

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In the *Inter Partes* Review of:

Trial Number: To Be Assigned

U.S. Patent No. 7,004,913

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Attorney Docket No.: 22344.04363

Inventor(s): Mark Rutenberg et al.

Panel: To Be Assigned

Assignee: CDx Laboratories, Inc.

Title: RETRACTABLE BRUSH FOR USE
WITH ENDOSCOPE FOR BRUSH
BIOPSY

Mail Stop *Inter Partes* Review
Commissioner for Patents
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PETITION FOR *INTER PARTES* REVIEW UNDER 37 C.F.R. 42.100

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On behalf of U.S. Endoscopy Group, Inc. (“U.S. Endoscopy”) and in accordance with 35 U.S.C. § 311 and 37 C.F.R. § 42.100, *inter partes* review is respectfully requested for claims 1-3 of U.S. Patent No. 7,004,913 (“the ‘913 Patent”)(Exhibit 1001).

I. OVERVIEW OF THE PETITION

The ‘913 Patent is directed to a brush for use in gathering samples of a very specific type of epithelium tissue--glandular epithelium. That is all it claims. Nothing more — nothing less. The ‘913 Patent has the exact same specification as its parent, U.S. Patent No. 6,676,609 (“the ‘609 Patent”). Not surprisingly, the ‘913 Patent is plagued by the same problem as its parent: both the problem and solution proposed by the ‘913 Patent and its parent are found in the prior art.

Like its parent, the ‘913 Patent states that a need exists for a brush that obtains complete biopsy samples, albeit limited to glandular epithelium tissue samples. Of course, this had been performed and disclosed years before the ‘913 Patent was even filed. Moreover, the ‘913 Patent relies on an undisclosed stiffness of brush bristles that generate “sufficient pressure” to gain allowance of its claims. The problem for the ‘913 Patent is that the prior art discloses all of this: the problem, the solution, the delivery method and even the simple idea of making the brush stiffer.

Finally, the ‘913 Patent relies on functional language to describe its apparatus yielding another sticky problem for the patentee—if the USPTO believes that the prior art inherently possesses the claimed function, it is the patentee’s burden to somehow rebut this finding. Given the simplicity of this claimed invention, that is not easily done.

In view of the prior art that is submitted with this Petition, this patent should have never issued. Petitioner thus respectfully requests that the petition be granted and that the USPTO cancel claims 1-3 of the ‘913 Patent.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(a)(1)

A. Real Party-In-Interest Under 37 C.F.R. § 42.8(b)(1)

The Petitioner, U.S. Endoscopy Group, Inc. (“U.S. Endoscopy”), is the Real Party-In-Interest. U.S. Endoscopy is a wholly-owned subsidiary of STERIS Corporation.

B. Related Matters Under 37 C.F.R. § 42.8(b)(2)

The ‘913 Patent is currently the subject of litigation brought by its putative assignee, CDx Diagnostics, Inc. (“CDx”) against U.S. Endoscopy in the Southern District of New York, Case No. 1:13-cv-5669-NSR. Its parent patent, U.S. Patent No. 6,676,609, is also the subject of a petition for *inter partes* review, filed concurrently herewith.

C. Lead and Back-Up Counsel Under 37 C.F.R. § 42.8(b)(3)

Lead Counsel: Todd R. Tucker (Registration No. 40,850)

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D. Service Information Under 37 C.F.R. § 42.8(b)(4)

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III. PAYMENT OF FEES UNDER 37 C.F.R. § 42.103

The undersigned authorizes the Office to charge the fees as set forth in 37 C.F.R. § 42.15(a) for this Petition for *Inter Partes* Review to Deposit Account No. 03-0172; any additional fees that might also be due are also authorized.

IV. REQUIREMENTS FOR *INTER PARTES* REVIEW UNDER 37 C.F.R. §§ 42.104

As set forth below and pursuant to 37 C.F.R. § 42.104, each requirement for *inter partes* review of the '913 Patent is satisfied.

A. Grounds for Standing Under 37 C.F.R. § 42.104(a)

Petitioner certifies pursuant to Rule 42.104(a) that the patent for which review is sought is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this Petition.

B. Identification of Challenge Under 37 C.F.R. § 42.104(b) and Relief Requested

1. *Claims for Which Inter Partes Review Is Requested Under 37 C.F.R. § 42.104(b)(1)*

Petitioner respectfully requests *inter partes* review of claims 1-3 of the '913 Patent and the cancellation of these claims as unpatentable.

2. *The Specific Art and Statutory Ground(s) on Which the Challenge Is Based Under 37 C.F.R. § 42.104(b)(2)*

Petitioner relies upon the following patents and printed publications:

Exhibit 1003 - U.S. Patent No. 5,535,756 to Parasher ("Parasher '756"), issued on July 16, 1996. Parasher '756 is available as prior art under 35 U.S.C. § 102(b).

Exhibit 1004 – "Endoscopic Retrograde Wire-Guided Cytology of Malignant Biliary Structures Using a Novel Scraping Brush", Vinod K. Parasher, et al. ("Parasher Article"), GASTROINTESTINAL ENDOSCOPY Vol. 48, No. 3, 1998. The Parasher Article is available as prior art under 35 U.S.C. § 102(b).

Exhibit 1005 – U.S. Patent No. 6,297,044 to Eisen ("Eisen"), issued on October 2, 2001. Eisen is available as prior art under 35 U.S.C. § 102(b) because all claims of the '913 Patent are only entitled to the priority date of December 17, 2002.

Exhibit 1006 – U.S. Patent No. 4,759,376 to Stormby ("Stormby"), issued on July 26, 1988. Stormby is available as prior art under 35 U.S.C. § 102(b).

Exhibit 1007 – Olympus 1992 Endo-Therapy System Catalog:

Gastrointestinal Devices (“Olympus Catalog”), printed no later than December 31, 1992. The Olympus Catalog is available as prior art under 35 U.S.C. § 102(b).

Exhibit 1008 – “Exploiting the ‘Toothpick Effect’ of the Cytobrush by Plastic Embedding of Cervical Samples”, by Mathilde Boon, et al. (“Boon”), ACTA CYTOLGICA, Jan-Feb 1991. Boon is available as prior art under 35 U.S.C. § 102(b).

Exhibit 1009 – “Surveillance of Patient’s With Barrett’s Esophagus for Dysplasia and Cancer with Balloon Cytology”, Gary W. Falk, et al. (“Falk”), Gastroenterology Vol. 112, No. 6 1997. Falk is available as prior art under 35 U.S.C. § 102(b).

Supporting Materials

Exhibit 1010 - Expert Declaration of Michel Kahaleh, M.D. (“Kahaleh”).

Petitioner requests cancellation of the challenged claims under the following statutory grounds:

Claim No.	Proposed Statutory Rejections for the ‘913 Patent
1-3	Claims 1-3 are anticipated under 35 U.S.C. § 102(b) by Parasher ‘756
3	Claim 3 is rendered obvious under 35 U.S.C. § 103(a) by Parasher ‘756 in view of Eisen
1-3	Claims 1-3 are rendered obvious under 35 U.S.C. § 103(a) by the Olympus Catalog in view of Eisen

1-3	Claims 1-3 are rendered obvious under 35 U.S.C. § 103(a) by the Olympus Catalog in view of Stormby and the Boon Article
1-3	Claims 1-3 are rendered obvious under 35 U.S.C. § 103(a) by the Olympus Catalog in view of Falk

Section V below demonstrates for each of the statutory grounds that there is a reasonable likelihood that Petitioner will prevail. See 35 U.S.C. 314(a).

3. Overview of the ‘913 Patent

The ‘913 Patent discloses and claims nothing more than a brush for taking a biopsy of a very particular type of epithelial tissue with the brush being deployed in an endoscope. The patent defines a brush biopsy only by identifying what it samples: the outermost surface of the glandular epithelium and the tissue beneath that starting point. The patent, however, does not claim the structure by which this is accomplished, but only claims the function — that the brush bristles exert some sufficient, yet undefined pressure to obtain this biopsy specimen. The patent is notably silent as to any measurement of stiffness or what is this sufficient pressure. Instead, it essentially says make a known brush stiffer:

The new preferred embodiment resembles, at least in appearance, a conventional endoscope with a brush carried therein, but is different from all prior art because of the *stiffness of the bristles of the brush enabling a disaggregated specimen of the whole tissue to be achieved with nonlacerational brushing techniques*. (Ex. 1001 at Col. 7:32-37)(Emphasis added).

