

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

Case No.: IPR2024-01330
U.S. Patent No. 11,970,746

PETITIONER'S DEMONSTRATIVES

Pursuant to the Board's Order Setting Oral Argument dated October 3, 2025,
Petitioner Geneoscopy, Inc.'s demonstratives are appended to this filing.

Dated: November 17, 2025

Respectfully submitted,

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ORAL ARGUMENT FOR IPR2024-01330

U.S. Patent No. 11,970,746

Petitioner's Hearing Demonstratives

November 20, 2025

Contents



Introduction



Ground I: Lenhard, Vilkin and Itzkowitz



Ground III: Shuber and Vilkin



Ground VI: Inbar, Vilkin, and Shuber



Grounds II, IV, VII: Ground I, III, and VI Prior Art with Kanaoka



Alleged Secondary Considerations



Challenged Claims

Introduction

(10) Patent No.: **US 11,970,746 B2**
(45) Date of Patent: ***Apr. 30, 2024**

(65)	Prior Publication Data US 2023/0313317 A1 Oct. 5, 2023
(63)	Related U.S. Application Data Continuation of application No. 17/936,335, filed on Sep. 28, 2022, now Pat. No. <u>11,634,781</u>, which is a continuation of application No. 15/634,607, filed on Jun. 27, 2017, which is a continuation of application No. 15/010,436, filed on Jan. 29, 2016, now abandoned, which is a continuation of application No. 13/147,570, filed as application No. PCT/GB2010/000180 on Feb. 3, 2010, now abandoned.
(60)	Provisional application No. 61/149,581, filed on Feb. 3, 2009.

The Claims of the '746 Patent are Broader than the Claims of the '781 Patent

US 11,634,781

United States Patent
Language

(12) Patent No.: US 11,634,781
(45) Date of Patent: Apr. 25, 2023

(54) Fecal Sample Processing and Analysis Comprising Collection of Blood

(71) Applicant: *Genzyme, Inc.*
(72) Inventor: *James S. C.*
(*) Notice: *See office action dated 10/1/2021.*

(21) Appl. No.: *16/811,111*
(22) Filed: *Mar. 1, 2020*

'781 Patent, Cl. 1

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:

- a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;
- b) removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;
- c) combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and
- d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.

Int. Cl. C12Q 1/02 (2006.01)
U.S. Cl. C12Q 1/02 (2006.01)
CPC C12Q 1/02 (2006.01)
Field of Cl. C12Q 1/02 (2006.01)
See applicant's specification for complete search history.

(56) References Cited:
U.S. Pat. Nos.: 4,432,975 A; 4,532,411 A; 4,808,418 A; 4,810,276 B1; 5,238,472 B2; 5,800,048 B2; 2002/004648 A1

Specification includes a Sequence Listing.
GenomeSeq Exhibit 1020, Page 1

US 11,970,746 B2

United States Patent
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(45) Date of Patent: Apr. 30, 2024

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(71) Applicant: *Genzyme, Inc.*
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'746 Patent, Cl. 1

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:

- a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;
- b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and
- c) in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container.

Int. Cl. C12Q 1/02 (2006.01)
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CPC C12Q 1/02 (2006.01)
Field of Cl. C12Q 1/02 (2006.01)
See applicant's specification for complete search history.

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The Claims of the '746 Patent are Broader than the Claims of the '781 Patent

