device may also be controlled by a tension, which may be a wire or polymer filament, or SMA actuator. The case of a single guidewire with a single degree of freedom (advance/retract) is a simplest case, but additional controls and degrees of freedom may be provided.

- In some cases, "blind" sampling may be accomplished, for example within a short canal, or at a distal portion of the
20 organ with respect to the orifice.

- In other cases, e.g., within a lumen of a larger organ, some imaging guidance is preferred. Therefore, the device may be used with an endoscope, and/or include an endoscopic camera, such as a 1-3mm endoscopic camera. Typically, such devices rely on fiber optics from the tip to the imager, for both illumination and imaging. However, according to one embodiment of the technology, the imager circuit and lens are present at the tip of the scope, which in turn is disposed proximate to the end of
25 the biopsy sampling device, to provide direct and real-time imaging of the biopsy procedure.

- For example, On Semiconductor provides various suitable devices, such as the MT9V115 1/13" VGA, OV6922 1/18" ¼ VGA imager, and OVM6946 1/18" 400x400 imager, which may be included as part of a subminiature module that transmits the image as a data stream over an electrical interconnection (or wirelessly). The imager is typically provided with a field of view facing the biopsy tool, with a set of LEDs, or LED illuminated fibers, illuminating the field. While the camera is not required in
30 all modes of operation, i.e., all sampling procedures, if provided, it may remain inserted into the orifice throughout the procedure. The camera may be present near the end of the sheath and advanced with the respective sheath of the biopsy tool into the organ during the procedure. The control for electronics including imaging functions and/or network communications may be based on a Linux or real-time Linux controller, and for example may include or be similar to a Raspberry Pi 4, ESP32, or other known controller or multi-core controller. Typically, a medical device will not employ consumer-grade devices or
35 operating systems, unless no harm can come to the patient from aberrant operation of the device. In the case of a biopsy device, harm is possible, and therefore secure hardware and software is preferred, with code and peripheral device authentication.

 Advantageously, a video signal from an imager may be carried using the guidewire(s) which control the biopsy tool

as electrical power and/or signal carriers. Note that the operating voltage is typically low, e.g., <3.3V, so a dangerous condition for the patient would not typically be present in case of electrical leakage. However, the power carrying members may be insulated to further reduce risk and enhance signal integrity. A wireless transmission may also be provided, for example to a nearby wireless receiver, avoiding the need for wired transmission. In that case, the device may have a self-contained battery, receive operating power over a conductor which advantageously may include the guidewire, or received power through inductive coupling. Since the preferred guidewire is multi-stranded, power and ground, and even signal, may be transmitted if the strands are mutually insulated. There is no compelling reason why a guidewire needs to be uninsulated, so this permits enhanced use of an existing structure, at low added cost and complexity. The tip of the device may include LED lighting. Indeed, in some cases, a fluorescent dye which selectively highlights suspect tissue may be employed, and a UV LED used to fluoresce the dye, to reveal areas that should be particularly sampled. In some cases, the dye is a UV activated therapeutic agent. In that case, the biopsy component of the catheter is optional.

The biopsy device according to one multiple biopsy sample embodiment provides a barrel cartridge with the various biopsy tools in angularly displaced positions, or a linear or rectangular array of biopsy tools. One way to selectively activate certain tools is to provide the barrel with a single active position, in which the manipulator controlled by the user provides functional control over a single one of the plurality of biopsy tips, e.g., extension and retraction of the sheath, and extension, retraction and rotation of the guidewire. As discussed above, a function for articulation of the sheath by tension on another actuation filament may also be provided. The remaining biopsy tools in the barrel may remain restrained in their undeployed positions, e.g., clamped in position. Therefore, the number of degrees of freedom for the actuator may be limited to the maximum required by any single tool, plus tool selection.

Because the barrel or array has a larger dimension than the minimum sheath diameter for a single tool, the barrel or array is maintained outside of the organ orifice, and a mechanism for engaging and disengaging each respective biopsy tool is also outside the organ orifice, which, for example, may rotate into position to release one tool while locking the others in retracted position. Thus, a relatively large array (circular or in a spatial array), e.g., 4-20mm, may be provided with 2-30 biopsy tools in reserve. The end of the barrel or actuator mechanism advantageously serves as the cervical stopper, to limit insertion distance of the sheath into the organ, e.g., uterus, and provide a well-defined positional reference.

According to one embodiment, each biopsy tool in the device is separate (i.e., has a distinct predetermined guidewire actuator), with no changeover in control. Thus, for a biopsy device with four deployable biopsy tools, there are four separate sheaths with respective guidewires extendable from the cartridge. This permits a physician to select the appropriate biopsy tools for a respective procedure, from generic or custom designs. The unused tools remain outside of the organ, while an active tool is in use. In some cases, multiple tools may be advanced into the organ, for example where an endoscope is provided as one of the available tools, and not linked to a particular or single biopsy tool.

On the other hand, in a second embodiment, a mechanism may be provided to mechanically separately engage e.g., the sheath, guidewire, and articulation wire for each separate biopsy tool, with a single control system extending from the cartridge which includes the multiplexed biopsy control paths, as well as an additional biopsy tool selection path. For example, a multi-way clamp, bayonet socket, quick-release, SMA actuator, or magnetic mechanism may be provided to individually engage the respective biopsy tool in the active position. The cartridge is typically round, and centered at the orifice during the procedure, so that the non-deployed biopsy devices are eccentric within the cartridge when not in use. As they are brought into the active position, such as by rotation of a lockout/clamp control, and centering, the controls for that respective

biopsy tool are also connected and made active.

A camera may also be attached to the active biopsy tool and advanced together with it. Alternately, the camera is inserted in advance of the biopsy tool, and is separately positioned from the biopsy tools.

5 It is noted that one or more tools may include an elastic, fluid-absorptive, textured surface to abrade a surface to expose and sample tissue, either alone or as part of another tool. According to one embodiment, the absorptive structure when dry is abrasive, and as it is hydrated, it becomes more pliant. The absorptive element may be impregnated with a salt or polymer, which is dissolved after brief exposure to intrauterine fluid.

10 In some cases, an electrical or electronic mechanism may be provided in the cartridge, for example to latch the mechanical controls, extend the sheath to a desired depth of insertion, rotate the brush, and retract the sheath and/or biopsy brush into the sheath. Typically, the extension of the biopsy brush and axial manipulation are user controlled, and not automated, though a completely automated biopsy is possible.

15 It is preferred that each biopsy tool have a mechanical limiter to control and constrain the movements within a predetermined range, wherein the predetermined range may differ for the various biopsy tools depending on their intended use of application. This helps avoid user error and resulting patient harm, and also helps reliably obtain usable specimens. Advantageously, axial control limits are referenced to the exterior surface surrounding the orifice of insertion, and the end of the barrel, a ring or protrusion surrounding the barrel, used to maintain this position reference without slipping into the orifice.

20 For example, the endocervical brush will typically have the sheath extend 0-2 cm past the orifice, and an endometrial brush will typically have the sheath extend 2-10 cm past the cervix, into the uterus, and a brush biopsy tool will extend 1-3 cm beyond the end of the sheath. The endocervical and endometrial brushes may be provided with or without suction, which may be provided by mechanical action of a plunger as the guidewire controlling the brush is withdrawn into the sheath, or by a vacuum provided through the sheath from the cartridge or beyond.