The patent, however, makes no mention of what the measure of stiffness should be.

The patent repeats in the Detailed Description that it is nothing more than a stiffer, prior art cytology brush:

[a]lthough the brush illustrated in Fig. 3 may appear similar to cytological brushes, it is different from cytological brushes in the *stiffness of the bristles*, enabling a deeper removal of cells from merely the superficial cytological layer. In the prior art, the bristle strength of the brush merely is to brush the exfoliated top surface of the cells for examination, while in the present invention, *the brush is stiff enough* to reach in through the basement membrane whether for squamous or glandular epithelium, in order to be certain that the brush biopsy of the invention conducts a biopsy, not merely a superficial cytology. (*Id.* at Col. 9:13-24)(Emphasis added).

In other words, the bristles must be stiff enough to permit “reaching beyond the basement membrane, whether in squamous or glandular epithelium.” (*Id.* at Col. 9:27-29). Of course, the ‘913 Patent is silent as to how this is accomplished.

The ‘913 patent’s parent application, now issued patent 6,676,609 (the ‘609 patent), claimed a biopsy brush penetrating into the epithelium. During prosecution of the ‘609 patent, the inventors amended the sole independent claim to specifically include the language “to conduct a biopsy” while further amending the claim to include sampling tissue located below the surface of the epithelium.

Additionally, the inventors argued to the USPTO examiner that a biopsy requires penetrating the uppermost layer of the epithelium and sampling cells in the layer

beneath this top layers and that the invention conducts this biopsy without cutting or lacerating:

The significant aspect of the present invention is the ability to conduct a biopsy of tissue which may lead to early detection of precancerous or cancerous conditions without the need for lacerational biopsy. The brush biopsy employed in this invention allows for sampling of whole tissue below the surface of the epithelium, because it is only with sampling of the entirety of the tissue that one can examine the cells and/or tissue to determine whether or not there are suspect cells. (Ex. 1002.)

During prosecution of the '913 patent, the inventors further amended the claim to include sampling tissue located within ***glandular epithelium***. (Ex. 1002.) The inventors argued to the USPTO examiner that the brush is stiff enough to pass from the uppermost surface, which is identified as basement membrane fragments. The claim was allowed after this amendment and argument.

4. *How the Challenged Claims Are to Be Construed Under 37 C.F.R. § 42.104(6)(3)*

In an *inter partes* review, the claim terms are presumed to have the meanings as detailed below. This Petition shows that the challenged claims of the '913 Patent are unpatentable when they are given their broadest reasonable interpretation in the light of the specification. *See* 37 C.F.R. 42.100(b); *see also In re Yamamoto*, 740 F.2d 1569, 1571 (Fed. Cir. 1984). Claim terms are also given their ordinary and customary meaning as would be understood by one of ordinary

skill in the art in the context of the entire disclosure. *In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Additionally, an inventor may act as his or her own lexicographer, so long as the definition is set forth in the specification with reasonable clarity, deliberateness and precision. *Renishaw PLC v. Marposs Societa' Per Azioni*, 158 F.3d 1243, 1249 (Fed. Cir. 1998).

“Channel extending the length of the endoscope”: – This phrase appears in Claim 1 and in the Specification at Col. 9, lines 24-27. (Ex. 1001.) On its face, it appears that the limitation should be afforded its ordinary meaning: **“an opening in an endoscope through which the brush passes”**. That said, the patentee’s questionable claim drafting has potentially created a situation where the claim limitation is insolubly ambiguous. The claim preamble reads “an apparatus to be used in conjunction with an endoscope...” but then the claim limitation reads a “said apparatus comprising a channel extending the length of the endoscope”, thereby seemingly claiming that the channel of the apparatus is something other than the channel of the endoscope. Thus, the claim should be afforded its broadest reasonable interpretation, which could encompass an opening in an endoscope, a channel or sleeve inside an opening in an endoscope or it is indefinite.

“Rod passing through said channel having a distal and a proximal end”:

This phrase appears in Claim 1. The term should be afforded its broadest

reasonable construction, which Petitioner submits is: “an elongated member whose distal end passes through a channel.”

“Retractable”: This phrase appears in the claims and in the Specification, although in the Specification it used in at least two different ways. Thus, it must be construed to cover both embodiments. The first embodiment is shown in Figures 1-2 where the disclosed brush includes two “jaws” that close shut and this is described as “retractable”. (Ex. 1001.) This brush also is pulled back or retracted into the channel. The second embodiment, seen in Figure 3, simply discloses pulling the brush into the channel which is described as “retractable”. Because the claim typically should cover both embodiments, the second definition of “retractable” must be applied. Accordingly, “retractable” means **“the brush is moved into the channel.”**

“Non-lacerational brush”: This terms appears in Claim 1 and is specifically defined by the patentee in the ‘913 Patent. In Column 2, Line 31 of the patent, the inventors without issue delineate that the term “lacerational” means “to incise or excise (i.e. lacerate) the lesion with a either a scalpel or a laser... .” (Ex. 1001.) The patentee further explains that non-lacerational is not a scalpel, is minimally invasive and to the extent it causes minor discomfort or bleeding, it is still somehow different than prior art scalpel trauma:

[f]or purposes of this patent application, the prior art scalpel procedure is defined as lacerational, whereas the novel invention herein is non-lacerational and therefore minimally invasive. To the extent that an abrasive brush has characteristics that may cause minor discomfort and or bleeding, there is substantial difference between the prior art scalpel trauma and the minimal trauma associated with the present invention. (*Id.* at Col. 6:25-32).

By starting this passage with the phrase “for purposes of this patent application,” the patentee made a clear indication that it is acting as its own lexicographer for the term “non-lacerational” and that this and only this definition can be applied to non-lacerational. Thus, the proper construction for “non-lacerational brush” is a **“brush that does not cut like a scalpel or laser, is minimally invasive and causes no more than minor discomfort and/or bleeding”**.

“Bear against the tissue being examined”: This term is entitled its broadest plain and ordinary meaning which is **“a brush that contacts the tissue”**.

“Being controlled by said rod to remove tissue from a tissue area being examined”: This term is also entitled to its broadest meaning which Petitioner submits is **“operating the rod to cause the brush to penetrate, drill or scrape into tissue”**.

“Said Brushing Apparatus”: This term has no antecedent basis so the patentee is forcing one of skill in the art to guess what is being claimed. That said, for purposes of this *inter partes* review, the patentee’s lack of claim drafting clarity forces one of skill in the art to assume that they are claiming a brush.

“Bristles which exert sufficient pressure to dislodge cells and pick up a specimen from said uppermost surface and said tissue therebelow”: this limitation is entitled to its broadest, most reasonable interpretation. Petitioner submits that for this *inter partes* review that the proper construction is “bristles having penetrating edges of a sufficient stiffness to obtain a biopsy sample including cells located below the surface layer of the epithelium where the epithelium is glandular epithelial tissue having a surface layer and a basement membrane.

“Glandular epithelium tissue”: A type of epithelium that secretes and is often found in ducts such as the bile duct. It includes at least a superficial or top layer and a basement membrane. These rest on the submucosa. (Ex. 1010, Kahaleh Declaration at ¶ 10.)

“Disaggregated specimen”: CDx specifically defined this term in the “Field of the Invention”. (Ex. 1001 at Col. 1: 34-37). The definition provided is that disaggregated specimen of the whole tissue means “at least glandular cells of

the top or superficial layer plus basement membrane fragments plus elements at the lamina propria”. To one of skill in the art, the term “lamina propria” means “submucosa”.

V. DETAILED EXPLANATION UNDER 37 C.F.R. §§ 42.104(b)(4) OF HOW THE CONSTRUED CLAIMS ARE UNPATENTABLE

A. Statement of Non-redundancy

The grounds raised in the following sections are meaningfully distinct from one another and rely upon fundamentally different types of cite prior art references. Petitioner urges the Board to adopt each ground of unpatentability presented in this Petition for at least the following reasons.