US 11,634,786

United States Patent

(12) **Language**

(10) Patent No.: US 11,634,786

(45) Date of Patent: Apr. 25, 2023

(54) Fecal Sample Processing and Analysis Comprising a Collection of Blood

(57) Abstract

(71) Applicant: Becton, Dickinson and Company

(72) Inventor: David J. B. Jones

(*) Notice: Section 101, 102, 103, 104, 105, 106, 107, 108, 109, 110, 111, 112, 113, 114, 115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132, 133, 134, 135, 136, 137, 138, 139, 140, 141, 142, 143, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, 163, 164, 165, 166, 167, 168, 169, 170, 171, 172, 173, 174, 175, 176, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189, 190, 191, 192, 193, 194, 195, 196, 197, 198, 199, 200, 201, 202, 203, 204, 205, 206, 207, 208, 209, 210, 211, 212, 213, 214, 215, 216, 217, 218, 219, 220, 221, 222, 223, 224, 225, 226, 227, 228, 229, 230, 231, 232, 233, 234, 235, 236, 237, 238, 239, 240, 241, 242, 243, 244, 245, 246, 247, 248, 249, 250, 251, 252, 253, 254, 255, 256, 257, 258, 259, 260, 261, 262, 263, 264, 265, 266, 267, 268, 269, 270, 271, 272, 273, 274, 275, 276, 277, 278, 279, 280, 281, 282, 283, 284, 285, 286, 287, 288, 289, 290, 291, 292, 293, 294, 295, 296, 297, 298, 299, 300, 301, 302, 303, 304, 305, 306, 307, 308, 309, 310, 311, 312, 313, 314, 315, 316, 317, 318, 319, 320, 321, 322, 323, 324, 325, 326, 327, 328, 329, 330, 331, 332, 333, 334, 335, 336, 337, 338, 339, 340, 341, 342, 343, 344, 345, 346, 347, 348, 349, 350, 351, 352, 353, 354, 355, 356, 357, 358, 359, 360, 361, 362, 363, 364, 365, 366, 367, 368, 369, 370, 371, 372, 373, 374, 375, 376, 377, 378, 379, 380, 381, 382, 383, 384, 385, 386, 387, 388, 389, 390, 391, 392, 393, 394, 395, 396, 397, 398, 399, 400, 401, 402, 403, 404, 405, 406, 407, 408, 409, 410, 411, 412, 413, 414, 415, 416, 417, 418, 419, 420, 421, 422, 423, 424, 425, 426, 427, 428, 429, 430, 431, 432, 433, 434, 435, 436, 437, 438, 439, 440, 441, 442, 443, 444, 445, 446, 447, 448, 449, 450, 451, 452, 453, 454, 455, 456, 457, 458, 459, 460, 461, 462, 463, 464, 465, 466, 467, 468, 469, 470, 471, 472, 473, 474, 475, 476, 477, 478, 479, 480, 481, 482, 483, 484, 485, 486, 487, 488, 489, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506, 507, 508, 509, 510, 511, 512, 513, 514, 515, 516, 517, 518, 519, 520, 521, 522, 523, 524, 525, 526, 527, 528, 529, 530, 531, 532, 533, 534, 535, 536, 537, 538, 539, 540, 541, 542, 543, 544, 545, 546, 547, 548, 549, 550, 551, 552, 553, 554, 555, 556, 557, 558, 559, 560, 561, 562, 563, 564, 565, 566, 567, 568, 569, 570, 571, 572, 573, 574, 575, 576, 577, 578, 579, 580, 581, 582, 583, 584, 585, 586, 587, 588, 589, 590, 591, 592, 593, 594, 595, 596, 597, 598, 599, 600, 601, 602, 603, 604, 605, 606, 607, 608, 609, 610, 611, 612, 613, 614, 615, 616, 617, 618, 619, 620, 621, 622, 623, 624, 625, 626, 627, 628, 629, 630, 631, 632, 633, 634, 635, 636, 637, 638, 639, 640, 641, 642, 643, 644, 645, 646, 647, 648, 649, 650, 651, 652, 653, 654, 655, 656, 657, 658, 659, 660, 661, 662, 663, 664, 665, 666, 667, 668, 669, 670, 671, 672, 673, 674, 675, 676, 677, 678, 679, 680, 681, 682, 683, 684, 685, 686, 687, 688, 689, 690, 691, 692, 693, 694, 695, 696, 697, 698, 699, 700, 701, 702, 703, 704, 705, 706, 707, 708, 709, 710, 711, 712, 713, 714, 715, 716, 717, 718, 719, 720, 721, 722, 723, 724, 725, 726, 727, 728, 729, 730, 731, 732, 733, 734, 735, 736, 737, 738, 739, 740, 741, 742, 743, 744, 745, 746, 747, 748, 749, 750, 751, 752, 753, 754, 755, 756, 757, 758, 759, 760, 761, 762, 763, 764, 765, 766, 767, 768, 769, 770, 771, 772, 773, 774, 775, 776, 777, 778, 779, 780, 781, 782, 783, 784, 785, 786, 787, 788, 789, 790, 791, 792, 793, 794, 795, 796, 797, 798, 799, 800, 801, 802, 803, 804, 805, 806, 807, 808, 809, 810, 811, 812, 813, 814, 815, 816, 817, 818, 819, 820, 821, 822, 823, 824, 825, 826, 827, 828, 829, 830, 831, 832, 833, 834, 835, 836, 837, 838, 839, 840, 841, 842, 843, 844, 845, 846, 847, 848, 849, 850, 851, 852, 853, 854, 855, 856, 857, 858, 859, 860, 861, 862, 863, 864, 865, 866, 867, 868, 869, 870, 