

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

U.S. Patent 11,970,746

DECLARATION OF BRENDAN T. JONES

1. I am an attorney at Foley Hoag LLP, and counsel of record for Geneoscopy, Inc. in the above-captioned matter. I am registered to practice before the United States Patent and Trademark Office.

2. Attached as EX1001 is a true and correct copy of U.S. Patent No. 11,970,746.

3. Attached as EX1004 is a true and correct copy of Konstanze Lenhard et al., “Analysis of Promoter Methylation in Stool: A Novel Method for the Detection of Colorectal Cancer,” *Clinical Gastroenterology and Hepatology*, 3:142-149 (2005) available at [https://www.cghjournal.org/article/S1542-3565\(04\)00624-X/fulltext](https://www.cghjournal.org/article/S1542-3565(04)00624-X/fulltext).

4. Attached as EX1005 is a true and correct copy of Alex Vilkin et al., “Performance Characteristics and Evaluation of an Automated-Developed and Quantitative, Immunochemical Fecal Occult Blood Screening Test,” *American Journal of Gastroenterology*, 100:2519-2525 (2005) available at https://journals.lww.com/ajg/abstract/2005/11000/performance_characteristics_and_evaluation_of_an.26.aspx.

5. Attached as EX1006 is a true and correct copy of Steven Itzkowitz et al., “Improved Fecal DNA Test for Colorectal Cancer Screening,” *Clinical Gastroenterology and Hepatology*, 5:111-117 (2007) available at [https://www.cghjournal.org/article/S1542-3565\(06\)01044-5/fulltext](https://www.cghjournal.org/article/S1542-3565(06)01044-5/fulltext).

6. Attached as EX1007 is a true and correct copy of U.S. Patent Publication No. US2006/0216714.

7. Attached as EX1008 is a true and correct copy of International Patent Application No. WO2005/113769.

8. Attached as EX1009 is a true and correct copy of International Patent Application Publication No. WO97/25925.

9. Attached as EX1010 is a true and correct copy of Dorothy Melvin and Marion Brooke, "Laboratory Procedures for the Diagnosis of Intestinal Parasites", U.S. Department of Health and Human Services Centers for Disease Control (1982).

10. Attached as EX1011 is a true and correct copy of Takashi Nishikawa et al., "A Simple Method of Detecting K-Ras Point Mutations in Stool Samples for Colorectal Cancer Screening Using One-Step Polymerase Chain Reaction/Restriction Fragment Length Polymorphism Analysis," *Clinica Chimica Acta*, 318:107–112 (2002) available at <https://www.sciencedirect.com/science/article/abs/pii/S0009898101008063>.

11. Attached as EX1012 is a true and correct copy of Nadie Kutzner et al., "Non-Invasive Detection of Colorectal Tumours by the Combined Application of Molecular Diagnosis and the Faecal Occult Blood Test," *Cancer Letters*, 229:33-

41 (2005) available at

<https://www.sciencedirect.com/science/article/abs/pii/S0304383504009796>.

12. Attached as EX1013 is a true and correct copy of Bernard Levin et al., “Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, a Joint Guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology,” *Gastroenterology*, 134:1570–1595 (2008) available at <https://www.sciencedirect.com/science/article/abs/pii/S0016508508002321>.

13. Attached as EX1014 is a true and correct copy of U.S. Provisional Patent Application US61/149,581.

14. Attached as EX1015 is a true and correct copy of the transmittal notice for U.S. Provisional Patent Application US61/149,581.

15. Attached as EX1016 is a true and correct copy of the LinkedIn profile of Dr. Joost Louwagie as obtained from <https://www.linkedin.com/in/joost-louwagie/?originalSubdomain=ch> on January 10, 2024.

16. Attached as EX1017 is a true and correct copy of Recorded Assignment of US Patent No. 11,634,781 dated April 25, 2017.

17. Attached as EX1018 is a true and correct copy the USPTO Nonfinal Office Action, dated July 6, 2023.

18. Attached as EX1019 is a true and correct copy of the Response to the USPTO Nonfinal Office Action filed on October 26, 2023.

19. Attached as EX1020 is a true and correct copy of is a true and correct copy of GP Young et al., “New Stool Screening Tests for Colorectal Cancer,” *Digestion*, 76:26-33 (2007) available at <https://karger.com/dig/article-abstract/76/1/26/105075/New-Stool-Screening-Tests-for-Colorectal-Cancer>.