B. Claims 1-3 are anticipated by Parasher ‘756

This section explains on an element-by-element basis exactly how Parasher ‘756 anticipates claims 1-3 of the ‘913 Patent. In short, Parasher ‘756 recognized as early as 1994 the need for a non-lacerating device capable of collecting biopsy tissue samples. (Ex. 1003 at 2:12-20.) Parasher ‘756 satisfied this need with a non-lacerating brush having stiff or semi-rigid bristles. (*Id.* at Abstract; 4:46-59)(Emphasis added.) Moreover, Parasher’s brush could be used with an endoscope to obtain biopsy samples of tissue in the bile duct, pancreatic duct, esophagus, stomach, large bowel, lungs, uterus, ureter, kidney, or the like. (*Id.* at 2:20-40.) In other words, Parasher’s brush had a broad range of uses in the

gastrointestinal tract and its lining of glandular epithelium as well as other areas of the body similarly lined with glandular epithelium tissue.

As can be seen below, Parasher's disclosed brush was a very straight-forward biopsy brush having a brush 3 with semi-rigid bristles 11 disposed within a sleeve 17:

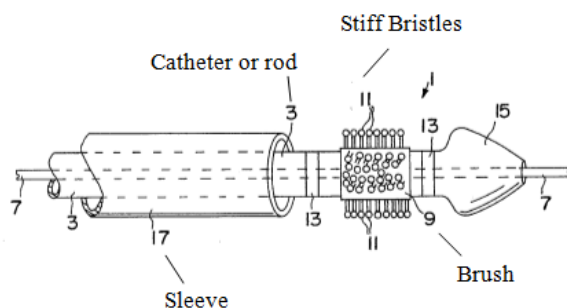


Fig. 3 of Parasher '756 (Annotated)

Additionally, Parasher disclosed in the very first paragraph of the patent that the brush of Figure 3 performed "scrape biopsies of structures within biological ducts." (*Id.* at 1:10-11.) Petitioner submits that without issue Parasher '756 anticipates the claims of the '913 Patent.

1. Claim 1: "An apparatus to be used in conjunction with an endoscope to examine tissue cells located within glandular epithelium, said glandular epithelium comprising tissue at the outermost surface thereof and tissue area below said outermost surface,"

As shown above in Annotated Figure 3, Parasher '756 disclosed a device 1 having a brush 9 with stiff or semi-rigid bristles 11. (*Id.* at Abstract; 4:46-59.)

The bristles 11 permitted the device 1 to collect biopsy tissue samples without laceration. (“[E]nable collection of a sample sufficient to qualify as a biopsy, but in a manner that reduces the risk of perforating the duct as compared with known techniques.”) (*Id.* at 2:17-19). The duct being brush biopsied could be any GI duct or other duct-like organs including the stomach and esophagus. (*Id.* at 2:35-40.) In certain embodiments, the bristles 11 were semi-rigid and had hook ends, ball-tips, mushroom tips, loops or the like that further facilitated collection of the cells and tissue. (*Id.* at Figs. 4a-4c; 5:46-57.)

Parasher ‘756 defined a biopsy sample as a gross tissue sample that includes the mucous lining of the duct, the tissue of the duct, and adjacent connective tissues (*e.g.*, the submucosa). (*Id.* at 1:54-67.) Before Parasher ‘756, biopsy samples were taken using instruments such as biopsy forceps or scalpels that cut away and remove chunks of tissue from the diseased area. (*Id.* at 2:1-10.) Parasher ‘756 disclosed that these prior art lacerational devices were not preferred because they ran the risk of perforating the duct. *Id.* The device 1 of Parasher ‘756, however, permitted the user to obtain the biopsy tissue samples that were equivalent to those obtained in procedures using the prior art lacerational devices without the risk of perforating the duct. (*Id.* at 2:1-40; 3:60-67.) One of ordinary skill in the art would understand that a biopsy sample necessarily includes fragments of the epithelial tissue, as well as portions of the basement membrane

and submucosa below the epithelium. (Ex. 1010 at ¶ 10; *see also* Ex. 1001 at 10:2-4.) (“[T]he brush biopsy of this invention is the equivalent of a lacerational biopsy.”).

Additionally, the device 1 of Parasher ‘756 may be used with an endoscope in order to obtain biopsy tissue samples from numerous areas within the body, for example, the bile duct, pancreatic duct, esophagus, stomach, large bowel, lungs, uterus, ureter, kidney, or the like. (Ex. 1003 at 2:20-40; 3:6-32.)

Moreover, glandular epithelium is a type of epithelium tissue that covers all major glands and is found in the esophagus and intestinal lining, as well as the bile and pancreatic ducts. (Ex. 1010 at ¶¶ 11-12.) Metaplastic glandular epithelial tissue is pre-malignant and potentially cancerous glandular epithelial tissue. (Ex. 1010 at ¶ 14.) Moreover, glandular epithelium has glandular cells on top of a basement membrane which in turn rests on the submucosa. (Ex. 1001 at 9:47-10:1.)

The device 1 of Parasher ‘756 may be used to obtain biopsy samples from internal organs having metaplastic glandular epithelial, such as the bile duct, pancreatic duct, esophagus, stomach, and large bowel. *Id.* Further, the bristles 11 of the brush 9 in Parasher ‘756 extend radially for about 1-3 mm, which is greater than 1000 microns in length, and obviously sufficiently long to reach into the

epithelium and beyond into the basement membrane or submucosa. (Ex. 1003 at 4:59-64.)

Thus, the device 1 of Parasher is an apparatus that may be used in conjunction with an endoscope to examine tissue cells located within glandular epithelium, said glandular epithelium comprising tissue at the outermost surface thereof and tissue area below said outermost surface.

2. Claim 1: “said apparatus comprising a channel extending the length of the endoscope;”

Fig. 3 of the ‘913 Patent (below) shows the preferred embodiment of the invention where the brush is carried within an endoscope.

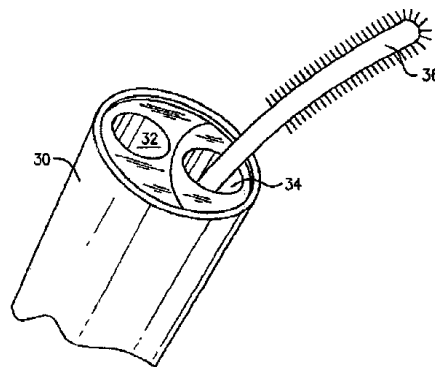


Fig. 3 of the ‘913 Patent

(Ex. 1001 at ‘913 Patent, 9:11-33 and 7:27-37.) (“More importantly, the new preferred embodiment resembles, at least in appearance, a conventional endoscope with a brush carried therein.”). The brush 36 of Fig. 3 merely has an elongate member and bristles, and is illustrated extending from a channel 34 in an

endoscope 30. *Id.* As explained in the ‘913 Patent, “[a]lthough the brush illustrated in Fig. 3 may appear similar to cytological brushes, it is different from cytological brushes in the stiffness of the bristles.” (Ex. 1001 at 9:11-33.) However, the ‘913 Patent fails disclose the actual stiffness, or even a range of stiffness, for the bristles.

In the ‘913 Patent’s grandparent case, U.S. Patent No. 6,494,845, the phrase “said endoscope comprises a channel extending the length of the endoscope” was included as the preamble of claims. (Emphasis added). In the ‘913 Patent (and its parent), the patentee inexplicably switched the term from “endoscope” to “apparatus.” This drafting error injects a potentially non-sensical claim into the mix because the apparatus for use with an endoscope is also the endoscope. Regardless, Parasher ‘756 disclosed that the device 1 is used in a channel of an endoscope that necessarily extends the length of the endoscope. (Ex. 1003 at 3:7-32; 5:58-6:20.) The device 1 of Parasher ‘756 also has a retractable sheath or sleeve 17 that extends through the channel of the endoscope. (*Id.* at 5:33-45; 5:58-6:20.) The sheath or sleeve 17 forms a channel that receives the catheter 3. *Id.* The sheath or sleeve 17 can be moved longitudinally relative to the catheter 3 to cover and expose the brush 9. *Id.* As such, the device 1 of Parasher ‘756 has a channel that extends the length of an endoscope.