871, 872, 873, 874, 875, 876, 877, 878, 879, 880, 881, 882, 883, 884, 885, 886, 887, 888, 889, 890, 891, 892, 893, 894, 895, 896, 897, 898, 899, 900, 901, 902, 903, 904, 905, 906, 907, 908, 909, 910, 911, 912, 913, 914, 915, 916, 917, 918, 919, 920, 921, 922, 923, 924, 925, 926, 927, 928, 929, 930, 931, 932, 933, 934, 935, 936, 937, 938, 939, 940, 941, 942, 943, 944, 945, 946, 947, 948, 949, 950, 951, 952, 953, 954, 955, 956, 957, 958, 959, 960, 961, 962, 963, 964, 965, 966, 967, 968, 969, 970, 971, 972, 973, 974, 975, 976, 977, 978, 979, 980, 981, 982, 983, 984, 985, 986, 987, 988, 989, 990, 991, 992, 993, 994, 995, 996, 997, 998, 999, 1000, 1001, 1002, 1003, 1004, 1005, 1006, 1007, 1008, 1009, 1010, 1011, 1012, 1013, 1014, 1015, 1016, 1017, 1018, 1019, 1020, 1021, 1022, 1023, 1024, 1025, 1026, 1027, 1028, 1029, 1030, 1031, 1032, 1033, 1034, 1035, 1036, 1037, 1038, 1039, 1040, 1041, 1042, 1043, 1044, 1045, 1046, 1047, 1048, 1049, 1050, 1051, 1052, 1053, 1054, 1055, 1056, 1057, 1058, 1059, 1060, 1061, 1062, 1063, 1064, 1065, 1066, 1067, 1068, 1069, 1070, 1071, 1072, 1073, 1074, 1075, 1076, 1077, 1078, 1079, 1080, 1081, 1082, 1083, 1084, 1085, 1086, 1087, 1088, 1089, 1090, 1091, 1092, 1093, 1094, 1095, 1096, 1097, 1098, 1099, 1100, 1101, 1102, 1103, 1104, 1105, 1106, 1107, 1108, 1109, 1110, 1111, 1112, 1113, 1114, 1115, 1116, 1117, 1118, 1119, 1120, 1121, 1122, 1123, 1124, 1125, 1126, 1127, 1128, 1129, 1130, 1131, 1132, 1133, 1134, 1135, 1136, 1137, 1138, 1139, 1140, 1141, 1142, 1143, 1144, 1145, 1146, 1147, 1148, 1149, 1150, 1151, 1152, 1153, 1154, 1155, 1156, 1157, 1158, 1159, 1160, 1161, 1162, 1163, 1164, 1165, 1166, 1167, 1168, 1169, 1170, 1171, 1172, 1173, 1174, 1175, 1176, 1177, 1178, 1179, 1180, 1181, 1182, 1183, 1184, 1185, 1186, 1187, 1188, 1189, 1190, 1191, 1192, 1193, 1194, 1195, 1196, 1197, 1198, 1199, 1200, 1201, 1202, 1203, 1204, 1205, 1206, 1207, 1208, 1209, 1210, 1211, 1212, 1213, 1214, 1215, 1216, 1217, 1218, 1219, 1220, 1221, 1222, 1223, 1224, 1225, 1226, 1227, 1228, 1229, 1230, 1231, 1232, 1233, 1234, 1235, 1236, 1237, 1238, 1239, 1240, 1241, 1242, 1243, 1244, 1245, 1246, 1247, 1248, 1249, 1250, 1251, 1252, 1253, 1254, 1255, 1256, 1257, 1258, 1259, 1260, 1261, 1262, 1263, 1264, 1265, 1266, 1267, 1268, 1269, 1270, 1271, 1272, 1273, 1274, 1275, 1276, 1277, 1278, 1279, 1280, 1281, 1282, 1283, 1284, 1285, 1286, 1287, 1288, 1289, 1290, 1291, 1292, 1293, 1294, 1295, 1296, 1297, 1298, 1299, 1300, 1301, 1302, 1303, 1304, 1305, 1306, 1307, 1308, 1309, 1310, 1311, 1312, 1313, 1314, 1315, 1316, 1317, 1318, 1319, 1320, 1321, 1322, 1323, 1324, 1325, 1326, 1327, 1328, 1329, 1330, 1331, 1332, 1333, 1334, 1335, 1336, 1337, 1338, 1339, 1340, 1341, 1342, 1343, 1344, 1345, 1346, 1347, 1348, 1349, 1350, 1351, 1352, 1353, 1354, 1355, 1356, 1357, 1358, 1359, 1360, 1361, 1362, 1363, 1364, 1365, 1366, 1367, 1368, 1369, 1370, 1371, 1372, 1373, 1374, 1375, 1376, 1377, 1378, 1379, 1380, 1381, 1382, 1383, 1384, 1385, 1386, 1387, 1388, 1389, 1390, 1391, 1392, 1393, 1394, 1395, 1396, 1397, 1398, 1399, 1400, 1401, 1402, 1403, 1404, 1405, 1406, 1407, 1408, 1409, 1410, 1411, 1412, 1413, 1414, 1415, 1416, 1417, 1418, 1419, 1420, 1421, 1422, 1423, 1424, 1425, 1426, 1427, 1428, 1429, 1430, 1431, 1432, 1433, 1434, 1435, 1436, 1437, 1438, 1439, 1440, 1441, 1442, 1443, 1444, 1445, 1446, 1447, 1448, 1449, 1450, 1451, 1452, 1453, 1454, 1455, 1456, 1457, 1458, 1459, 1460, 1461, 1462, 1463, 1464, 1465, 1466, 1467, 1468, 1469, 1470, 1471, 1472, 1473, 1474, 1475, 1476, 1477, 1478, 1479, 1480, 1481, 1482, 1483, 1484, 1485, 1486, 1487, 1488, 1489, 1490, 1491, 1492, 1493, 1494, 1495, 1496, 1497, 1498, 1499, 1500, 1501, 1502, 1503, 1504, 1505, 1506, 1507, 1508, 1509, 1510, 1511, 1512, 1513, 1514, 1515, 1516, 1517, 1518, 1519, 1520, 1521, 1522, 1523, 1524, 1525, 1526, 1527, 1528, 1529, 1530, 1531, 1532, 1533, 1534, 1535, 1536, 1537, 1538, 1539, 1540, 1541, 1542, 1543, 1544, 1545, 1546, 1547, 1548, 1549, 1550, 1551, 1552, 1553, 1554, 1555, 1556, 1557, 1558, 1559, 1560, 1561, 1562, 1563, 1564, 1565, 1566, 1567, 1568, 