20. Attached as EX1021 is a true and correct copy of Lydia Guittet et al., “Comparison of A Guaiac Based And An Immunochemical Faecal Occult Blood Test In Screening For Colorectal Cancer In A General Average Risk Population,” *Gut*, 56:210-214 (2007) available at <https://gut.bmj.com/content/56/2/210.short>.

21. Attached as EX1022 is a true and correct copy of Jeff Olson et al., “DNA Stabilization is Critical for Maximizing Performance of Fecal DNA-Based Colorectal Cancer Tests,” *Diagnostic Molecular Pathology*, 3:183-191 (2005) available at https://journals.lww.com/molecularpathology/abstract/2005/09000/dna_stabilization_is_critical_for_maximizing.11.aspx.

22. Attached as EX1023 is a true and correct copy of N. Hoepffner et al., “Comparative Evaluation of a New Bedside Faecal Occult Blood Test in a Prospective Multicentre Study,” *Alimentary Pharmacology & Therapeutics*,

23:145-154 (2006) available at

<https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2036.2006.02702.x>.

23. Attached as EX1024 is a true and correct copy of Jordan Nechvatal et al., "Fecal Collection, Ambient Preservation, and DNA Extraction for PCR Amplification of Bacterial And Human Markers from Human Feces," *Journal of Microbiological Methods*, 72(2):124-32 (2008) available at <https://www.sciencedirect.com/science/article/abs/pii/S0167701207003843>.

24. Attached as EX1025 is a true and correct copy the article, "FDA Approves Exact Sciences' Cologuard; First and Only Stool DNA Noninvasive Colorectal Cancer Screening Test", PR NEWSWIRE, dated August 12, 2014 available at <https://investor.exactsciences.com/investor-relations/press-releases/press-release-details/2014/FDA-Approves-Exact-Sciences-Cologuard-First-and-Only-Stool-DNA-Noninvasive-Colorectal-Cancer-Screening-Test/default.aspx>.

25. Attached as EX1026 is a printout of Exact Sciences Corporation's "Patents and Trademarks" webpage at <https://www.exactsciences.com/patents-and-trademarks/> as visited on August 9, 2024.

26. Attached as EX1027 is printout of Exact Sciences Corporation's "Patents and Trademarks" webpage, dated December 6, 2014, downloaded from Wayback Machine at

<https://web.archive.org/web/201406015245/http://www.exactsciences.com/patents-and-trademarks/> on August 9, 2024.

27. Attached as EX1028 is a true and correct copy of U.S. Patent No. 9,163,278.

28. Attached as EX1029 is a true and correct copy of the Response to USPTO Nonfinal Office Action filed on July 31, 2015.

29. Attached as EX1030 is a true and correct copy of U.S. Patent No. 11,634,781.

30. Attached as EX1031 is a true and correct copy of Geneoscopy, Inc.'s Petition filed in IPR2024-00459.

31. Attached as EX1032 is a true and correct copy of Exact Sciences Corporation's Preliminary Response filed in IPR2024-00459.

32. Attached as EX1033 is a true and correct copy of the Patent Trial and Appeal Board's Institution Decision in IPR2024-00459.

33. Attached as EX1034 is a true and correct copy of JB Simon, "Occult Blood Screening for Colorectal Carcinoma: A Critical Review," *Gastroenterology*, 88:820-837 (1985).

34. Attached as EX1035 is a true and correct copy of D. Sidransky, "Identification of Ras Oncogene Mutations in the Stool of Patients with Curable

Colorectal Tumors,” *Science*, 256:102–105 (1992) available at <https://www.science.org/doi/abs/10.1126/science.1566048>.

35. Attached as EX1036 is a true and correct copy of Hannes Müller et al., “Methylation Changes in Faecal DNA: A Marker for Colorectal Cancer Screening?” *Lancet*, 63:1283-1285 (2004) available at [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(04\)16002-9/abstract](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(04)16002-9/abstract).

36. Attached as EX1037 is a true and correct copy of Kornel Schuebel et al., “Comparing the DNA Hypermethylome with Gene Mutations in Human Colorectal Cancer,” *PLoS Genet.* 3:1709–1723 (2007) available at <https://journals.plos.org/plosgenetics/article?id=10.1371/journal.pgen.0030157>.