3. Claim 1: “said apparatus comprising a rod passing through said channel having a distal and proximal end;”

Parasher ‘756 discloses this claim limitation. The device 1 of Parasher ‘756 comprises a catheter 3 that passes through the retractable sheath or sleeve 17 and also the channel of the endoscope. (*Id.* at Figs. 1-3; 3:7-32; 5:58-6:20.) The catheter 3 has a distal and proximal end. *Id.* Obviously, the catheter operates and is a rod. As such, the device 1 of Parasher ‘756 has a rod passing through the channel having a distal end and proximal end.

4. Claim 1: “a retractable non-lacerational brush attached to the distal end of the rod,”

Parasher ‘756 discloses this limitation. A quick review of Figures 1-3 immediately shows that the brush 9 of Parasher ‘756 is attached to the distal end of the catheter 3. (*Id.* at Figs. 1-3; 4:46-58.) Furthermore, the brush 9 can be retracted into the channel of the endoscope. (*Id.* at 3:7-32.) (“The end of the catheter with the brush is withdrawn from the duct through the endoscope or into a sleeve provided to protect the sample.”); (*Id.* at 5:58-6:20.) It can also be retracted into the sheath or sleeve 17. (*Id.* at 3:1-7; 5:33-45.)

And as explained above, the brush 9 was without issue non-lacerational. As set forth in Parasher ‘756, the brush 9 was capable of collecting tissue samples sufficient to qualify as a biopsy, but in a manner that was safer and reduces the risk

of perforating the duct as compared with known lacerational techniques. (*Id.* at 2:1-40; 3:60-67.) The brush 9 of Parasher ‘756 plainly taught a retractable non-lacerational brush attached to the distal end of a rod.

5. Claim 1: “said brush being movable to bear against the tissue being examined and being controlled by said rod to remove tissue from a tissue area being examined,”

Parasher ‘756 discloses this claim limitation. The catheter 3 of the device 1 can be manipulated by the user such that the brush 9 bears against the tissue examined, removing samples of the tissue that cling to the bristles 11 of the brush. (*Id.* at 3:20-40; 6:1-15.) (“Catheter 3 then is pushed and pulled, back and forth, several times such that sample scrapings of tissue and brushings of cells from the stricture cling to bristles 11 of brush 9, more particularly being captured by the bristle structures.”). Accordingly, the brush 9 of Parasher ‘756 is movable to bear against the tissue being examined and is controlled by a rod to remove tissue from a tissue area being examined.

6. Claim 1: “said brushing apparatus comprising bristles which exert sufficient pressure to dislodge cells and to pick up a specimen from said uppermost surface and said tissue therebelow.”

As explained above in the claim construction section, there is no antecedent basis for the term “said brushing apparatus.” Assuming that this error can be

overcome, Petitioner submits that it is readily apparent that Parasher '756 disclosed this claim limitation. As discussed above, the brush 9 of the device 1 of Parasher '756 had stiff or semi-rigid bristles 11. These stiff or semi-rigid bristles permit the device to collect biopsy tissue samples without laceration. (*Id.* at Abstract; 2:1-40; 4:46-59.) The bristles 11 may have features that further facilitate collection of the cells and tissue, *e.g.*, hook ends, ball-tips, mushroom tips, loops or the like. (*Id.* at Figs. 4a-4c; 5:46-57.) Also, a biopsy sample collected by the bristles 11 of the brush 9 would necessarily include tissue located below the outermost surface of glandular epithelium. (*Id.* at 1:54-67; 2:17-19; 2:35-40; *see also* Ex. 1010 at ¶ 10.) As such, the brush 9 of Parasher '756 comprises bristles which exert sufficient pressure to dislodge cells and to pick up a specimen from the uppermost surface and the tissue area therebelow.

Moreover, the Parasher Article further illustrates that the brush of Parasher '756 was actually used to obtain a biopsy sample of tissue located below the outermost surface of the epithelium.¹ (*See* Ex. 1004.) The Parasher Article is authored by the sole inventor of Parasher '756 and describes patient trials of the device disclosed in Parasher '756. The device used in the trials included a specially designed brush having semi-rigid and rough bristles made from a

¹ The Parasher Article is being used as a secondary reference to show the inherent characteristics of the brush disclosed in Parasher '756, *see* MPEP § 2131.01.

Velcro® pad. (Ex. 1004 at 290-91.) These trials determined that this brush was capable of penetrating the glandular epithelium to obtain a biopsy sample and that the brush design could be used to generate even more scraping force. *Id.* By teaching that it obtained a biopsy, it necessarily establishes that the brush dislodged cells to pick up a specimen of glandular epithelium including its uppermost surface as well as the tissue below (*e.g.*, the basement membrane.)

All limitations of claim 1 are disclosed by Parasher — the claim is without issue anticipated.

7. Claim 2: “An apparatus as set forth in claim 1, wherein said brush bristles are at least 1000 microns in length.”

The claim construction for this limitation is simple—the bristles are least 1000 micron long, (which is 1 mm). Parasher ‘756 disclosed that the bristles 11 of the brush 9 may extend “radially about 1 to 3 mm”—which is 1000-3000 microns. (*Id.* at 4:59-64.) Thus, brush 9 of Parasher ‘756 had bristles 11 that were at least 1000 microns in length and all other limitations are present as described above. Claim 2 is anticipated by Parasher ‘756.

8. Claim 3: “An apparatus as set forth in claim 1, wherein said specimen picked up comprises a disaggregated specimen.”

One of ordinary skill in the art would understand that a biopsy sample necessarily includes fragments of the epithelial tissue, as well as portions of the

basement membrane and submucosa. (Ex. 1010 at ¶ 10; *see* Ex. 1001 at 6:46-53.)

(“By rubbing harder than normal cytological sampling and using a stiff device which penetrates epithelium, one can reach to the basement membrane without lacerating.”). Parasher ‘756 explicitly taught one of skill in the art that its brush obtained this sample. The brush of Parasher ‘756 acquired a biopsy sample that included the mucous lining of the duct, the tissue of the duct, and even adjacent connective tissues (*i.e.*, the submucosa or lamina propria). (*Id.* at 1:54-67.) Its brush had stiff or semi-rigid bristles 11 that permitted the device 1 to collect such biopsy tissue samples without laceration. (*Id.* at Abstract; 2:1-40; 4:46-59.)

Further, the brush 9 has long bristles (*e.g.*, about 1 to 3 mm) more than capable of reaching into the basement membrane or submucosa. (*Id.* at 4:59-64; *see also* Ex. 1010 at 11, 16.) When the device 1 is used to obtain biopsy samples of metaplastic glandular epithelial tissue, the biopsy sample would then obviously be a disaggregated specimen of glandular cells, basement membrane fragments, and elements of the submucosa. Parasher picked up the whole tissue specimen as required by claim 4. Hence, claim 4 is anticipated by Parasher ‘756.

C. Claim 3 is Rendered Obvious by Parasher ‘756 in view of Eisen

This section explains on an element-by-element basis exactly how claim 3 of the ‘913 Patent is rendered obvious by Parasher ‘756 in view of Eisen. First, Eisen is prior art to claims 1-3 because those claims are only supported by the material

added in the patent C-I-P. Eisen is thus prior art under 32 U.S.C. § 102(b).

Second, Parasher '756 recognized as early as 1994 the need for a non-lacerating device capable of collecting biopsy tissue samples. (*Id.* at 2:12-20.) Parasher '756 satisfied this need with a non-lacerating brush having stiff or semi-rigid bristles. (*Id.* at Abstract; 4:46-59)(Emphasis added.) Moreover, Parasher's brush could be used with an endoscope to obtain biopsy samples of tissue in the bile duct, pancreatic duct, esophagus, stomach, large bowel, lungs, uterus, ureter, kidney, or the like. (*Id.* at 2:20-40.) In other words, Parasher's brush had a broad range of uses in the gastrointestinal tract and its lining of glandular epithelium as well as other areas of the body similarly lined with glandular epithelium tissue. Additionally, Parasher disclosed in the very first paragraph of the patent that the brush of Figure 3 performed "scrape biopsies of structures within biological ducts." (*Id.* at 1:10-11.)