1569, 1570, 1571, 1572, 1573, 1574, 1575, 1576, 1577, 1578, 1579, 1580, 1581, 1582, 1583, 1584, 1585, 1586, 1587, 1588, 1589, 1590, 1591, 1592, 1593, 1594, 1595, 1596, 1597, 1598, 1599, 1600, 1601, 1602, 1603, 1604, 1605, 1606, 1607, 1608, 1609, 1610, 1611, 1612, 1613, 1614, 1615, 1616, 1617, 1618, 1619, 1620, 1621, 1622, 1623, 1624, 1625, 1626, 1627, 1628, 1629, 1630, 1631, 1632, 1633, 1634, 1635, 1636, 1637, 1638, 1639, 1640, 1641, 1642, 1643, 1644, 1645, 1646, 1647, 1648, 1649, 1650, 1651, 1652, 1653, 1654, 1655, 1656, 1657, 1658, 1659, 1660, 1661, 1662, 1663, 1664, 1665, 1666, 1667, 1668, 1669, 1670, 1671, 1672, 1673, 1674, 1675, 1676, 1677, 1678, 1679, 1680, 1681, 1682, 1683, 1684, 1685, 1686, 1687, 1688, 1689, 1690, 1691, 1692, 1693, 1694, 1695, 1696, 1697, 1698, 1699, 1700, 1701, 1702, 1703, 1704, 1705, 1706, 1707, 1708, 1709, 1710, 1711, 1712, 1713, 1714, 1715, 1716, 1717, 1718, 1719, 1720, 1721, 1722, 1723, 1724, 1725, 1726, 1727, 1728, 1729, 1730, 1731, 1732, 1733, 1734, 1735, 1736, 1737, 1738, 1739, 1740, 1741, 1742, 1743, 1744, 1745, 1746, 1747, 1748, 1749, 1750, 1751, 1752, 1753, 1754, 1755, 1756, 1757, 1758, 1759, 1760, 1761, 1762, 1763, 1764, 1765, 1766, 1767, 1768, 1769, 1770, 1771, 1772, 1773, 1774, 1775, 1776, 1777, 1778, 1779, 1780, 1781, 1782, 1783, 1784, 1785, 1786, 1787, 1788, 1789, 1790, 1791, 1792, 1793, 1794, 1795, 1796, 1797, 1798, 1799, 1800, 1801, 1802, 1803, 1804, 1805, 1806, 1807, 1808, 1809, 1810, 1811, 1812, 1813, 1814, 1815, 1816, 1817, 1818, 1819, 1820, 1821, 1822, 1823, 1824, 1825, 1826, 1827, 1828, 1829, 1830, 1831, 1832, 1833, 1834, 1835, 1836, 1837, 1838, 1839, 1840, 1841, 1842, 1843, 1844, 1845, 1846, 1847, 1848, 1849, 1850, 1851, 1852, 1853, 1854, 1855, 1856, 1857, 1858, 1859, 1860, 1861, 1862, 1863, 1864, 1865, 1866, 1867, 1868, 1869, 1870, 1871, 1872, 1873, 1874, 1875, 1876, 1877, 1878, 1879, 1880, 1881, 1882, 1883, 1884, 1885, 1886, 1887, 1888, 1889, 1890, 1891, 1892, 1893, 1894, 1895, 1896, 1897, 1898, 1899, 1900, 1901, 1902, 1903, 1904, 1905, 1906, 1907, 1908, 1909, 1910, 1911, 1912, 1913, 1914, 1915, 1916, 1917, 1918, 1919, 1920, 1921, 1922, 1923, 1924, 1925, 1926, 1927, 1928, 1929, 1930, 1931, 1932, 1933, 1934, 1935, 1936, 1937, 1938, 1939, 1940, 1941, 1942, 1943, 1944, 1945, 1946, 1947, 1948, 1949, 1950, 1951, 1952, 1953, 1954, 1955, 1956, 1957, 1958, 1959, 1960, 1961, 1962, 1963, 1964, 1965, 1966, 1967, 1968, 1969, 1970, 1971, 1972, 1973, 1974, 1975, 1976, 1977, 1978, 1979, 1980, 1981, 1982, 1983, 1984, 1985, 1986, 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016, 2017, 2018, 2019, 2020, 2021, 2022, 2023, 2024, 2025, 2026, 2027, 2028, 2029, 2030, 2031, 2032, 2033, 2034, 2035, 2036, 2037, 2038, 2039, 2040, 2041, 2042, 2043, 2044, 2045, 2046, 2047, 2048, 2049, 2050, 2051, 2052, 2053, 2054, 2055, 2056, 2057, 2058, 2059, 2060, 2061, 2062, 2063, 2064, 2065, 2066, 2067, 2068, 2069, 2070, 2071, 2072, 2073, 2074, 2075, 2076, 2077, 2078, 2079, 2080, 2081, 2082, 2083, 2084, 2085, 2086, 2087, 2088, 2089, 2090, 2091, 2092, 2093, 2094, 2095, 2096, 2097, 2098, 2099, 2100, 2101, 2102, 2103, 2104, 2105, 2106, 2107, 2108, 2109, 2110, 2111, 2112, 2113, 2114, 2115, 2116, 2117, 2118, 2119, 2120, 2121, 2122, 2123, 2124, 2125, 2126, 2127, 2128, 2129, 2130, 2131, 2132, 2133, 2134, 2135, 2136, 2137, 2138, 2139, 2140, 2141, 2142, 2143, 2144, 2145, 2146, 2147, 2148, 2149, 2150, 2151, 2152, 2153, 2154, 2155, 2156, 2157, 2158, 2159, 2160, 2161, 2162, 2163, 2164, 2165, 2166, 2167, 2168, 2169, 2170, 2171, 2172, 2173, 2174, 2175, 2176, 2177, 2178, 2179, 2180, 2181, 2182, 2183, 2184, 2185, 2186, 2187, 2188, 2189, 2190, 2191, 2192, 2193, 2194, 2195, 2196, 2197, 2198, 2199, 2200, 2201, 2202, 2203, 2204, 2205, 2206, 2207, 2208, 2209, 2210, 2211, 2212, 2213, 2214, 2215, 2216, 2217, 2218, 2219, 2220, 2221, 2222, 2223, 2224, 2225, 2226, 2227, 2228, 2229, 2230, 2231, 2232, 2233, 2234, 2235, 2236, 2237, 2238, 2239, 2240, 2241, 2242, 2243, 2244, 2245, 2246, 2247, 2248, 2249, 2250, 2251, 2252, 2253, 2254, 2255, 2256, 2257, 2258, 2259, 2260, 2261, 2262, 2263, 2264, 2265, 22