37. Attached as EX1038 is a true and correct copy of Lanlan Shen, et al., “Integrated Genetic and Epigenetic Analysis Identifies Three Different Subclasses of Colon Cancer,” *Proc Natl. Acad. Sci. U.S.A.* 104(47): 18654–18659 (2007) available at <https://www.pnas.org/doi/abs/10.1073/pnas.0704652104>.

38. Attached as EX1039 is a true and correct copy of Tagore, K.S., et al., “Review Article: the Evolution to Stool DNA Testing for Colorectal Cancer,” *Aliment Pharmacol. Ther.* 19: 1225-1233 (2004) available at <https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2036.2004.02005.x>.

39. Attached as EX1040 Rennert et al., “Detecting K-Ras Mutations in Stool from Fecal Occult Blood Test Cards in Multiphasic Screening for Colorectal Cancer,” *Cancer Letters*, 253:258-264 (2007) available at <https://www.sciencedirect.com/science/article/abs/pii/S0304383507000420>.

40. Attached as EX1041 is a true and correct copy of U.S. Patent No. 5,198,365.

41. Attached as EX1042 is a true and correct copy of Thomas Imperiale et al., “Fecal DNA Versus Fecal Occult Blood for Colorectal-Cancer Screening in an Average-Risk Population,” *New England Journal Medicine*, 351(26): 2704-2714 (2004) available at <https://www.nejm.org/doi/full/10.1056/NEJMoa033403>.

42. Attached as EX1043 is a true and correct copy of David Ahlquist et al., “Stool DNA and Occult Blood Testing for Screen Detection of Colorectal Neoplasia,” *Annals of Internal Medicine*, 149(7): 441–W81 (2008).

43. Attached as EX1044 is a true and correct copy of G.P. Young, “Fecal Immunochemical Tests (FIT) vs. Office-Based Guaiac Fecal Occult Blood Test (FOBT),” *Practical Gastroenterology*, 28(6): 46-56 (2004) available at <https://www.acpjournals.org/doi/abs/10.7326/0003-4819-149-7-200810070-00004>.

44. Attached as EX1045 is a true and correct copy of Karl, et al., Improved Diagnosis of Colorectal Cancer Using a Combination of Fecal Occult Blood and Novel Fecal Protein Markers,” *Clinical Gastroenterology and Hepatology*,

6:1122–1128 (2008) available at

<https://www.sciencedirect.com/science/article/abs/pii/S1542356508003455>.

45. Attached as EX1046 is a true and correct copy of Victoria White and Richard Miller, “Colorectal Cancer: Prevention and Early Diagnosis,” *Medicine*, 35(6) 297-301 (2007) available at

<https://www.sciencedirect.com/science/article/abs/pii/S1357303907000758>.

46. Attached as EX1047 is a true and correct copy of Suzanne Mahon, “Prevention and Screening of Gastrointestinal Cancers,” *Seminars in Oncology Nursing*, 25(1): 15-31 (2009) available at

<https://www.sciencedirect.com/science/article/abs/pii/S0749208108000788>.

47. Attached as EX1048 is a true and accurate copy of U.S. Patent No. 9,891,223.

48. Attached as EX1049 is a true and correct copy of Donald Ostrow, “Tests for Fecal Occult Blood, in Clinical Methods: The History, Physical, and Laboratory Examinations.” Boston: Butterworths; Chapter 98 (1990) available at

<https://www.ncbi.nlm.nih.gov/books/NBK445/>.

49. Attached as EX1050 is a true and correct copy of U.S. Patent No. 7,195,878.

50. Attached as EX1051 is a true and correct copy of Charles Kahi et al., “Screening, Surveillance, and Primary Prevention for Colorectal Cancer: A Review

of the Recent Literature,” *Gastroenterology*, 135: 380-399 (2008) available at [https://www.gastrojournal.org/article/S0016-5085\(08\)00969-4/fulltext](https://www.gastrojournal.org/article/S0016-5085(08)00969-4/fulltext).

51. Attached as EX1052 is a true and correct copy of H Zou et al., “Highly Methylated Genes in Colorectal Neoplasia: Implications for Screening,” *Cancer Epidemiol Biomarkers Preview*, 16(12):2686-96 (2007) available at <https://aacrjournals.org/cebp/article/16/12/2686/260084/Highly-Methylated-Genes-in-Colorectal-Neoplasia>.