25 According to another embodiment, instead of a plunger, O-ring or piston within the sheath immediately proximal to the brush and distal to the cervical stop, it is also possible to generate a sampling vacuum at a more proximal region of the biopsy device, e.g., that is not inserted into the cervix, and has a larger diameter. This may be at or distal to the cervical stop. Thus, the volume drawn into the sheath by displacement of the guidewire at this wider cross section region will exceed the volume of the brush tip, permitting a larger volume sample, and/or higher vacuum force. A fluid, such as water, saline or silicone oil, may be provided in the sheath surrounding the guidewire, to permit hydraulic communication of the vacuum instead of pneumatic communication. The water, saline or oil may be confined to the device, and isolated from the biopsy sample and patient.

30 A puncher or cup biopsy tool are typically used under visual observation with the video imager, and may be less mechanically constrained in this circumstance, since the user is presumed to have control over the device during use.

Therefore, the present design permits multiple biopsies to be taken in a single session, from different regions of the organ, and maintained segregated from each other. From a patient perspective, this is advantageous, because the sampling procedure is facilitated, and the combined time and economic burden will typically be less than if separate biopsy tools are employed. Further, compatibility with a single imager used for a plurality of biopsy procedures is also efficient. Finally, in the case of a cartridge that disconnects from a standard handle, the cartridge provides an efficient way to organize and label (identify) the samples from a single patient, and makes pathological examination of the various samples from the same

patient and same organ more efficient. Finally, because each sample is accurately depth labelled with respect to the orifice, clinically important information is obtained, as compared to traditional biopsy tools which do not provide an accurate depth reference. It is noted that a memory card, such as a micro-SD card, may be associated with the cartridge, which includes video and/or manipulation history information for each biopsy tool, which is automatically recorded and maintained, and which may be readily passed to the pathologist or made part of the patient's record. As discussed above, a non-contact electronic identification and/or information storage and/or secure authentication device may be employed, such as an ISO 14443 RFID device, to avoid contamination issues when using a contact device. Alternately, a barcode may be employed which allows reading of a record in a database or distributed database/blockchain.

It is an object to provide a flexible coaxial tissue sampling device, comprising: a sheath having a wall and a hollow space inside the wall; a displaceable wire within the hollow space, the displaceable wire having a first end extending from a proximal end of the sheath and second end configured, in a first state, to extend from a distal end of the sheath, and in a second state, to retract into the distal end of the sheath; the second end of the displaceable wire comprising a suction element, a cellular sampling structure, and a porous absorptive material, wherein the cellular sampling structure and the porous absorptive material are external to the sheath in the first state and internal to the sheath in the second state and the suction element is proximal to the cellular sampling structure and the porous absorptive material; the flexible coaxial structure being configured such that a tension on the first end of the displaceable wire at the proximal end of the sheath results in a retraction of the displaceable wire from the first state to the second state, to cause a displacement into the sheath of the displaceable wire and a corresponding proximal displacement of suction element, the cellular sampling structure, and the porous absorptive material, with suction of media external to the sheath into the distal end of the sheath, the porous absorptive material being configured to retain a fluid sample obtained in the first state after transition to the second state.

It is also an object to provide a flexible coaxial tissue sampling device, comprising: a sheath having a wall and a hollow space inside the wall; a displaceable wire within the hollow space, the displaceable wire having a first end extending from a proximal end of the sheath and second end configured, in a first state, to extend from a distal end of the sheath, and in a second state, to retract into the distal end of the sheath; the second end of the displaceable wire comprising a cellular sampling structure and a porous absorptive material, wherein the cellular sampling structure and the porous absorptive material are external to the sheath in the first state and internal to the sheath in the second state; the flexible coaxial structure being configured such that a tension on the first end of the displaceable wire at the proximal end of the sheath results in a retraction of the displaceable wire from the first state to the second state, to cause a displacement into the sheath of the displaceable wire, the cellular sampling structure, and the porous absorptive material, the porous absorptive material being configured to retain a fluid sample obtained in the first state after transition to the second state and to protect tissue from contact with the second end of the displaceable wire.

It is a further object to provide a biopsy method, comprising: providing a flexible coaxial structure comprising a sheath having a wall and a hollow space inside the wall; a displaceable wire within the hollow space, the displaceable wire having a first end extending from a proximal end of the sheath and second end configured, in a first state, to extend from a distal end of the sheath, and in a second state, to retract into the distal end of the sheath; the second end of the displaceable wire comprising a cellular sampling structure and a porous absorptive material, wherein the cellular sampling structure and the porous absorptive material are external to the sheath in the first state and internal to the sheath in the second state; inserting the distal end of the sheath through a cervix, past the internal cervical os, into a uterus, while the flexible coaxial

structure is in the second state; pushing the first end of the displaceable wire into the sheath, to cause the flexible coaxial structure to assume the first state; manipulating the displaceable wire to obtain a cellular sample with the cellular sampling structure rubbing against the endometrium and the porous absorptive material absorbing fluid while protecting the endometrium from intrusion by a tip of the displaceable wire; applying a tension on the first end of the displaceable wire at the proximal end of the sheath to cause a retraction of the displaceable wire from the first state to the second state, and consequent withdrawal of the displaceable wire, the cellular sampling structure, and the porous absorptive material into the sheath, while retaining the absorbed fluid in the porous absorptive material; and capping the distal end of the sheath with the porous absorptive material to prevent contamination of a biopsy sample retained on the cellular sampling structure by cells within the cervix and vagina.

10 The cellular sampling structure may comprise a brush having a plurality of radially extending bristles from the displaceable wire and terminating in the porous absorptive material comprising an atraumatic bulb, covered by an open cell foam layer,

further comprising a suction element displaceable with the displaceable wire and proximal to the cellular sampling structure and the porous absorptive material, configured to create a negative pressure within the sheath distal to the suction element when the displaceable wire is withdrawn into the sheath.

15 The porous absorptive material may cap the second end of the displaceable wire and protects tissue from damage by a tip of the displaceable wire. The porous absorptive material may be formed at a tip of the second end of the displaceable wire. The porous absorptive material in the second state and the sheath may together protect a biopsy sample within the sheath obtained during transition from the first state to the second state from contamination during withdrawal of the distal end from a patient. The porous absorptive material may be adapted for absorbing a biopsy sample for nucleic acid analysis. The porous absorptive material may be a sponge.

The cellular sampling structure may comprise a brush. The brush may comprise a plurality of bristles extending radially from the displaceable wire.

25 The coaxial structure may be configured to be inserted through an internal cervical os of a uterus of a human to retrieve an endometrial biopsy sample, having a depth adjustable during a biopsy procedure while the coaxial structure is maintained in the first state, by sliding of a depth stop on the sheath.

30 The coaxial structure may be configured to be inserted to a determined depth through an internal cervical os of a uterus of a human, to retrieve an endometrial biopsy sample, and to be withdrawn from the cervix. The coaxial structure may be further configured to be: inserted into the cervical os with the displaceable structure in the second state to a predetermined depth; extended into the first state with the cellular sampling structure within the uterus; manipulated by a user by movement of the first end of the displaceable structure to dislodge cells within the uterus; retracted into the second state within the uterus, to cause the vacuum to withdraw a liquid sample surrounding the cellular sampling structure in to the distal end of the sheath; and retracted from the cervical os with the displaceable structure in the second state.

35 The cellular sampling structure may comprise a spirally twisted steel wire with bristles extending therefrom, welded to a proximal guidewire.

The porous absorptive material formed at the second end may comprise a urethane foam provided over a cap terminating the spirally twisted steel wire.

The sheath may have an outer diameter of about 0.15" and a length between 20 and 50 cm.

The tissue sampling device may further comprise a slidable skirt stopper provided on an exterior surface of the flexible sheath, configured to prevent insertion of the flexible sheath within the uterus of a patient beyond an axial location of the skirt stopper.