Third, Eisen disclosed a brush 126 used for obtaining biopsy samples of epithelial tissue for the diagnosis of cancer.

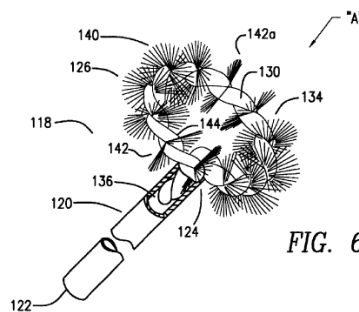


Fig. 6 of Eisen

(Ex. 1005 at 2:20-32; 5:59-67.) The bristles 140 of the brush 126 were stiff or semi-rigid and permitted the brush to penetrate all layers of the epithelium without laceration. (*Id.* at 12:30-45; 13:48-14:7.) Eisen's brush 126 was capable of obtaining the same biopsy tissue samples as prior lacerational devices. (*Id.* at 14:1-7.) ("[T]he cytologic sample obtained by the present invention is the functional equivalent of the tissue core type of sample taken by the prior art lacerating biopsy technique, and yet is obtained without the patient discomfort, scarring, and other difficulties potentially associated with a lacerating biopsy."). Eisen explains that the brush may be used in various areas of the body, including the oral cavity and esophagus while being capable of traversing difficult angles and narrow passages within the body. (*Id.* at 4:24-30; 11:19-26.) Thus, Eisen discloses a brush with stiff bristles capable of obtaining biopsy samples of all layers of the epithelium without laceration.

Finally, it would be obvious to one of ordinary skill in the art to modify the brush of Parasher '756 to include the features of Eisen's brush. The patents are in the same field and a person of skill would recognize to modify one in view of the other. Both brushes have the same purpose and perform the same function - obtaining biopsy samples of the epithelium without laceration for the diagnosis of cancer. Both brushes are capable of traversing angles and narrow passages within the body. Modifying the brush of Parasher '756 to be the brush of Eisen is a

simple substitution of one brush for another to obtain predictable results. It would also be nothing more than using known techniques to improve similar devices.


1. Claim 3: “An apparatus as set forth in claim 1, wherein said specimen picked up comprises a disaggregated specimen.”

Petitioner submits that Parasher ‘756 disclosed each and every limitation of claim 3. If Parasher ‘756 is found by the Board not to disclose this feature (which Petitioner respectfully submits is clearly found in Parasher ‘756), then such a feature is clearly disclosed in view of Eisen.

The bristles 140 of the brush 126 in Eisen are stiff or semi-rigid and permit the brush to penetrate all layers of the epithelium without laceration. (*Id.* at 12:30-45; 13:48-14:7.) The brush 126 also has long bristles (*e.g.*, 0.25 inch) more than capable of reaching to the submucosa. (*Id.* at 12:5-7; *see also* Ex. 1010 at ¶ 6.) When the device of Eisen is used to obtain biopsy samples of metaplastic glandular epithelial tissue, the biopsy sample would then necessarily comprise a disaggregated specimen of glandular cells, basement membrane fragments, and elements of the submucosa. (Ex. 1010 at ¶ 10.) Claim 3 is rendered obvious by Parasher ‘756 in view of Eisen.

D. Claims 1-3 are rendered obvious by the Olympus Catalog in view of Eisen

The use of a brush in an endoscope was clearly known prior to the filing date of the '913 Patent. The Olympus Catalog disclosed multiple brushes designed for use with an endoscope to collect cells in the gastrointestinal tract:

 <p>Disposable Brush with Reusable Sheath and Handle—Appropriate for collecting cells from hard tissue because the brush has relatively stiff bristles. Metal coil sheath makes positioning easier and protects the cells from contamination. Set includes one handle, one sheath and twelve brushes. Replacement brushes available in packages of twelve.</p>	GIF GIF CF (S) (M)	2.0 2.8 2.8–3.7	BC-5K BC-9L BC-9L
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Olympus Catalog p. 11

(Ex. 1007.) These brushes have a brush with bristles, a wire, a sheath, and a handle. *Id.* Certain brushes including Model Numbers BC-5K and BC-9L are “appropriate for collecting cells from hard tissue because the brush has relatively stiff bristles.” *Id.* (For purposes of this petition, the BC-5K and BC-9L models are collectively hereinafter referred to as “the brush of the Olympus Catalog.”) The Olympus Catalog also identified that it was well known to modify the stiffness of the bristles to yield a desired amount of cells. *Id.* (“Special nylon bristles offer the appropriate degree of stiffness to yield a high number of cells for accurate diagnosis”). Without issue, the Olympus Catalog clearly discloses cytology brushes that may be used with an endoscope to collect tissue samples within the body.

Eisen disclosed a brush 126 used for obtaining biopsy samples of epithelial tissue for the diagnosis of cancer. (Ex. 1005 at 2:20-32; 5:59-67.) The bristles 140 of the brush 126 were stiff or semi-rigid and permitted the brush to penetrate all layers of the epithelium without laceration. (*Id.* at 12:30-45; 13:48-14:7.) Eisen's brush 126 was capable of obtaining the same biopsy tissue samples as prior lacerational devices. (*Id.* at 14:1-7.) (“[T]he cytologic sample obtained by the present invention is the functional equivalent of the tissue core type of sample taken by the prior art lacerating biopsy technique, and yet is obtained without the patient discomfort, scarring, and other difficulties potentially associated with a lacerating biopsy.”). Eisen further explains that the brush may be used in various areas of the body, including the oral cavity and esophagus while being capable of traversing difficult angles and narrow passages within the body. (*Id.* at 4:24-30; 11:19-26.) Thus, Eisen discloses a brush with stiff bristles capable of obtaining biopsy samples of all layers of the epithelium without laceration.

It is respectfully submitted that it would be routine and obvious to one of ordinary skill in the art to modify the brush of the Olympus Catalog in view of Eisen. Both brushes have the same purpose and perform the same function - obtaining tissue samples within the body — as that “disclosed” in the ‘913 Patent. Further, where both brushes are designed to traverse passages within the body.

Modifying the brush of the Olympus Catalog to be the brush of Eisen is a simple substitution of one brush for another to obtain predictable results.

1. Claim 1: “An apparatus to be used in conjunction with an endoscope to examine tissue cells located within glandular epithelium, said glandular epithelium comprising tissue at the outermost surface thereof and tissue area below said outermost surface,”

As discussed above, the brush of the Olympus Catalog without issue may be used in conjunction with an endoscope to examine tissue cells. (Ex. 1007 at Olympus Catalog, p. 11.) Further, Eisen discloses a brush with stiff bristles capable of obtaining biopsy samples of all layers of the epithelium without laceration.

As explained above, glandular epithelial tissue is a type of epithelium tissue that covers all major glands and is found in the esophagus and intestinal lining. Further, the ‘913 Patent indicates that glandular epithelial tissue is found in the lower gastrointestinal tract and is approximately 1000 microns deep. (Ex. 1001 at 5:28-32 and 9:41-46.) The brush 126 of Eisen is capable of obtaining a biopsy sample of glandular epithelial tissue. The bristles 140 of the brush 126 are stiff or semi-rigid and permit the brush to penetrate all layers of the epithelium without laceration. (*Id.* at 12:30-45 and 13:48-14:7.) The brush 126 also has long bristles (*e.g.*, 0.25 inch) more than capable of reaching the glandular epithelial tissue. (*Id.*

at 12:5-7.) Further, the brush 126 of Eisen may be used to obtain biopsy samples of epithelial tissue in areas of the body where glandular epithelial tissue is found. (*Id.* at 4:24-30 and 11:19-26.) The endoscope can also be used to deliver the brush to the lower gastrointestinal tract where glandular epithelial tissue is found. As such, the brush of the Olympus Catalog modified in view of Eisen results in an obvious apparatus to be used in conjunction with an endoscope to examine tissue cells located within glandular epithelium, said glandular epithelium comprising tissue at the outermost surface thereof and tissue area below said outermost surface.