52. Attached as EX1053 is a true and correct copy of Susumu Eguchi et al., “Mutations of the P53 Gene in Stool of Patients with Resectable Colorectal Cancer,” *Cancer*, 77:1707–1710 (1996) available at [https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.1002/\(SICI\)1097-0142\(19960415\)77:8%3C1707::AID-CNCR43%3E3.0.CO;2-0](https://acsjournals.onlinelibrary.wiley.com/doi/abs/10.1002/(SICI)1097-0142(19960415)77:8%3C1707::AID-CNCR43%3E3.0.CO;2-0).

53. Attached as EX1054 is a true and correct copy of E. Villa, et al., “Identification of Subjects at Risk for Colorectal Carcinoma through a Test Based on K-Ras Determination in the Stool,” *Gastroenterology*, 110:1346–1353 (1996) available at [https://www.gastrojournal.org/article/S0016-5085\(96\)00204-1/fulltext](https://www.gastrojournal.org/article/S0016-5085(96)00204-1/fulltext).

54. Attached as EX1055 is a true and correct copy of Boynton et al., “DNA Integrity as a Potential Marker for Stool-based Detection of Colorectal Cancer,” *Clinical Chemistry*, 49:7 1058–1065 (2003) available at <https://academic.oup.com/clinchem/article/49/7/1058/5641839>.

55. Attached as EX1056 is a true and correct copy of J. Milburn Jessup et al., “Diagnosing Colorectal Carcinoma: Clinical and Molecular Approaches,” *A Cancer Journal for Clinicians*, 47(2):70-92 (1997) available at <https://europepmc.org/article/med/9074487>.

56. Attached as EX1057 is a true and correct copy of WD Chen et al., “Detection in Fecal DNA of Colon Cancer-Specific Methylation of the Nonexpressed Vimentin Gene.” *Journal of National Cancer Institute*, 97:1124-1132 (2005) available at <https://academic.oup.com/jnci/article/97/15/1124/2521303>.

57. Attached as EX1058 is a true and correct copy of Steven Itzkowitz, “A Simplified, Noninvasive Stool DNA Test for Colorectal Cancer Detection,” *American Journal of Gastroenterology*, 103:2862-2870 (2008) available at https://journals.lww.com/ajg/abstract/2008/11000/a_simplified,_noninvasive_stool_dna_test_for.29.aspx.

58. Attached as EX1059 is a true and correct copy of L-C Li and R. Dahiya, “MethPrimer: Designing Primers for Methylation Pcrs,” *Bioinformatics*, 18(11): 1427-1431 (2002) available at <https://academic.oup.com/bioinformatics/article/18/11/1427/177964>.

59. Attached as EX1060 is a true and correct copy of Shigeru Kanaoka et al., “Potential Usefulness of Detecting Cyclooxygenase 2 Messenger RNA in Feces for

Colorectal Cancer Screening,” *Gastroenterology*, 127:422-427 (2004) available at <https://www.sciencedirect.com/science/article/abs/pii/S0016508504008686>.

60. Attached as EX1061 is a true and correct copy of Y. Matsumura and D. Tarin, “Significance of CD44 Gene Products for Cancer Diagnosis and Disease Evaluation,” *Lancet*, 340:1053-1058 (1992) available at <https://www.sciencedirect.com/science/article/abs/pii/014067369293077Z>.

61. Attached as EX1062 is a true and correct copy of Y Mastumura et al., “Non-Invasive Detection of Malignancy by Identification of Unusual CD44 Gene Activity in Exfoliated Cancer Cells,” *BMJ*, 308:619-624 (1994) available at <https://www.bmj.com/content/308/6929/619.abstract>.

62. Attached as EX1063 is Wai Leung et al., “Detection of Hypermethylated DNA or Cyclooxygenase-2 Messenger RNA in Fecal Samples of Patients with Colorectal Cancer or Polyps,” *American Journal Gastroenterology*, 102: 1070-1076 (2007) available at https://journals.lww.com/ajg/abstract/2007/05000/detection_of_hypermethylated_dna_or.24.aspx.

63. Attached as EX1064 is a true and accurate copy of Farid Ahmed et al., “Transcriptomic Molecular Markers for Screening Human Colon Cancer in Stool and Tissue,” *Cancer Genomics and Proteomics*, 4:1-20 (2007) available at <https://cgp.iiarjournals.org/content/4/1/1.short>.