5 One embodiment provides at least two flexible coaxial structures, each having a respective sheath, a respective displaceable wire, a respective suction element, a respective cellular sampling structure and a respective porous absorbent material; and a housing, configured to selectively engage and disengage a respective displaceable wire of a respective flexible structure to a user interface, such that when engaged, tension and compression are passed from the user interface to the displaceable structure to transition the displaceable structure between the first state and the second state, and when disengaged, tension and compression are not passed from the user interface to the displaceable structure.

10 The tissue sampling device may further comprise an electrical motor configured to move the displaceable structure, e.g., axially and rotationally.

It is therefore an object to provide a tissue sampling device, comprising: a flexible sheath having at least a distal portion configured to maintain an internal vacuum; a displaceable structure within the sheath, to form a coaxial structure; the displaceable structure having a first end extending from a proximal end of the sheath and second end configured to, in a first state, extend from a distal end of the sheath, and in a second state, to be retracted into the distal end of the sheath; the second end of the displaceable structure having a cellular sampling structure, preceded by a proximal suction element and having a distal porous absorptive material formed at the distal tip; and the coaxial structure being configured such that a tension on the first end of the displaceable structure at the proximal end of the sheath results in a retraction of the displaceable structure from the first state to the second state, to generate the suction to cause a displacement of media external to the sheath into the sheath distal to the piston.

20 The tissue sampling device may further comprise an element displaceable with the displaceable structure, configured to create a negative pressure within the tubular sheath distal to the element when the displaceable wire is withdrawn into the tubular sheath.

The cellular sampling structure may comprise a brush.

25 The brush may comprise a plurality of bristles extending radially from the displaceable structure. The brush may have a helical cross-section profile.

The coaxial structure may be configured for insertion to a predetermined depth into a cervical os of a uterus of a human, to retrieve an endometrial biopsy sample, and to be withdrawn from the cervical os of the uterus.

30 The coaxial structure may be further configured to be: inserted into the cervical os with the displaceable structure in the second state to a predetermined depth; extended into the first state with the cellular sampling structure within the uterus; manipulated by a user by movement of the first end of the displaceable structure to dislodge cells within the uterus; retracted into the second state within the uterus, to cause the vacuum to withdraw a liquid sample surrounding the cellular sampling structure in to the distal end of the sheath; and retracted from the cervical os with the displaceable structure in the second state.

35 The cellular sampling structure may comprise spirally twisted steel wire with bristles extending therefrom, welded to a proximal guidewire. The distal porous absorptive material formed at the distal tip may comprise a urethane foam provided over a cap terminating the spirally twisted steel wire.

The sheath may have an outer diameter of about 0.15" and a length between 20 and 50 cm.

The tissue sampling device may further comprise a skirt stopper provided on an exterior surface of the flexible sheath, configured to prevent insertion of the flexible sheath within the uterus of a patient beyond an axial location of the skirt stopper. The skirt stopper may comprise a flanged element on an outer surface of the flexible sheath, and the flexible sheath is configured for insertion into the cervical os of a uterus of a human to the predetermined depth, to retrieve an endometrial biopsy sample from inside the uterus, and to be withdrawn from the cervical os of the uterus after the endometrial biopsy sample is obtained, further configured to be: inserted into the cervical os with the displaceable wire in the second state to the predetermined depth; extended into the first state with the cellular sampling device within the uterus; manipulated by movement of the first end of the displaceable wire to dislodge endometrial cells; retracted into the second state within the uterus, to draw the vacuum to withdraw a liquid sample surrounding the cellular sampling device in to the distal end of the tubular sheath; and retracted from the cervical os with the displaceable wire in the second state.

The tissue sampling device may further comprise a plurality of flexible sheaths, each having at least a distal portion configured to maintain an internal vacuum; a respective of displaceable structure within each flexible sheath, to form a set of coaxial structures; and a housing, configured to selectively attach a respective displaceable structure to a user interface, such that when engaged, tension and compression are passed from the user interface to the displaceable structure to transition the displaceable structure between the first state and the second state, and when disengaged, tension and compression are not passed from the user interface to the displaceable structure.

The tissue sampling device may further comprise an electrical motor configured to displace the displaceable structure. The tissue sampling device may further comprise an electrical motor configured to rotate the cellular sampling structure.

It is also an object to provide a multiple-sample biopsy device, comprising: a plurality of flexible sheaths; a displaceable structure within each sheath, to form a coaxial structure; each displaceable structure having a first end extending from a proximal end of the sheath and second end configured to, in a first state, extend from a distal end of the sheath, and in a second state, to be retracted into the distal end of the sheath; the second end of the displaceable structure having a cellular sampling structure distally terminated in a porous absorptive foam; and a housing, configured to selectively attach a respective displaceable structure to a user interface, such that when engaged, tension and compression are passed from the user interface to the displaceable structure to transition the displaceable structure between the first state and the second state, and when disengaged, tension and compression are not passed from the user interface to the displaceable structure.

It is also an object to provide a tissue sampling method, comprising: providing a coaxial structure, comprising a flexible sheath having at least a distal portion configured to maintain an internal vacuum, and a displaceable structure within the sheath, to form a coaxial structure, the displaceable structure having a first end extending from a proximal end of the sheath and second end configured to, in a first state, extend from a distal end of the sheath, and in a second state, to be retracted into the distal end of the sheath, and the second end of the displaceable structure having a cellular sampling structure, preceded by a piston and terminated by a porous absorptive tissue-abrasive structure; and applying a tension on the first end of the displaceable structure at the proximal end of the sheath to cause retraction of the displaceable structure from the first state to the second state, generating the vacuum.

The coaxial structure further may comprise a skirt around the flexible sheath, configured to limit an insertion depth of the flexible sheath into a human cervix.

The coaxial structure may be configured for insertion into the cervical os of uterus of a human to the predetermined

insertion depth defined by an axial position of the skirt around the flexible sheath, to retrieve an endometrial biopsy sample, and to be withdrawn from the cervical os of the uterus.

5 The method may further comprise: inserting the distal portion of the coaxial structure into the cervical os of a uterus, with the displaceable structure in the second state to the predetermined depth; extending the distal portion of the coaxial structure into the first state with the cellular sampling structure within the uterus; manipulating the first end of the displaceable structure to dislodge cells within the uterus; retracting the coaxial structure into the second state within the uterus, to cause the vacuum to withdraw a liquid sample surrounding the cellular sampling structure in to the distal end of the sheath; and retracting the distal portion of the coaxial structure from the cervical os with the displaceable structure in the second state.

10 The cellular sampling structure may comprise a brush having a plurality of radially extending bristles from the displaceable structure and terminating in an atraumatic bulb, covered by an open cell foam layer.

The cellular sampling structure may comprise a spirally twisted flexible wire with bristles extending therefrom, may further comprise twisting the guidewire to thereby rotate the cellular sampling structure.

15 It is another object to provide a flexible coaxial biopsy device, comprising: a tubular sheath having a wall configured to maintain an internal vacuum with respect to an exterior of the tubular sheath; a displaceable wire within the tubular sheath; and a cellular sampling device distally terminated with a porous absorptive structure, each of the cellular sampling device and the porous absorptive structure being configured to disrupt a surface of a tissue, mounted on the displaceable structure distal to the element, configured to protrude from a distal end of the tubular sheath when the displaceable element is disposed in a first state, and to be contained within the distal end of the tubular sheath when the displaceable element is
20 disposed in a second state.

The flexible coaxial biopsy device may further comprise a flanged element on an outer surface of the tubular sheath, configured to limit a depth of insertion of the tubular sheath into a cervix.