The Claims of the '746 Patent were Rejected for Obviousness-type Double Patenting over the Claims of the '781 Patent, which Exact Overcame by Filing a Terminal Disclaimer

► **Claim(s) 1-20** is/are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1-20 of U.S. Patent No. 11,634,781 (hereinafter "US -781").

Although the conflicting claims are not identical, they are not patentably distinct from each other. For example, Claim 1 of US-781 teach a method of processing a freshly-collected fecal sample without freezing that comprises collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject; in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container.

EX1018
(OA Dated July 6, 2023),
at 4

Solely in the interest of expediting prosecution, Applicant herewith files terminal disclaimers over Application Ser. No. 18/179,961 and US Patent No. 11,634,781 to obviate the present rejections. Applicant notes that the filing of a terminal disclaimer to obviate a rejection based on non-statutory double patenting is not an admission of the propriety of the rejection.

EX1019
(OAR Dated October 6, 2023),
at 6

Petition, at 10-11

Demonstrative Exhibit - Not Evidence

Overlapping Grounds of Unpatentability were Asserted Against '781 Patent in IPR2024-00459

IPR2024-00459 ('781 Patent)

Ground	Claims	Prior Art
I	1-9, 11, 14-20	Lenhard, Vilkin, and Itzkowitz
II	12 and 13	Lenhard, Vilkin, Itzkowitz, and Kanaoka
III	10	Lenhard, Vilkin, Itzkowitz, and Derks
IV	1-9, 11, 14-20	Shuber and Vilkin
VI	12 and 13	Shuber, Vilkin, and Kanaoka
VII	10	Shuber, Vilkin, and Derks

Current IPR ('746 Patent)

Ground	Claims	Prior Art
I	1-4, 14-19	Lenhard, Vilkin, and Itzkowitz
II	12 and 13	Lenhard, Vilkin, Itzkowitz, and Kanaoka
III	1-4, 14-19	Shuber and Vilkin
IV	12 and 13	Shuber, Vilkin, and Kanaoka
V	1 and 2*	Inbar
VI	1-4, 14-19	Inbar, Vilkin, and Shuber
VII	12 and 13	Inbar, Vilkin, Shuber, and Kanaoka

*** Patent Owner Statutorily Disclaimed claims 1 and 2 prior to institution of Current IPR (See: EX 2041)**

Petition, at 1-2, 12; EX1031 (IPR2025-00459 Petition), at 12; EX2041 (Disclaimer), at 3

IPR2024-00459: The Board Found the Narrower Claims of the '781 Patent Obvious

FWD

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Page 39
Date: July 9, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.
EXACT SCIENCES CORPORATION,
Patent Owner.

IPR2024-00459
Patent 11,634,781 B2

Before RYAN H. FLAX, DAVID COTTA, and JAMIE T. WISZ,
Administrative Patent Judges.