64. Attached as EX1065 is a true and correct copy of D.A. Ahlquist et al., “Colorectal Cancer Screening by Detection of Altered Human DNA in Stool: Feasibility of a Multitarget Assay Panel,” *Gastroenterology*, 119(5):1219-1227 (2000) available at <https://www.sciencedirect.com/science/article/abs/pii/S0016508500895268>.

65. Attached as EX1066 is a true and correct copy of D.A. Ahlquist et al., “Molecular Stool Screening for Colorectal Cancer. Using DNA Markers May Be Beneficial, But Large Scale Evaluation is Needed.” *BMJ*, 29;321(7256):254-5 (2000) available at <https://www.bmj.com/content/321/7256/254.short>.

66. Attached as EX1067 is a true and correct copy of International Patent Application Publication No. WO2009/102788.

67. Attached as EX1068 is a true and correct copy U.S. Patent No. 5,741,650.

68. Attached as EX1069 is a true and correct copy of U.S. Patent No. 5,952,178.

69. Attached as EX1070 is a true and correct copy of I Hirata et al., “Usefulness of Fecal Lactoferrin and Hemoglobin in Diagnosis of Colorectal Diseases,” *World Journal of Gastroenterology*, 14;13(10):1569-74 (2007) available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4146900/>.

70. Attached as EX1071 is a true and correct D.A. Ahlquist et al., “A Stool Collection Device: The First Step in Occult Blood Testing,” *Annals of Internal*

Medicine, (108)4:609-612 (1988) available at

<https://www.acpjournals.org/doi/abs/10.7326/0003-4819-108-4-609>.

71. Attached as EX1072 is a true and correct copy of the online version of Konstanze Lenhard et al., “Analysis of Promoter Methylation in Stool: A Novel Method for the Detection of Colorectal Cancer,” *Clinical Gastroenterology and Hepatology*, 3:142-149 (2005), obtained from [https://www.cghjournal.org/article/S1542-3565\(04\)00624-X/fulltext](https://www.cghjournal.org/article/S1542-3565(04)00624-X/fulltext), on January 9, 2024.

72. Attached as EX1073 is a true and correct International Patent Application Publication No. WO2008/084219.

73. Attached as EX1074 is a true and correct copy of the online version of Steven Itzkowitz et al., “Improved Fecal DNA Test for Colorectal Cancer Screening,” *Clinical Gastroenterology and Hepatology*, 5:111-117 (2007), as obtained from [https://www.cghjournal.org/article/S1542-3565\(06\)01044-5/fulltext](https://www.cghjournal.org/article/S1542-3565(06)01044-5/fulltext), on January 9, 2024.

74. Attached EX1075 is a true and correct copy of a December 13, 2006 press release obtained from <https://www.sciencedaily.com/releases/2006/12/061213104115.htm#> on January 9, 2024.

75. Attached as EX1076 is a true and correct copy of the Cologuard Patient Guide available at

https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130017C.pdf.

76. Attached as EX1077 is a true and correct copy of Imperiale, et al., “Multitarget Stool DNA Testing for Colorectal-Cancer Screening,” *The New England Journal of Medicine*, 370(14):1287-1297 (2014) available at

<https://www.nejm.org/doi/full/10.1056/NEJMoa1311194>.

77. Attached as EX1078 is a true and correct copy of Exact Sciences Corporation’s 2023 Form 10-K.

78. Attached as EX1079 is a true and correct copy of Exact Science’s webpage regarding the Cologuard test as obtained from <https://www.exactsciences.com/our-tests/cologuard> on August 15, 2024.

79. Attached as EX1080 is a true and correct copy of the Cologuard Physician Brochure available at

https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130017C.pdf.

80. Attached as EX1081 is a true and correct copy of the Cologuard sDNA-based Colorectal Cancer Screening Test Instructions for Use available at

https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130017C.pdf.

81. Attached EX1082 is a true and correct copy of Duncan Whitney Ph.D.’s Declaration submitted in IPR2024-00459.

I declare, under penalty of perjury under the laws of the United States, that the foregoing is true and accurate.

Dated: August 20, 2024

/Brendan T. Jones/
Brendan T. Jones
Reg. No. 65,077