The cellular sampling device may comprise a plurality of bristles extending outwards from the displaceable wire, terminating at the distal end in an atraumatic bulb covered by the porous absorptive structure comprising a foam layer.

25 The flexible coaxial biopsy device may be configured for insertion into the cervical os of a uterus of a human to the predetermined depth, to retrieve an endometrial biopsy sample from inside the uterus, and to be withdrawn from the cervical os of the uterus after the endometrial biopsy sample is obtained.

The flexible coaxial biopsy device may further comprise an element that creates a negative pressure within the tubular sheath when the displaceable wire is withdrawn into the tubular sheath.

30 The biopsy brush described above may also be revised for use as an anal biopsy brush, and an endometrial biopsy brush and anal biopsy brush may be provided together as a kit, optionally alone with a vial of preservative solution (for a single brush), or a plurality of vials of preservative for a kit. The kit is preferably a sterile package, which may be double wrapped, containing the biopsy brush or bushes, a vial or vials of preservative, and optionally an acceptable lubricant for cytological sampling, and optionally a disposable sterile sheet or drape.

35 The anal biopsy brush differs from an intrauterine biopsy brush in that it will be shorter, since the working distance between the physician or caregiver and patient orifice is less. The, for intrauterine use, the sheath is typically 20-25 cm long, with a 4 cm long brush and 2 cm exposed guidewire, such that the wire is 26-31 cm long, past the end of the handle to which it is bound, with a skirt on the sheath about 4 cm from the distal end.

An anal biopsy brush sheath will typically be 8-12 cm long, with the skirt about 4 cm from the distal end. For example, an anal biopsy brush may have a sheath 8 cm long with the skirt located 4 cm from the distal end, having a guidewire 14-18 cm long for sampling in the rectum up to 6 cm past the end of the sheath. The absorptive tip is preferably provided.

- 5 A kit may therefore include a long intrauterine biopsy device having a sheath length of about 20 cm, a short anal biopsy device having a sheath length of about 8 cm, two vials of cytological preservative, a packet of water-based cytologically acceptable lubricant (e.g., Surgilube®, which preferably does not include carbomers), a sterile drape, and package insert labelling instructions (which may be imprinted on the packaging as appropriate). Any lubricant should be applied on the exterior of the sheath, between the skirt or flange and distal tip, with the brush in the retracted position, with care taken to
- 10 avoid getting lubricant on the end of the sheath or brush.

BRIEF DESCRIPTION OF THE DRAWINGS

- Figs. 1 and 2 show a first embodiment of the biopsy device according to the present invention with a cylindrical sponge cap in the retracted and extended state.
- 15 Figs. 3 and 4 show a prior art Tao Brush in the retracted and extended state with respect to the sheath, respectively; Figs. 5 and 6 show a second embodiment of the biopsy device according to the present invention with a round cap, in the retracted and extended state;
- Fig. 7 shows transfer of the biopsy sample to a tube containing brush cytology preservative;
- Figs. 8A and 8B show a Pipelle endometrial biopsy device of the prior art, in the extended and retracted states,
- 20 respectively;
- Figs. 9 and 10A-10C show a prior art endometrial biopsy brush with suction, according to U.S. patent Nos. 9,351,712, 8,920,336, 8,517,956, and 8,348,856;
- Fig. 11 shows a guidewire and biopsy brush according to the present invention with a sponge covering an atraumatic bulb;
- 25 Fig. 12 shows a narrow sheath with skirt stopper installed according to the present invention;
- Fig. 13 shows a complete biopsy device with manually operable handle, skirt stopper, sheath, guidewire, brush, O-ring, and a sponge covering an atraumatic bulb according to the present invention;
- Fig. 14 shows an arrangement of an independently controllable, biopsy multiple sample, biopsy device showing four similar biopsy sampling tools;
- 30 Fig. 15 shows an arrangement of an independently controllable, biopsy multiple sample, biopsy device showing four different biopsy sampling tools;
- Fig. 16 shows a detail of a selector which permits manipulation of a single biopsy sampling tool in a barrel cartridge;
- Fig. 17 shows a skirt stopper according to the present invention;
- Fig. 18 shows a side perspective view of a prototype biopsy device, having an absorptive sponge material at the distal
- 35 tip of the biopsy device, with a schematic representation of absorption of a sample;
- Fig. 19 shows a specimen collection container, with a pocket to retain the biopsy brush;
- Fig. 20A shows insertion of a prior art biopsy tool into the uterus;
- Fig. 20B shows manipulation of a prior art biopsy tool into the uterus for tissue sampling;

Fig. 20C shows withdrawal of a prior art sampling brush into a sheath for subsequent removal from the uterus;

Fig. 21A shows a side view of vaginal canal/uterus in cross section;

Fig. 21B shows that the device according to the present invention travels into the vaginal canal, enters cervix, and stops when the skirt touches the cervix with the brush encased within the sheath inside the uterus; and

5 Fig. 21C shows the brush extending in full length of the inside the cavity of the uterus, with an absorptive sponge covering an atraumatic bulb and the distal tip.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Example 1: A preferred embodiment of the present invention consists of an intrauterine biopsy device having an
10 outer thin walled tube of approximately 2.25 mm outside diameter and 1.2 mm inside diameter; length is between 20-50 cm, e.g., 22 cm. This tube may be a clear, bendable but self-supporting plastic tube, made e.g., of nylon. The guidewire is preferably a twisted stainless steel wire of approximately 0.1-0.2 mm diameter, having sufficient mechanical properties to convey the forces for extension and retraction of the brush during use. At the distal end of the guidewire is a biopsy brush, shown in Figs. 8 and 11, tipped with an atraumatic bulb. The brush may be about 4 cm long, and extend about 2 cm past the
15 end of the sheath when extended. The O-ring preferably remains within the sheath over the entire range of travel, to avoid problems re-engaging the end of the sheath. For example, the O-ring (or more generally, plunger attached to the wire) may be, for example, 2-5 mm from the end of the sheath when extended.

An anal biopsy device may also be provided, having an outer thin walled tube of approximately 2.25 mm outside diameter and 1.2 mm inside diameter; length is between 8-12, e.g., 8 cm. This tube may be a clear, bendable but self-
20 supporting plastic tube, made e.g., of nylon. The guidewire is preferably a twisted stainless steel wire of approximately 0.1-0.2 mm diameter, having sufficient mechanical properties to convey the forces for extension and retraction of the brush during use. At the distal end of the guidewire is a biopsy brush, shown in Figs. 8 and 11, tipped with an atraumatic bulb. The brush for the anal biopsy device may also be 4 cm long, with the O-ring or plunger 2-5 mm from the end of the sheath when the brush is extended.

25 The wire may be periodically marked, such as in 1 cm increments, so that the physician or biopsy device operator can estimate the brush insertion with respect to the proximal end of the sheath.

At one end, the one that enters the uterus or anus, the biopsy brush is formed. A tight-fitting O-ring around the guidewire, similar to that shown in Figs. 10A-10C, acts as a piston and creates the suction as the obturator is withdrawn through the outer thin walled tube.

30 In another embodiment, the O-ring may be disposed about 2.5 cm from the tip, with the brush extending about 1.5 cm from the tip, with 1 cm of bare wire between them.

As shown in Figs. 9, 10 and 11, a skirt stopper is provided about the exterior of the thin walled tube, near the distal end, which may be in fixed position or manually slidable. The skirt is approximately 1 cm in diameter, and may be formed of nylon, polyurethane, silicone, neoprene, or other medically acceptable plastic or rubber. Typically, the skirt is fixed in position,
35 and may be glued (e.g., UV activated methyl-methacrylate adhesive) or molded to the sheath in position.