FLAX, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

4. Summary and Conclusion

Having considered the arguments and evidence presented at trial, we find Petitioner has shown by a preponderance of the evidence that claims 1–9, 11, and 14–20 are unpatentable as obvious over Lenhard, Vilkin, and Itzkowitz, that claims 12 and 13 are unpatentable as obvious over this same prior art combination adding Kanaoka’s disclosed techniques of using RNA as a CRC biomarker,

FWD

4. Summary and Conclusion

Having considered the arguments and evidence presented at trial, we find Petitioner has shown by a preponderance of the evidence that claims 1–9, 11, and 14–20 are unpatentable as obvious over Shuber and Vilkin, claims 12 and 13 are unpatentable as obvious over Shuber, Vilkin, and Kanaoka,

EX1087 (FWD), at 57, 69; Reply, at 1-2, 14, 18-19

Demonstrative Exhibit - Not Evidence

Claims of the '746 Patent Are Directed to Performance of Two Prior Art Assays to Detect CRC in a Fecal Sample

United States Patent

(10) Patent No.: US 11,970,746 B2
(12) Date of Patent: Apr. 30, 2024

Lawage

FECAL SAMPLE PROCESSING AND ANALYSIS COMPRISING DETECTION OF BLOOD

(54) Applicant: Exact Sciences Corporation, Madison, WI (US)

(72) Inventor: Janet Lawage, Denmark (CL)

(73) Assignee: Exact Sciences Corporation, Madison, WI (US)

(*) Notice: Subject to any disclaimer, the term of this patent, which was filed in the United States on Jan. 15, 2016, has been adjusted under 35 U.S.C. 154(b) by 0.6 years to expire on Feb. 13, 2032.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: 18/476,945

(22) Filed: Mar. 7, 2023

(65) Prior Publication Data

US 2023/031317 A1 Oct. 5, 2023

Related U.S. Application Data

(63) Continuation of U.S. application Ser. No. 17/400,000, filed on Jun. 28, 2022, now Pat. No. 11,074,781, which is a continuation of application No. 15/634,607, filed on Jan. 28, 2018, now Pat. No. 10,410,436, filed on Jan. 29, 2016, now Pat. No. 9,818,416, which is a continuation of application No. 13/147,576, filed on Feb. 13, 2016, now abandoned.

(60) Provisional Application No. 61/149,581, filed on Feb. 3, 2009.

Foreign Application Priority Data

(30) Feb. 3, 2010 (WO) PCT/GB2010/00180

(51) Int. Cl.
C12Q 1/0484

(52) G01N 1/3374

(53) C12Q 1/0486 (2013.01); G01N 1/03746

(54) G01N 1/0374 (2013.01); G01N 1/03746

(55) G01N 1/0374 (2013.01); G01N 1/03746

(56) G01N 1/0374 (2013.01); G01N 1/03746

(57) G01N 1/0374 (2013.01); G01N 1/03746

(58) Field of Invention: The present invention relates to the field of

fecal sample processing and analysis, and more particularly to the

analysis of fecal samples for the detection of blood.

See application file for complete search history.

US2023/031317 A1

(56)

References Cited

U.S. PATENT DOCUMENTS

4,447,251 A

4,448,251 A

4,449,251 A

4,450,251 A

4,451,251 A

4,452,251 A

4,453,251 A

4,454,251 A

4,455,251 A

4,456,251 A

4,457,251 A

4,458,251 A

4,459,251 A

4,460,251 A

4,461,251 A

4,462,251 A

4,463,251 A

4,464,251 A

4,465,251 A

4,466,251 A

4,467,251 A

4,468,251 A

4,469,251 A

4,470,251 A

4,471,251 A

4,472,251 A

4,473,251 A

4,474,251 A

4,475,251 A

4,476,251 A

4,477,251 A

4,478,251 A

4,479,251 A

4,480,251 A

4,481,251 A

4,482,251 A

4,483,251 A

4,484,251 A

4,485,251 A

4,486,251 A

4,487,251 A

4,488,251 A

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4,49

3. A method of processing a fecal sample, the method comprising:

- a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising:
 - i) a sealed sealable vessel containing a first portion of a fecal sample and a stabilizing buffer; and
 - ii) a sealed sealable container containing a second portion of a fecal sample and a solution that prevents denaturation or degradation of blood proteins found in a fecal sample,wherein the pair of portions are obtained by the method of claim 1;
- b) extracting nucleic acid from the first portion of the fecal sample;
- c) testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid; and
- d) testing the second portion of the fecal sample for an amount of a blood protein present in the second portion of the fecal sample.

State of the Art: Fecal DNA CRC Assays

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:

- a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;
- b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and

3. A method of processing a fecal sample, the method comprising:

- a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising:
 - i) a sealed sealable vessel containing a first portion of a fecal sample and a stabilizing buffer; and

b) extracting nucleic acid from the first portion of the fecal sample;

c) testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid;

Petition, at 1, 15-17; EX1006 (Itzkowitz); EX1008 (Shuber)

Demonstrative Exhibit - Not Evidence



Steps of at-home fecal DNA assay,
as disclosed in
Itzkowitz (EX1006) and
Shuber (EX1008)

State of the Art: Immunochemical Fecal Occult Blood Tests (iFOBT or FIT)

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:

a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;

c) in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container.

3. A method of processing a fecal sample, the method comprising:

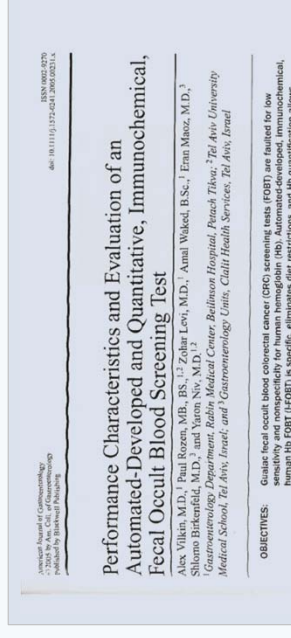
a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising:

ii) a sealed sealable container containing a second portion of a fecal sample and a solution that prevents denaturation or degradation of blood proteins found in a fecal sample,

d) testing the second portion of the fecal sample for an amount of a blood protein present in the second portion of the fecal sample.