2. Claim 1: “said apparatus comprising a channel extending the length of the endoscope;”

The brush of the Olympus Catalog is used in a channel of an endoscope that necessarily extends the length of the endoscope and thus satisfies this claim limitation. (Ex. 1007 at 5-7 and 11.) The stiff bristles of the brush in the Olympus Catalog are also incorporated into the wire that is movable relative to the sheath that protects the sample from contamination. *Id.* The sheath forms a channel that receives the wire and the brush. *Id.* The wire is moved relative to the sheath by use of the handle to cover and expose the brush. *Id.* As such, the brush of the Olympus Catalog has a channel that extends the length of an endoscope.

3. Claim 1: “said apparatus comprising a rod passing through said channel having a distal and proximal end;”

The wire of the brush of the Olympus Catalog passes through the sheath and also the channel of the endoscope. (*Id.* at 5-7 and 11.) The wire has a distal and proximal end. *Id.* As such, the brush of the Olympus Catalog has a rod passing through the channel having a distal and proximal end and thereby disclosed this limitation.

4. Claim 1: “a retractable non-lacerational brush attached to the distal end of the rod,”

The brush of the Olympus Catalog is attached to the distal end of the wire. (*Id.* at 5-7 and 11.) The brush can be retracted into the channel of the endoscope and also into the sheath. *Id.* Further, as discussed in the background section of the ‘913 Patent, cytology brushes are considered by the Applicant to be non-lacerational. (Ex. 1001 at 3:31-4:24.) As such, the brush of the Olympus Catalog modified with the brush of Eisen is a retractable non-lacerational brush attached to the distal end of the rod as recited in claim 1.

5. Claim 1: “said brush being movable to bear against the tissue being examined and being controlled by said rod to remove tissue from a tissue area being examined,”

The wire of the brush of the Olympus Catalog can be manipulated by the user such that the brush bears against the tissue examined, removing samples of the tissue that cling to the stiff bristles of the brush. (Ex. 1007 at 5-7 and 11.) As such, the brush of the Olympus Catalog is movable to bear against the tissue being examined and is controlled by a rod to remove tissue from a tissue area being examined.

6. Claim 1: “said brushing apparatus comprising bristles which exert sufficient pressure to dislodge cells and pick up a specimen from said uppermost surface and said issue area therebelow.”

As discussed above, the brush 126 of Eisen is capable of obtaining a biopsy sample of glandular epithelial tissue. The bristles 140 of the brush 126 are stiff or semi-rigid and permit the brush to penetrate all layers of the epithelium without laceration. (Ex. 1005 at 12:30-45 and 13:48-14:7.) The brush 126 also has long bristles (*e.g.*, 0.25 inch) more than capable of reaching the glandular epithelial tissue. (*Id.* at 12:5-7.) Further, the brush 126 of Eisen may be used to obtain biopsy samples of epithelial tissue in areas of the body where glandular epithelial tissue is found. (*Id.* at 4:24-30 and 11:19-26.) As such, the brush of Eisen comprises bristles which exert sufficient pressure to dislodge cells and pick up a specimen a specimen from said uppermost surface and said issue area therebelow. Moreover, the bristles of the brush of the Olympus Catalog has stiff bristles. (Ex.

1007 at 11.) Thus, as disclosed above, the combination of the brush of the Olympus Catalog in view of Eisen disclosed each and every limitation of claim 1. Accordingly, claim 1 is rendered obvious by this combination.

7. Claim 2: “An apparatus as set forth in claim 1, wherein said brush bristles are at least 1000 microns in length.”

1000 microns equals 1 mm. As shown on page 11 of the Olympus Catalog, the cytology brushes with stiff bristles can be used in endoscope channels ranging in size from 2.0 to 3.7 mm. *Id.* Thus, the larger brushes will not fit in the smaller endoscope channels or different sizes would not be needed. Also, as shown, the diameter of the bristles is larger than the sheath when the brush is exposed. *Id.* Thus, the length of the bristles of the larger brushes is at least greater than 1 mm or half the diameter of the smallest channel. As such, the brush of the Olympus Catalog has bristles that are at least 1000 microns in length. Hence, claim 2 is rendered obvious by the Olympus Catalog in view of Eisen.

8. Claim 3: “An apparatus as set forth in claim 3, wherein said specimen picked up comprises a disaggregated specimen.”

The Olympus-Eisen combination also teaches claim 3 and thus renders it obvious. The bristles 140 of the brush 126 in Eisen are stiff or semi-rigid and permit the brush to penetrate all layers of the epithelium without laceration. (Ex. 1005 at 12:30-45; 13:48-14:7.) The brush 126 also has long bristles (*e.g.*, 0.25

inch) more than capable of reaching to the submucosa. (Id. at 12:5-7.) When the device of Eisen is used to obtain biopsy samples of metaplastic glandular epithelial tissue, the biopsy sample would then necessarily comprise a disaggregated specimen of glandular cells, basement membrane fragments, and elements of the submucosa. (Ex. 1010 at ¶ 13.) Claim 3 is rendered obvious by Olympus Catalog in view of Eisen.

E. Claims 1-3 are rendered obvious by the Olympus Catalog in view of Stormby and the Boon Article

As discussed, the Olympus Catalog disclosed multiple cytological brushes designed for use with an endoscope to collect cells in the gastrointestinal tract including one with relatively stiff bristles. Without issue, the Olympus Catalog clearly discloses brushes that may be used with an endoscope to collect tissue samples within the body.

It was also known prior to the filing date of the '913 Patent that a cytology brush can be used to sample epithelial tissue. For example, the Boon Article disclosed that a known cytology brush called the Cytobrush® could be used to remove and sample fragments of the epithelial for the diagnosis of cancer. (Ex. 1008 at 57-58.) In particular, the author of the Boon Article found that the bristles of the Cytobrush® have a so-called “toothpick effect” that easily dislodges epithelial fragments. *Id.* Put another way, the “toothpick effect” is a phenomenon where the bristles of a brush penetrate through the epithelium.

Nonetheless, this technique also has a disadvantage. The bristles of the Cytobrush easily dislodge epithelial fragments, both normal and abnormal. In many cases with cervical neoplasia, the smear contains not only a monolayer of abnormal cells, but, in addition, many neoplastic epithelial fragments.

Boon p. 57

Because these fragments were also present in large quantities in our correctly diagnosed cancer cases, we realized that the bristles of the Cytobrush have a "toothpick effect," easily dislodging these epithelial fragments from the endocervical canal. This is well illustrated by the scanning electron microscopy pictures of Glenthøj et al.⁸

By this embedding method, the disadvantage of the Cytobrush (the dislodging of epithelial fragments) is turned into an advantage.

Boon, p. 58

The Boon Article directly contradicts the Applicant's statements in the background section of the '913 Patent that the Examiner probably relied on during prosecution. In the background section, the Applicant discussed prior art cytological sampling tools and, in particular, the Cytobrush®. (Ex. 1001 at 4:13-24.) The Applicant distinguished these cytological sampling tools, including the Cytobrush®, on the basis that these tools only sweep exfoliated cells and are incapable of penetrating and sampling epithelium tissue. (*Id.* at 3:64-5:7.) CDx was clearly wrong on this front being as discovery of the "toothpick effect" demonstrates that these brushes could penetrate much deeper. Moreover, the Applicant repeatedly distinguished the claimed apparatus from these prior art

cytological brushes merely on the basis that the bristles of the claimed brush have a different stiffness than the bristles of the cytological brushes. (Ex. 1001 at 6:46-53; 9:13-33.) The Applicant did not disclose the actual stiffness, or even a range of stiffness, for the bristles of the claimed apparatus — just the vague concept “stiffer”.

The Applicant of the ‘913 Patent identified U.S. Patent 4,759,376 (“Stormby”) as being directed to the Cytobrush® discussed in the background section. (*Id.* at 4:13-4:24.) As shown below, Stormby disclosed a cytology brush 4 having a conically shaped tip 5 with nylon bristles. (Ex. 1006 at 2:27-57.) Various parameters of the cytology brush are also disclosed in Stormby, including the number, length, diameter, stiffness, and density of the bristles. *Id.*

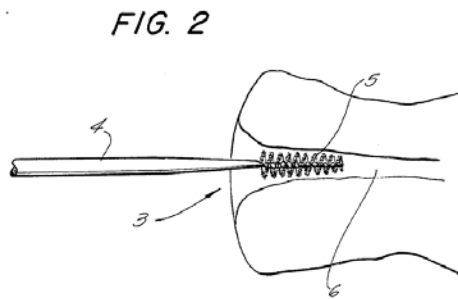


Fig. 2 of Stormby

Thus, Stormby discloses the Cytobrush® discussed in the Boon Article and the background section of the ‘913 Patent.