The biopsy device is use as follows: (a) The brush is retracted completely into the outer sheath. (b) The sheath is inserted, through the vagina, into the cervix, until the skirt stopper meets the external os of the cervix. The tip of the brush should be displaced from the fundus. (c) The outer sheath is pulled back until it stops, i.e., abuts the handle. The brush is then

rotated by holding the sheath still and turning the handle. For example, the brush may be rotated in a clockwise manner until a reference mark on the handle indicates completion of a 360° turn, and then rotated counterclockwise until the reference mark on the handle indicates completion of a -360° turn. Alternately, the brush may be rotated in only one direction by completing 4 or 5 360° rotations. In some cases, the brush may be repositioned axially, though it should not be withdrawn into the sheath until the sampling is completed. (d) After sampling with the brush, the guidewire is pulled at the handle, until the sheath hits the stop (e.g., the edge of the handle), thereby suctioning fluid surrounding the tip into the sheath, and then withdrawing the brush into the sheath. (e) After withdrawal of the device from the vagina, the brush and fluids in the sheath are immersed in a cytology preservative, such as formalin, and the sample is washed from the brush into the preservative by moving the brush in and out of the sheath immersed in the fluid.

10 The invention may be used, for example, to sample the inside of the uterus to diagnose abnormalities. It can detect or exclude a cancer. It can obtain an adequate tissue sample to determine infertility causes.

The anal brush is similarly employed. Such a biopsy tool typically has a shorter sheath and guidewire than an endocervical brush biopsy tool, because of the easier anatomical access. For example, the sheath may be 10-15 cm long, and the brush may extend 2-6 cm beyond the end of the sheath. As with the endocervical brush biopsy tool described above, a skirt is preferably provided which prevents insertion of the sheath into the anus beyond the sheath, to provide a physical reference distance for insertion. In some cases, the skirt may be repositioned on the sheath, to permit the physician the ability to determine at what depth of insertion the sample should be acquired. Advantageously, the readjustment requires more force than would be available by applying an unconstrained compression of the sheath against the skirt stopper, so that the position is maintained during use, but the stiction force can be overcome when the biopsy tool is external to the body.

20 A rough absorptive tip may be provided to abrade the uterine surface and absorb a liquid sample during the biopsy.

Example 2: According to a second embodiment, a multiple sample biopsy device is provided, capable of obtaining and segregating a plurality of biopsy samples taken in a single session. This therefore requires a plurality of biopsy brushes or tools, and a plurality of sheaths in which the tools are extended and retracted.

25 As discussed above, a depth of insertion positional reference, such as a skirt stopper may be provided. However, where the multiple biopsy tool system has a mechanism maintained outside of the orifice, the diameter of the tool may be sufficiently large to act as the stopper without additional structures.

According to one design, each biopsy tool is separate, including a sheath and guidewire control. A set of biopsy tools are aggregated in an outer tube housing. The tube has a conical internal profile at the distal end, so that a single biopsy tool may be advanced past the end of the housing, into the orifice or canal from which a biopsy is to be taken. In some cases, endoscopic guidance of the biopsy is desired, and in that case, a second sheath which supports the endoscope and lighting may be advanced as well. The endoscope sheath may also inject saline for visualization, though in the case of a brush biopsy, this is disfavored, since the saline will wash away the dislodged cells, and reduce the positional accuracy of sampling. An inert gas, such as CO₂ may also be injected through the sheath, in known manner. One or more tools may have a rough absorptive tip may be provided to abrade the uterine surface and absorb a liquid sample during the biopsy.

35 For example, the biopsy brush may be provided in a 3 mm tube, with 6 separate brushes provided within a housing. A stop may be provided at the proximal end of each sheath within the housing, to prevent over-withdrawal. Markings may be provided on each sheath, to inform the physician about the depth of insertion. In some cases, the physician may intend graduated sampling at a series of depths in the orifice, and advantageously, each respective sheath may have a stopper which

limits its depth of insertion, and provides the physician with haptic feedback when that depth is achieved. This stopper may be a simple O-ring or clamp, which is adjusted by the physician for each biopsy sampling tool, before the procedure. The guidewire for each sampling tool may also have depth limits. Of course, the retracted position with the biopsy tool fully withdrawn into the sheath represents one extreme, and a clamp or limit may be provided on the manipulation end to control how far the guidewire may be extended beyond the end of the sheath.

In this first design, each biopsy brush may be of known type, with the optional addition of the insertion and retraction limiters, and an optional absorptive tip, and indeed, the housing for arranging a multiple biopsy sample session may itself may be provided independent of the biopsy brushes. Note that the absorptive structure need not be at the extreme tip, and in fact may be displaced in some cases. In general, the larger housing diameter avoids the need for a separate skirt stopper, though the housing may terminate in a skirt stopper.

Example 3: According to a second design of the multiple sample biopsy device, a single manipulator extends from a housing, which itself contains a plurality of biopsy tools.

As discussed above, a depth of insertion positional reference, such as a skirt stopper may be provided. However, where the multiple biopsy tool system has a mechanism maintained outside of the orifice, the diameter of the tool may be sufficiently large to act as the stop without additional structures.

Thus, a selectively engageable coupling is provided between a single guidewire and the various tools. The coupling thus links the guidewire, that extends to a physician manipulation interface, such as a grasping element, a handle, or a pivotal mechanism, to the individual guidewire for each tool. Advantageously, the plurality of tools are provide in a rotating barrel, which serves as the housing. Each biopsy tool, when engaged with the manipulation guidewire, can be advanced with its respective sheath an insertion distance, and then the biopsy head advanced beyond the sheath, and twisted or otherwise manipulated to obtain a biopsy sample. The biopsy head is then withdrawn back into the sheath, the sheath with biopsy head covered then withdrawn back into the cartridge, and the barrel twisted so another biopsy tool may then be engaged.

Therefore, the coupling is a coaxial coupling, which separately links and controls the sheath and the guidewire within each respective sheath. For example, within the cartridge, the end of the sheath may terminate in a steel ring, which is magnetically permeable. Thus, a magnetic coupling can be used to connect and disconnect the sheaths. Further, the inactive biopsy tools may also be held in place by another magnet, which is typically an electromagnet, or a permanent magnet with an electromagnetic release. The guidewire may be selectively connected to the external manipulation guidewire with a spring-loaded clamp. As the barrel is turned, the spring-loaded clamp releases, and re-engages as it reaches the next detent position with the next biopsy tool aligned with the spring clamp. Within the barrel, the guidewire from the biopsy tool extends beyond the proximal end of the respective sheath.

The barrel is typically at least as long as the desired depth of insertion of the sheath into the patient. Thus, if it is desired to have a 12 cm depth of insertion, the barrel mechanism may be 13-16 cm long.

As shown in Fig. 14, a plurality of similar brushes are provided in a cartridge. In Fig. 15 a plurality of different brushes are provided in the cartridge. The cartridge has an exit port for the engaged biopsy tool. Each brush has its own associated sheath, which may be independently advanced into the patient, depending on which tool is engaged. A mechanism at the proximal end of the housing controls the selection of the barrel position by an angle of rotation, the latching of the sheath of the respective active tool to the tool advancement control, the clamping of the guidewire of the respective active tool to the guidewire control for manipulation by the physician, and in some cases, other controls, such as deflection angle of the sheath.

Fig. 16 shows an end view of a portion of the mechanism in the barrel, wherein one guidewire is free to be manipulated by the physician, while access for manipulation of the other guidewires is locked out.