Petition, at 1, 14-15; EX1005 (Vilkin)

Demonstrative Exhibit - Not Evidence



Steps of at-home iFOBT assay, as disclosed in Vilkin (EX1005)

The standard guaiac fecal occult blood test (g-FOBT) is flawed for its low sensitivity for significant colorectal neoplasia (colorectal cancer (CRC) and advanced adenomatous polyps (AAP)), and low specificity due to nonspecificity for polyps (AAP), and low specificity due to nonspecificity for polyps (AAP). The introduction of such methodology, for large-scale screening, necessitates the development of a test with its true sensitivity and specificity for colorectal neoplasia versus colonoscopy in different clinical settings, and demonstrates which level of fecal iFB should trigger follow-up.

Specific aims were to determine 1) test-development reproducibility, 2) effect of temperature and duration of storage on fecal sample stability, 3) inpatient daily i-FOBT test variance, 4) sensitivity and specificity for neoplasia found

The automated-developed and quantitative i-FOBT is the first iFB specific, eliminates the need for diet restrictions, and the iFB quantification allows selection of a suitable threshold level for follow-up colonoscopy (5-7, 9-12). The introduction of such methodology, for large-scale screening, necessitates the development of a test with its true sensitivity and specificity for colorectal neoplasia versus colonoscopy in different clinical settings, and demonstrates which level of fecal iFB should trigger follow-up.

Specific aims were to determine 1) test-development reproducibility, 2) effect of temperature and duration of storage on fecal sample stability, 3) inpatient daily i-FOBT test variance, 4) sensitivity and specificity for neoplasia found

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2019

Gastroenterology Exhibit 1005, Page 3

[illegible]

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:
 - a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;
 - b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and
 - c) in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container.

- Petition, at 1, 14-17; EX1005 (Vilkin); EX1006 (Itzkowitz); EX1008 (Shuber)
- Demonstrative Exhibit - Not Evidence

Ground I: Lenhard, Vilkin and Itzkowitz

Claims 1-4, 14-19

IPR2024-00459: The Board Found the Narrower Claims of the '781 Patent Obvious Over Lenhard, Itzkowitz, and Vilkin

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Page 39
Date: July 9, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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Before RYAN H. FLAX, DAVID COTTA, and JAMIE T. WISZ,
Administrative Patent Judges.

FLAX, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

FWD

Based on the above, we find that the combination of Lenhard, Vilkin, and Itzkowitz teaches or suggests each step and element of claims 1–9, 11, and 14–20, and that the addition to this prior art combination of the subject matter taught by Kanaoka and Derks teaches or suggests the subject matter of claims 10, 12, and 13. Contrary to Patent Owner’s argument, we find no unreasonable “picking and choosing” in Petitioner’s citations to the teachings of Vilkin and Itzkowitz because the subject matter they disclose and that would be incorporated into the methods of Lenhard is the substantial focus of each reference rather than a mere component that might be selected from a great number of options. *See* Ex. 1005; Ex. 1006.

FWD

Based on the above, we conclude there would have been significant motivation for the person of ordinary skill in the art to combine Lenhard, Vilkin, and Itzkowitz (and also Kanaoka and Derks for their limited purposes) and that Petitioner has identified a reason with rational underpinning why the ordinarily skilled artisan would have done so with a reasonable expectation of success.

EX1087 (FWD), at 50, 53; Reply, at 1-2

Demonstrative Exhibit - Not Evidence

15

Lenhard's Combined Test

Sample collected

Sample received at
diagnostic laboratory

Portion of sample removed and
tested by gFOBT

DNA extracted from remaining
portion of sample

Extracted DNA tested for
DNA methylation

Petition, at 13, 19-20; EX1004 (Lenhard)

Demonstrative Exhibit - Not Evidence

Lenhard

CLINICAL GASTROENTEROLOGY AND HEPATOLOGY 2005;3:140-149

Analysis of Promoter Methylation in Stool: A Novel Method for the Detection of Colorectal Cancer

KONSTANZE LENHARD,* GUIDO T. BOMMER, SILKE ASUTAY,* ROLF SCHAUER,*
TOMAS BRADLETZ, BURKHARD GÖKE,* ROLF LAMERZ,* and FRANK T. KOLLIGS*

From the *Department of Gastroenterology, University of Erlangen, Germany; and the *Institute of Pathology, University of Erlangen, Germany