It is respectfully submitted that it would be routine and obvious to one of ordinary skill in the art to modify the brush of the Olympus Catalog to be the

Cytobrush® of Stormby. Both brushes have the same purpose and perform the same function - obtaining tissue samples within the body — as that “disclosed” in the ‘913 Patent. Further, where both brushes are designed to traverse passages within the body. Modifying the brush of the Olympus Catalog to be the Cytobrush® of Stormby is a simple substitution of one brush for another to obtain predictable results. And most telling, the Boon Article describes the Cytobrush® of Stormby and explains that the *brush can be used to remove and sample fragments of the entire epithelium for the diagnosis of cancer.*

1. Claim 1: “An apparatus to be used in conjunction with an endoscope to examine tissue cells located within glandular epithelium, said glandular epithelium comprising tissue at the outermost surface thereof and tissue area below said outermost surface,”

As discussed above, the brushes of the Olympus Catalog without issue may be used in conjunction with an endoscope to examine tissue cells. (Ex. 1007 at 11.) Furthermore, the Boon Article explained that the Cytobrush® of Stormby can be used to remove and sample fragments of the epithelium for the diagnosis of cancer. (Ex. 1008 at 57-58.)

Glandular epithelial tissue is a type of epithelium tissue that covers all major glands and is found in the esophagus and intestinal lining, as well as the bile and pancreatic ducts. (Ex. 1010 at ¶ 12.) Furthermore, “metaplastic” is an adjective

describing the glandular epithelial tissue and merely means that the tissue has changed form, *e.g.*, cancerous tissue. (Ex. 1010 at ¶ 14.) The '913 Patent indicates that glandular epithelial tissue is found in the lower gastrointestinal tract and the bristles of the brush must be at least 1000 microns in length to reach the depth of the glandular epithelium. (Ex. 1001 at 5:28-35 and 9:41-46.) Additionally, the bristles of the Cytobrush® of Stormby are greater than 1000 microns in length. (Ex. 1006 at 2:40-50.) As such, the brush of the Olympus Catalog modified with the Cytobrush® of Stormby is an apparatus that can be used in conjunction with an endoscope to examine tissue cells located within glandular epithelium, said glandular epithelium comprising tissue at the outermost surface thereof and tissue area below said outermost surface.

2. Claim 1: “said apparatus comprising a channel extending the length of the endoscope;”

The brush of the Olympus Catalog is used in a channel of an endoscope that necessarily extends the length of the endoscope and thus satisfies this claim limitation. (Ex. 1007 at 5-7 and 11.) The stiff bristles of the Olympus brush are also incorporated into the wire that is movable relative to the sheath that protects the sample from contamination. *Id.* The sheath forms a channel that receives the wire and the brush. *Id.* The wire is moved relative to the sheath by use of the

handle to cover and expose the brush. *Id.* As such, the brush of the Olympus Catalog has a channel that extends the length of an endoscope.

3. Claim 1: “said apparatus comprising a rod passing through said channel having a distal and proximal end;”

The wire of the brush of the Olympus Catalog passes through the sheath and also the channel of the endoscope. *Id.* The wire has a distal and proximal end. *Id.* As such, the brush of the Olympus Catalog has a rod passing through the channel having a distal and proximal end and thereby disclosed this limitation.

4. Claim 1: “a retractable non-lacerational brush attached to the distal end of the rod,”

The brush of the Olympus Catalog is attached to the distal end of the wire. *Id.* The brush can be retracted into the channel of the endoscope and also into the sheath. *Id.* Further, as discussed in the background section of the ‘913 Patent, prior art cytology brushes, such as the Cytobrush® of Stormby, are considered by the Applicant to be non-lacerational. (Ex. 1001 at 3:31-4:24.) (“[A] technique known as cytology is commonly utilized as an alternative to performing a lacerating biopsy and histological evaluation.”). As such, the brush of the Olympus Catalog modified with the Cytobrush® of Stormby is a retractable non-lacerational brush attached to the distal end of the rod as recited in claim 1.

5. Claim 1: “said brush being movable to bear against the tissue being examined and being controlled by said rod to remove tissue from a tissue area being examined,”

The wire of the brush in the Olympus Catalog can be manipulated by the user such that the brush bears against the tissue examined, removing samples of the tissue that cling to the stiff bristles of the brush. (Ex. 1007 at 5-7 and 11.) As such, the brush of the Olympus Catalog is movable to bear against the tissue being examined and is controlled by a rod to remove tissue from a tissue area being examined.

6. Claim 1: “said brushing apparatus comprising bristles which exert sufficient pressure to dislodge cells and pick up a specimen from said uppermost surface and said issue area therebelow.”

As discussed above, the Cytobrush® of Stormby can be used to remove and sample fragments of the epithelial for the diagnosis of cancer. (Ex. 1008 at 57-58, 63.) In particular, the bristles of the Cytobrush® have a “toothpick” effect that easily dislodges epithelial fragments that are used for both diagnostic and quantitative microscopy. *Id.* As such, the Cytobrush® of Stormby comprises bristles which exert sufficient pressure to dislodge cells and pick up a specimen a specimen from said uppermost surface and said issue area therebelow. Moreover, the bristles of the brush of the Olympus Catalog are indeed stiff bristles. (Ex. 1007

at 11.) Thus, as disclosed above, the consideration of the Olympus Catalog in view of Stormby and the Boon Article disclosed each and every limitation of claim 1. Accordingly, claim 1 is rendered obvious by this combination.

7. Claim 2: “An apparatus as set forth in claim 1, wherein said brush bristles are at least 1000 microns in length.”

Without issue, the Olympus-Boon-Stormby combination taught this limitation. First, 1000 microns equals 1 mm. As explained in Stormby, the bristles of its brush 4 have a lengths of 5.4 and 7.5 mm — obviously this is at least 1 mm. (Ex. 1006 at 2:40-50.) As such, the brush 4 has bristles that taught the limitation at “at least 1000 microns in length”. Hence, claim 2 is rendered obvious by the Olympus Catalog in view of Stormby and the Boon Article.

8. Claim 3: “An apparatus as set forth in claim 3, wherein said specimen picked up comprises a disaggregated specimen.”

The Olympus-Boon-Stormby combination also teaches claim 3 and thus renders it obvious. One of ordinary skill in the art would understand that a biopsy sample includes fragments of the epithelial tissue, as well as portions of the basement membrane and submucosa below the epithelium. (Ex. 1010 at ¶ 10.) As discussed above, the brush of the Olympus Catalog modified with the Cytobrush® of Stormby is an apparatus having stiff bristles that can be used to obtain samples of metaplastic glandular epithelial tissue. Furthermore, the brush has long bristles

(*e.g.*, 5.4 and 7.5 mm) more than capable of reaching to the submucosa. (Ex. 1006 at 2:40-50.) When the apparatus is used to obtain biopsy samples of metaplastic glandular epithelial tissue, the biopsy sample would then necessarily comprise a disaggregated specimen of glandular cells, basement membrane fragments, and elements of the submucosa. Hence, claim 3 is rendered obvious by the Olympus Catalog in view of Stormby and the Boon Article.

F. Claims 1-3 are rendered obvious by the Olympus Catalog in view of Falk

As discussed above, the Olympus Catalog disclosed multiple cytological brushes designed for use with an endoscope to collect cells in the gastrointestinal tract. (Ex. 1007 at 11.) The cytological brushes have a brush with bristles, a wire, a sheath, and a handle. *Id.* Further, certain brushes have stiff bristles for collecting cells from hard tissue. *Id.* The Olympus Catalog also identified that it was well-known to modify the stiffness of the bristles to yield a desired amount of cells. *Id.* It is indisputable that the Olympus Catalog clearly disclosed cytology brushes with stiff bristles that could be used with an endoscope to collect tissue samples within the body. *Id.*

Falk discussed the use of an endoscopic cytology brush to detect neoplasia at an early stage in patients with Barrett's esophagus. (Ex. 1009, p. 1787). In particular, the endoscopic cytology brush was used to obtain specimens of columnar epithelium. (*Id.* at 1793.) Although Falk discusses using a cytology

brush by C.R. Bard Inc., other known endoscopy cytology brushes, such as in the Olympus catalog brush with stiff bristles, could certainly be used to obtain the samples. (*Id.* at 1789; see also Ex. 1010 at ¶ 17.)