Fig. 14 shows a bulb provided just proximal to each sampling brush, which is provided to draw a sampling vacuum when the respective brush is withdrawn back into the sheath.

5 In Fig. 15, only one biopsy tool has such a feature. The biopsy sampling tools, may be, for example, an endocervical sampler, an endometrial sampler, a punch sampler, and an endometrial sampler with suction.

In some cases, the sheath itself may be articulable or angularly guidable to direct the biopsy tool to a desired region. The articulable sheath may be a single axis, i.e., a curvature of the end of the sheath, typically as a result of a tension on a tensile element such as cable, guidewire or filament attached to the wall of the sheath, not shown in the figures... By
10 controlling the angle of curvature, and the rotational angle of the sheath with respect to the organ, a reasonable range of control is provided. Similarly, a punch, or snare, or encapsulating biopsy device may also be controlled by a tension, which may be a wire or polymer filament. Thus, the case of a single guidewire with a single degree of freedom (advance/retract) is a simplest case, and additional controls and degrees of freedom may be provided. Note that an SMA actuator may also be used to alter the tension. The controls for these tools may also be selectively engaged through a mechanism, or provided
15 individually to the user.

An endoscopic imager (not shown in the figures) may be provided, preferably as a feature of the housing, so that it may be used with various biopsy tools within the housing. For example, a 1-3mm endoscopic camera with fiber optic or direct LED lighting, may be provided, e.g., the On Semiconductor OVM6946 1/18" 400x400 imager.

Example 4: Fig. 18 shows a side perspective view of a prototype biopsy device, having an absorptive sponge
20 material at the distal tip of the biopsy device. A longer foam tip allows for more fluid absorption but requires that the brush is shorter for the same length device. The foam may have a length of 0.25". The absorptive foam tip is placed over an acrylic ball at the end of the guidewire, which is free from bristles for the length of the foam. The foam may be attached to the brush by using FEP heat shrink to compress the proximal end of the foam, and applying UV glue (Loctite 4011 or 4306 or AA 3979) prior to removing the heat shrink.

25 The sheath has an OD of 0.150". When retracted, the maximum fluid sample drawn by the vacuum was 0.51 ml. The volume absorbed by the foam tip was 0.03-0.05 ml for water and 0.62-0.72 for 5000 cSt fluid.

The brush may be straight natural 6-12 Nylon filament, on a 304SS core, terminated in an acrylic ball. The twisted wire for the brush is welded to the core wire proximate to the brush. The preferred embodiment dimensions are as follows:

Overall Length: $12" \pm 0.125"$, Distance from Tip to Bristles: 0.25"
30 Core Wire 304SS spring tempered, Diameter: 0.018", Twisted Wire 304SS Diameter 0.037"
Brush Diameter: $0.118" \pm 0.010"$, Brush Length: $1.25" \pm 0.125"$
Bristles Straight Natural 6-12 Nylon Filament 0.003" Single Stem/Single Spiral, angled at 45° from the core wire
Acrylic Ball on Tip: $0.055" \pm 0.015"$ Diameter

The handle is, e.g., textured and ergonomically shaped with a concave profile, Tecoflex 60D with 20% BaSO₄, about
35 1.5" long and 0.313" diameter.

The skirt is polycarbonate (Calibre 2061) or silicone, 0.787" diameter, 0.742" long, with a biconic intersection profile with angles of 30° and 60°, and smoothed edges.

Nusil Med-360 silicone fluid, 1000 cP, may be used to lubricate the sheath, and seal the vacuum draw mechanism.

The plunger for drawing vacuum is 0.118" long, 0.135" diameter formed of NuSil-4970 silicone, and has sealing surfaces at each end with a central recess. The plunger is compression fit around the wire, proximal to the brush.

The foam tip is, for example, a urethane foam, which in a prototype was obtained from a Puritan 1135 Purswab® foam-tipped applicator (Puritan Medical Products Co., Guilford, ME), though in practice, will be custom made.

5 The device is designed to maximize cell collection during the biopsy process in doctor's office. It combines global endometrial disruption using a brush, with a built-in suction process and absorption, created by a sponge. A series of tests allowed selection of an optimal brush. It has a smaller diameter, compared to its competitors ($0.118" \pm 0.010"$ and length of $1.25" \pm 0.125"$) promoting a reduction in discomfort during the procedure, while providing a satisfactory tissue sampling.

10 After tissue disruption is completed, the sponge tip absorbs additional fluid and material and the device creates a vacuum that aspirates further tissue sample into the device sheath. The idea of aspiration differs from suction used in other devices. The suction will not directly obtain the tissue from the uterine wall, and rather it will aspirate the tissue that was previously scraped off the uterine wall by the brush assuring a better patient experience. The sponge tip prevents the puncture of the uterine wall and due to absorption provides additional tissue collection and fluid intake. A guard (e.g., formed of polycarbonate) rests on the cervix during the procedure and prevents over-insertion of the device.

15 The procedure proceeds as follows:

1. Procedure: Place the patient in lithotomy position, generally shown in Fig. 21A. Gently insert the speculum and open to expose the uterine cervix. Fig. 21A shows a side view of vaginal canal/uterus in cross section. Only the labia, vagina, cervix, and uterus are depicted, as well as an outline of the patient's skin. The position of the pelvis and legs will suggest the patient is in the examination position.
- 20 2. Assure that the brush is completely retracted into the outer sheath.
3. Gently insert the outer sheath of the device though the cervix into the uterus and stop when the skirt (guard) touches the cervix. (Fig. 21B)
4. Extend the brush by gentle push of the handle until resistance of the tip is upon meeting the fundus of the uterus. (Fig. 21C)
- 25 5. Rotate the sampler in a clockwise manner and complete up four or five 360° rotations.
6. The sponge on the tip protects the fundus from piercing. It creates additional tissue sampling by absorption of the fluid and the cells from the uterus.
7. Pull the handle back. The suction created by the plunger located inside of the sheath provides aspiration of the cells and prevents loss of the sample from the brush.
- 30 8. Immediately immerse the sample into the preservative solution, see Fig. 7 or Fig. 19.
9. Handle the sample and brush as directed by the pathology lab.

Fig. 18 shows a detail of a tip of the biopsy brush, wherein a sponge sits at the tip of the device, distal to the brush, and provides cushioning of the tip as well as a volume for sampling of cell-containing fluid from the endometrium.

35 Fig. 19 shows a specimen collection container, with a pocket to retain the biopsy brush, e.g., after it is cut or severed from the full biopsy device. The specimen collection container may have an RFID, bar code, or 2D bar code (or QR code) for identification. In some cases, the RFID is transferred from the full biopsy device to the specimen collection container with the biopsy brush portion thereof. The pocket may be tamper-evident, and thus provide increased security and authentication through the chain of transport.

CLAIMS

What is claimed is:

1. A flexible coaxial tissue sampling device, comprising:
a sheath having a wall and a hollow space inside the wall;
5 a displaceable wire within the hollow space, the displaceable wire having a first end extending from a proximal end of the sheath and second end configured, in a first state, to extend from a distal end of the sheath, and in a second state, to retract into the distal end of the sheath;
the second end of the displaceable wire comprising a suction element, a cellular sampling structure, and a porous absorptive material, wherein the cellular sampling structure and the porous absorptive material are external to the sheath in
10 the first state and internal to the sheath in the second state and the suction element is proximal to the cellular sampling structure and the porous absorptive material;
the flexible coaxial structure being configured such that a tension on the first end of the displaceable wire at the proximal end of the sheath results in a retraction of the displaceable wire from the first state to the second state, to cause a displacement into the sheath of the displaceable wire and a corresponding proximal displacement of suction element, the
15 cellular sampling structure, and the porous absorptive material, with suction of media external to the sheath into the distal end of the sheath, the porous absorptive material being configured to retain a fluid sample obtained in the first state after transition to the second state.
2. The tissue sampling device according to claim 1, wherein the porous absorptive material caps the second end of the displaceable wire and protects tissue from damage by a tip of the displaceable wire.
- 20 3. The tissue sampling device according to claim 1, wherein the porous absorptive material is formed at a tip of the second end of the displaceable wire.
4. The tissue sampling device according to claim 1, wherein the porous absorptive material in the second state and the sheath protect a biopsy sample within the sheath obtained during transition from the first state to the second state from contamination during withdrawal of the distal end from a patient.
- 25 5. The tissue sampling device according to claim 1, wherein the porous absorptive material is adapted for absorbing a biopsy sample for nucleic acid analysis.
6. The tissue sampling device according to claim 1, wherein the porous absorptive material is a sponge.
7. The tissue sampling device according to claim 1, wherein the cellular sampling structure comprises a brush.
8. The tissue sampling device according to claim 7, wherein the brush comprises a plurality of bristles
30 extending radially from the displaceable wire.
9. The tissue sampling device according to claim 1, wherein the coaxial structure is configured to be inserted through an internal cervical os of a uterus of a human to retrieve an endometrial biopsy sample, having a depth adjustable during a biopsy procedure while the coaxial structure is maintained in the first state, by sliding of a depth stop on the sheath.
10. The tissue sampling device according to claim 1, wherein the coaxial structure is configured to be inserted
35 to a determined depth through an internal cervical os of a uterus of a human, to retrieve an endometrial biopsy sample, and to be withdrawn from the cervix.
11. The tissue sampling device according to claim 10, wherein the coaxial structure is further configured to be: inserted into the cervical os with the displaceable structure in the second state to a predetermined depth;

extended into the first state with the cellular sampling structure within the uterus;
manipulated by a user by movement of the first end of the displaceable structure to dislodge cells within the uterus;
retracted into the second state within the uterus, to cause the vacuum to withdraw a liquid sample surrounding the
cellular sampling structure in to the distal end of the sheath; and

5 retracted from the cervical os with the displaceable structure in the second state.

12. The tissue sampling device according to claim 1, wherein the cellular sampling structure comprises a
spirally twisted steel wire with bristles extending therefrom, welded to a proximal guidewire.

13. The tissue sampling device according to claim 12, wherein the porous absorptive material is provided at the
second end and comprises a urethane foam provided over a cap terminating the spirally twisted steel wire.

10 14. The tissue sampling device according to claim 1, wherein the sheath has an outer diameter of about 0.15"
and a length between 20 and 50 cm.

15. The tissue sampling device according to claim 1, further comprising a slidable skirt stopper provided on an
exterior surface of the flexible sheath, configured to prevent insertion of the flexible sheath within the uterus of a patient
beyond an axial location of the skirt stopper.

15 16. The tissue sampling device according to claim 1, comprising:
at least two flexible coaxial structures, each having a respective sheath, a respective displaceable wire, a respective
suction element, a respective cellular sampling structure and a respective porous absorbent material; and
a housing, configured to selectively engage and disengage a respective displaceable wire of a respective flexible
structure to a user interface, such that when engaged, tension and compression are passed from the user interface to the
20 displaceable structure to transition the displaceable structure between the first state and the second state, and when
disengaged, tension and compression are not passed from the user interface to the displaceable structure.

17. The tissue sampling device according to claim 1, further comprising an electrical motor configured to move
the displaceable structure.

25 18. A flexible coaxial tissue sampling device, comprising:
a sheath having a wall and a hollow space inside the wall;
a displaceable wire within the hollow space, the displaceable wire having a first end extending from a proximal end
of the sheath and second end configured, in a first state, to extend from a distal end of the sheath, and in a second state, to
retract into the distal end of the sheath;

30 the second end of the displaceable wire comprising a cellular sampling structure and a porous absorptive material,
wherein the cellular sampling structure and the porous absorptive material are external to the sheath in the first state and
internal to the sheath in the second state;

35 the flexible coaxial structure being configured such that a tension on the first end of the displaceable wire at the
proximal end of the sheath results in a retraction of the displaceable wire from the first state to the second state, to cause a
displacement into the sheath of the displaceable wire, the cellular sampling structure, and the porous absorptive material, the
porous absorptive material being configured to retain a fluid sample obtained in the first state after transition to the second
state and to protect tissue from contact with the second end of the displaceable wire.

19. The tissue sampling device according to claim 18,
wherein the cellular sampling structure comprises a brush having a plurality of radially extending bristles from the

displaceable wire and terminating in the porous absorptive material comprising an atraumatic bulb, covered by an open cell foam layer;

further comprising a suction element displaceable with the displaceable wire and proximal to the cellular sampling structure and the porous absorptive material, configured to create a negative pressure within the sheath distal to the suction element when the displaceable wire is withdrawn into the sheath.

20. A biopsy method, comprising:

providing a flexible coaxial structure comprising a sheath having a wall and a hollow space inside the wall; a displaceable wire within the hollow space, the displaceable wire having a first end extending from a proximal end of the sheath and second end configured, in a first state, to extend from a distal end of the sheath, and in a second state, to retract into the distal end of the sheath; the second end of the displaceable wire comprising a cellular sampling structure and a porous absorptive material, wherein the cellular sampling structure and the porous absorptive material are external to the sheath in the first state and internal to the sheath in the second state;

inserting the distal end of the sheath through a cervix, past the internal cervical os, into a uterus, while the flexible coaxial structure is in the second state;

pushing the first end of the displaceable wire into the sheath, to cause the flexible coaxial structure to assume the first state;

manipulating the displaceable wire to obtain a cellular sample with the cellular sampling structure rubbing against the endometrium and the porous absorptive material absorbing fluid while protecting the endometrium from intrusion by a tip of the displaceable wire;

applying a tension on the first end of the displaceable wire at the proximal end of the sheath to cause a retraction of the displaceable wire from the first state to the second state, and consequent withdrawal of the displaceable wire, the cellular sampling structure, and the porous absorptive material into the sheath, while retaining the absorbed fluid in the porous absorptive material; and

capping the distal end of the sheath with the porous absorptive material to prevent contamination of a biopsy sample retained on the cellular sampling structure by cells within the cervix and vagina.

21. A tissue sampling device, comprising a coaxial structure comprising a flexible tubular sheath having at least a distal portion configured to maintain an internal vacuum and a displaceable structure within the sheath, the displaceable structure having a first end extending from a proximal end of the sheath and second end configured to, in a first state, extend from a distal end of the sheath, and in a second state, to be retracted into the distal end of the sheath, the second end of the displaceable structure having a cellular sampling structure, preceded by a proximal suction element and having a porous absorptive material, and the coaxial structure being configured such that a tension on the first end of the displaceable structure at the proximal end of the sheath results in a retraction of the displaceable structure from the first state to the second state, to generate the suction to cause a displacement of media external to the sheath into the sheath distal to the piston.

22. The tissue sampling device according to claim 21, wherein the porous absorptive material is formed at the distal tip of the second end.

23. The tissue sampling device according to claim 21, wherein the porous absorptive material is adapted for absorbing a biopsy sample for nucleic acid analysis.

24. The tissue sampling device according to claim 21, wherein the porous absorptive material is a sponge.

25. The tissue sampling device according to claim 21, wherein the porous absorptive material is a sponge formed at the distal tip of the second end.