Moreover, it is respectfully submitted that it would be routine and obvious to one of ordinary skill in the art to modify the brush of the Olympus Catalog to be the brush discussed in Falk. Both brushes have the same purpose and perform the same function - obtaining tissue samples within the body. Additionally, both brushes are designed to be used with an endoscope and traverse passages within the body. Modifying the brush of the Olympus Catalog to be the brush of Falk is a simple substitution of one brush for another to obtain predictable results — hallmark of obviousness.

1. Claim 1: “An apparatus to be used in conjunction with an endoscope to examine tissue cells located within glandular epithelium, said glandular epithelium comprising tissue at the outermost surface thereof and tissue area below said outermost surface,”

The coordination of the Olympus Catalog and Falk teaches this limitation. As discussed above, the brushes of the Olympus Catalog may be used in conjunction with an endoscope to examine tissue cells. (Ex. 1007 at 11.). Furthermore, Falk explained that an endoscopy cytology brush can be used to

remove and sample epithelial tissue for the diagnosis of cancer. (Ex. 1009 at 1787-1797).

Glandular epithelial tissue is a type of epithelium tissue that covers all major glands and is found in the esophagus and intestinal lining, as well as the bile and pancreatic ducts. (Ex. 1010 at ¶ 12.) ¶ Metaplastic” is an adjective describing the glandular epithelial tissue and merely means that the tissue has changed form, *e.g.*, potentially cancerous tissue. (Id. at ¶ 14.) The ‘913 Patent indicates that glandular epithelial tissue is found in the lower gastrointestinal tract and the bristles of the brush must be at least 1000 microns in length to reach the depth of the glandular epithelium. ‘913 Patent, 5:28-35 and 9:41-46. As discussed above, the brush of the Olympus Catalog modified with the brush of Falk is an apparatus that can be used in conjunction with an endoscope to examine tissue cells located within epithelium tissue. The endoscope can be used to deliver the brush to the lower gastrointestinal tract where glandular epithelial tissue is found according to the ‘913 Patent. Further, the bristles of the brush in the Olympus Catalog are greater than 1000 microns in length. (Ex. 1007 at p. 11.).

As such, the brush of the Olympus Catalog modified with the brush of Falk is an apparatus that can be used in conjunction with an endoscope to examine tissue cells located within glandular epithelium, said glandular epithelium

comprising tissue at the outermost surface thereof and tissue area below said outermost surface.

2. Claim 1: “said apparatus comprising a channel extending the length of the endoscope;”

Again, the combination of the Olympus Catalog and Falk renders this limitation obvious. The brush of the Olympus Catalog is used in a channel of an endoscope that necessarily extends the length of the endoscope. (Ex. 1007 at 5-7 and 11). The stiff bristles of the brush are also incorporated into the wire which is movable relative to the sheath that protects the sample from contamination. *Id.* The sheath forms a channel that receives the wire and the brush. *Id.* The wire is moved relative to the sheath by use of the handle to cover and expose the brush. *Id.* As such, the brush of the Olympus Catalog has a channel that extends the length of an endoscope.

3. Claim 1: “said apparatus comprising a rod passing through said channel having a distal and proximal end;”

The combination of the Olympus brush and Falk disclose this limitation without issue. The wire of the brush of the Olympus Catalog passes through the sheath and also the channel of the endoscope. (Ex. 1007 at 5-7 and 11). The wire has a distal and proximal end. *Id.* As such, the brush of the Olympus Catalog has a rod passing through the channel having a distal and proximal end.

4. Claim 1: “a retractable non-lacerational brush attached to the distal end of the rod,”

The brush of the Olympus Catalog is attached to the distal end of the wire. (Ex. 1007 at 5-7 and 11). The brush can be retracted into the channel of the endoscope and also into the sheath. *Id.* Further, as discussed in the background section of the ‘913 Patent, cytology brushes are considered by the Applicant to be non-lacerational. (Ex. 1001 at 3:31-4:24.) As such, the brush of the Olympus Catalog modified with the brush of Falk is a retractable non-lacerational brush attached to the distal end of the rod as recited in claim 1.

5. Claim 1: “said brush being movable to bear against the tissue being examined and being controlled by said rod to remove tissue from a tissue area being examined,”

The wire of the brush in the Olympus Catalog can be manipulated by the user such that the brush bears against the tissue examined, removing samples of the tissue that cling to the stiff bristles of the brush. (Ex. 1007 at 5-7 and 11). As such, the brush of the Olympus Catalog is movable to bear against the tissue being examined and is controlled by a rod to remove tissue from a tissue area being examined.

6. Claim 1: “said brushing apparatus comprising bristles which exert sufficient pressure to dislodge cells and pick up a specimen from said uppermost surface and said tissue area therebelow.”

As discussed above, the brush of Falk can be used to remove and sample epithelial tissue for the diagnosis of cancer. (Ex. 1009 at 1787-1797). As such, the brush of Falk comprises bristles which exert sufficient pressure to conduct a biopsy to dislodge cells and pick up a specimen of tissue located below the surface of epithelium. Moreover, the brush in the Olympus Catalog has stiff bristles that may be used to obtain epithelial tissue. (Ex. 1007 at 11; *see* Ex. 1001 at 6:46-53) (“By rubbing harder than normal cytological sampling and using a stiff device which penetrates epithelium, one can reach to the basement membrane without lacerating.”). Thus, claim 1 is rendered obvious by the Olympus Catalog in view of Falk.

7. Claim 2: “An apparatus as set forth in claim 1, wherein said brush bristles are at least 1000 microns in length.”

1000 microns equals 1 mm. As shown on page 11 of the Olympus Catalog, the cytology brushes with stiff bristles can be used in endoscope channels ranging in size from 2.0 to 3.7 mm. (Ex. 1007 at 11). Thus, the larger brushes will not fit in the smaller endoscope channels or different sizes would not be needed. Also, as shown, the diameter of the bristles is larger than the sheath when the brush is

exposed. *Id.* Thus, the length of the bristles of the larger brushes is at least greater than 1 mm or half the diameter of the smallest channel. As such, the brush of the Olympus Catalog has bristles that are at least 1000 microns in length. Hence, claim 2 is rendered obvious by the Olympus Catalog in view of Falk.

8. Claim 3: “An apparatus as set forth in claim 3, wherein said specimen picked up comprises a disaggregated specimen.”

One of ordinary skill in the art would understand that a biopsy sample includes fragments of the epithelial tissue, as well as portions of the basement membrane and submucosa below the epithelium. (Ex. 1010 at ¶ 10.) As discussed above, the brush of the Olympus Catalog modified with the brush of Falk is an apparatus having stiff bristles that can be used to obtain samples of metaplastic glandular epithelial tissue. Further, the brush of the Olympus Catalog is available with long bristles (*e.g.*, greater than 1 mm) that are capable of reaching to the submucosa. (Ex. 1007 at 11.) When the apparatus is used to obtain biopsy samples of metaplastic glandular epithelial tissue, the biopsy sample would then necessarily comprise a disaggregated specimen of glandular cells, basement membrane fragments, and elements of the submucosa. Hence, claim 4 is rendered obvious by the Olympus Catalog in view of Falk.

VI. CONCLUSION

For the foregoing reasons, *inter partes* review of claims 1-3 of U.S. Patent No. 7,004,913 is respectfully requested.

Respectfully submitted,

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**CERTIFICATE OF SERVICE ON PATENT OWNER
UNDER 37 C.F.R. § 42.105(a)**

Pursuant to 37 C.F.R. §§ 42.8(e) and 42.105(b), the undersigned certifies that on the 15th day of April, 2014, a complete and entire copy of this Petition for *Inter Partes* Review and all supporting exhibits were provided via Federal Express, postage prepaid, to the Patent Owner by serving the correspondence address of record for the '913 Patent:

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