26. The tissue sampling device according to claim 21, further comprising a pump, configured to create a negative pressure within the sheath distal to draw therein a fluid biopsy sample.

5 27. The tissue sampling device according to claim 21, wherein the cellular sampling structure comprises a brush.

28. The tissue sampling device according to claim 27, wherein the brush comprises a plurality of bristles extending radially from the displaceable structure.

29. The tissue sampling device according to claim 27, wherein the brush has a helical cross-section profile.

10 30. The tissue sampling device according to claim 21, wherein the coaxial structure is configured for insertion to a predetermined depth into an internal cervical os of a uterus of a human, to retrieve an endometrial biopsy sample, and to be withdrawn from the cervix.

31. The tissue sampling device according to claim 30, wherein the coaxial structure is further configured to be:
15 inserted into the cervical os with the displaceable structure in the second state to a predetermined depth;
extended into the first state with the cellular sampling structure within the uterus;
manipulated by a user by movement of the first end of the displaceable structure to dislodge cells within the uterus;
retracted into the second state within the uterus, to cause the vacuum to withdraw a liquid sample surrounding the
cellular sampling structure in to the distal end of the sheath; and
retracted from the cervix with the displaceable structure in the second state.

20 32. The tissue sampling device according to claim 21, wherein the cellular sampling structure comprises a spirally twisted steel wire with bristles extending therefrom, welded to a proximal guidewire.

33. The tissue sampling device according to claim 32, wherein the porous absorptive material is provided at the second end distal and comprises a urethane foam provided over a cap terminating the spirally twisted steel wire.

25 34. The tissue sampling device according to claim 21, wherein the sheath has an outer diameter of about 0.15" and a length between 20 and 50 cm.

35. The tissue sampling device according to claim 21, further comprising a skirt stopper provided on an exterior surface of the sheath, configure to prevent insertion of the sheath within the uterus of a patient beyond an axial location of the skirt stopper.

30 36. The tissue sampling device according to claim 35, wherein the skirt stopper comprises a flanged element on an outer surface of the sheath, and the sheath is configured for insertion into the internal cervical os of a uterus of a human to the predetermined depth,

further configured to be:
inserted into the internal cervical os with the displaceable wire in the second state to the predetermined depth;
extended into the first state with the cellular sampling device within the uterus;
35 manipulated by movement of the first end of the displaceable wire to dislodge endometrial cells;
retracted into the second state within the uterus, to draw a vacuum to withdraw a liquid sample surrounding the
cellular sampling device into the distal end of the sheath; and
retracted from the cervical os with the displaceable wire in the second state.

37. The tissue sampling device according to claim 21, comprising:
a plurality of flexible sheaths, each having at least a distal portion configured to maintain an internal vacuum;
a respective of displaceable structure within each flexible sheath, to form a set of coaxial structures; and
a housing, configured to selectively attach a respective displaceable structure to a user interface, such that when
5 engaged, tension and compression are passed from the user interface to the displaceable structure to transition the
displaceable structure between the first state and the second state, and when disengaged, tension and compression are not
passed from the user interface to the displaceable structure.

38. The tissue sampling device according to claim 21, further comprising an electrical motor configured to
axially displace the displaceable structure.

10 39. The tissue sampling device according to claim 21, further comprising an electrical motor configured to
rotate the cellular sampling structure.

40. A multiple-sample biopsy device, comprising:
a plurality of flexible sheaths;
a displaceable structure within each sheath, to form a coaxial structure;
15 each displaceable structure having a first end extending from a proximal end of the sheath and second end
configured to, in a first state, extend from a distal end of the sheath, and in a second state, to be retracted into the distal end of
the sheath;

the second end of the displaceable structure having a cellular sampling structure distally terminated in a porous
absorptive foam; and
20 a housing, configured to selectively attach a respective displaceable structure to a user interface, such that when
engaged, tension and compression are passed from the user interface to the displaceable structure to transition the
displaceable structure between the first state and the second state, and when disengaged, tension and compression are not
passed from the user interface to the displaceable structure.

41. A tissue sampling method, comprising:
25 providing a coaxial structure, comprising a flexible sheath having at least a distal portion configured to maintain an
internal vacuum, and a displaceable structure within the sheath, to form a coaxial structure, the displaceable structure having
a first end extending from a proximal end of the sheath and second end configured to, in a first state, extend from a distal end
of the sheath, and in a second state, to be retracted into the distal end of the sheath, and the second end of the displaceable
structure having a cellular sampling structure, preceded by a piston and terminated by a porous absorptive tissue-abrasive
30 structure; and

applying a tension on the first end of the displaceable structure at the proximal end of the sheath to cause retraction
of the displaceable structure from the first state to the second state, generating the vacuum.

42. The method according to claim 41, wherein the coaxial structure further comprises a skirt around the
flexible sheath, configured to limit an insertion depth of the flexible sheath into a human cervix.

35 43. The method according to claim 42, wherein the coaxial structure is configured for insertion into the internal
cervical os of uterus of a human to the predetermined insertion depth defined by an axial position of the skirt around the
flexible sheath, to retrieve an endometrial biopsy sample, and to be withdrawn from the cervix.

44. The method according to claim 43, further comprising:

inserting the distal portion of the coaxial structure into the cervical os of a uterus, with the displaceable structure in the second state to the predetermined depth;

extending the distal portion of the coaxial structure into the first state with the cellular sampling structure within the uterus;

5 manipulating the first end of the displaceable structure to dislodge cells within the uterus;

retracting the coaxial structure into the second state within the uterus, to cause the vacuum to withdraw a liquid sample surrounding the cellular sampling structure in to the distal end of the sheath; and

retracting the distal portion of the coaxial structure from the cervix in the second state.

45. The method according to claim 41, wherein the cellular sampling structure comprises a brush having a plurality of radially extending bristles from the displaceable structure and terminating in an atraumatic bulb, covered by an open cell foam layer.

46. The method according to claim 41, wherein the cellular sampling structure comprises a spirally twisted flexible wire with bristles extending therefrom, further comprising twisting the guidewire to thereby rotate the cellular sampling structure.

15 47. A flexible coaxial biopsy device, comprising:

a tubular sheath having a wall configured to maintain an internal vacuum with respect to an exterior of the tubular sheath having a displaceable wire within the tubular sheath; and

20 a cellular sampling device distally terminated with a porous absorptive structure, each of the cellular sampling device and the porous absorptive structure being configured to disrupt a surface of a tissue, mounted on the displaceable structure distal to the element, configured to protrude from a distal end of the tubular sheath when the displaceable element is disposed in a first state, and to be contained within the distal end of the tubular sheath when the displaceable element is disposed in a second state.

48. The flexible coaxial biopsy device according to claim 47, further comprising a flanged element on an outer surface of the tubular sheath, configured to limit a depth of insertion of the tubular sheath into a cervix.

25 49. The flexible coaxial biopsy device according to claim 47, wherein the cellular sampling device comprises a plurality of bristles extending outwards from the displaceable wire, terminating at the distal end in an atraumatic bulb covered by the porous absorptive structure comprising a foam layer.

50. The flexible coaxial biopsy device according to claim 47, configured for insertion into the internal cervical os of a uterus of a human to the predetermined depth, to retrieve an endometrial biopsy sample from inside the uterus, and to be withdrawn from the external cervical os of the uterus after the endometrial biopsy sample is obtained.

30 51. The flexible coaxial biopsy device according to claim 47, further comprising an element that creates a negative pressure within the tubular sheath when the displaceable wire is withdrawn into the tubular sheath.