Background & Aims: Detection of tumor-derived DNA alterations in stool is an intriguing new approach with high potential for the noninvasive detection of colorectal cancer (CRC). Because of heterogeneity of tumors, usually multiple markers distributed throughout the human colon are required to detect CRC. However, the use of markers with high sensitivity and good specificity are needed. We explored the potential of a single epigenetic marker in comparison with fecal occult blood testing (FOBT) for the detection of CRC. **Methods:** Methylation-specific polymerase chain reaction (PCR) was performed to analyze hypermethylated in cancer 1 (HIC1) promoter methylation status in a blinded fashion in stool samples from 100 patients with colorectal adenoma >1 cm, 9 with hyperplastic polyps, 4 with chronic inflammatory bowel disease, and 32 with endoscopically normal colon. **Results:** Ninety-seven percent of the stool samples contained amplifiable DNA. Forty-two percent of the samples from patients with colorectal adenoma >1 cm were positive for HIC1 promoter methylation. No methylated HIC1 promoter DNA was detected in the fecal DNA from patients with endoscopically normal colon. **Conclusions:** The use of a single epigenetic marker HIC1 promoter methylation carries a high potential for the remote detection of CRCs. We postulate that a panel of merely a few genetic and epigenetic markers will be required for the highly sensitive and specific detection of CRCs and adenomas in fecal samples from affected patients.

Colorectal cancer (CRC) is one of the leading causes of cancer-related morbidity and mortality.¹ About 40% of patients die within 5 years of being diagnosed. This mainly is attributable to late presentation with locally advanced or metastatic disease in one third of cases, precluding curative surgery.² The majority of CRCs remain undetected until late stages, starting a time period of usually more than 10 years.³ Detection

of early disease and precancerous adenomatous lesions leads to a decreased risk of CRC and thus to a reduced mortality.⁴⁻⁶ Therefore, there is a strong rationale for screening programs. Sigmoidoscopy, colonoscopy, and fecal occult blood test (FOBT) alone or in combination with endoscopy, are recommended for screening of the average-risk population.⁶ However, FOBT, when applied regularly, can detect precancerous lesions only in 10% to 15% of cases with endoscopic follow-up.^{7,8} In contrast, colonoscopy, in 1998, only 37% of eligible adults in the United States had been screened for CRC in the previous 5 years.⁹

Detection of tumor-derived genetic changes in stool is a promising new approach for CRC screening. Studies in patients with colorectal adenomas and adenocarcinomas in oncogenes,¹⁰⁻¹² and tumor-suppressor genes,¹³⁻¹⁹ as well as changes in microsatellite markers,²⁰ Two recent studies required the analysis of up to 15 different genetic markers²¹ or 144 aliquots from each stool²² for the detection of 91% and 61% of CRCs and adenomas, respectively. Such a high number of markers and the need for a high degree of sensitivity and specificity. This precludes their application for intensive and costly. The identification of new markers with high sensitivities and specificities is needed. So far, little attention has been paid to DNA hypermethylation as a potential stool marker for CRC.

Methylation-specific PCR (MS-PCR) has been used successfully to detect DNA methylation in primary tumors and in various body fluids.²³ The feasibility of amplification of methylated DNA by PCR has been demonstrated in stool samples.^{24,25} Methylation-specific polymerase chain reaction (PCR) (MS-PCR) has been used successfully to detect DNA methylation in primary tumors and in various body fluids.²³ The feasibility of amplification of methylated DNA by PCR has been demonstrated in stool samples.^{24,25}

Abbreviations used in this paper: G, guanine; HIC1, hypermethylated in cancer 1; MSP, methylation-specific PCR; PCR, polymerase chain reaction; T, thymine.

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1542-3566/05/030140-10\$15.00
DOI: 10.1016/j.cgh.2005.02.024
Gastroenterology Exhibit 1004, Page 1

IPR2024-00459: The Board Found Lenhard Unquestionably Teaches a Combined Blood and Nucleic Acid Test

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Page: 39
Date: July 9, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

FWD

Lenhard unquestionably teaches a combined blood and nucleic acid, dual-portioned, fecal screening test for CRCs, but it is by no means the only incidence or suggestion of such in the prior art of record.

Before RYAN H.
Administrative Law Judge
FLAX, *Adminis*

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

EX1087 (FWD), at 47; Reply, at 5;
Demonstrative Exhibit - Not Evidence

Lenhard Discloses a Test that Combines a Fecal DNA Assay and an FOBT

tissue.³¹ We show that HIC1 promoter methylation can be detected frequently and with high specificity in stool samples from patients with CRCs. The combination of HIC1 methylation analysis with FOBT allowed for the detection of two thirds of CRCs.

more adenomas (31% vs. 8%, $P = .14$). In addition, specificity of the HIC1 assay was higher (97.9% vs. 89.9%, $P = .102$). The combination of both assays resulted in increased detection rates for CRCs (65%; 95% CI, 44%–83%). Although the combined test detected all localized cancers, no increase in the sensitivity for adenoma was seen.

The use of the DNA methylation marker, HIC1 promoter methylation, allowed for the highly specific detection of CRCs in 42% and of adenomas ≥ 1 cm in 31% of cases. Interestingly, sensitivity was quite high for early cancers and higher for adenoma than FOBT. The combination of HIC1 MSP with FOBT resulted in the detection of almost two thirds of CRCs.

Table 4. Positivity Rates of the Fecal DNA Assay, FOBT, and Combination of the Tests

	HIC1		FOBT		Combined	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
All cancers	11/26 (42)	23%–63%	9/26 (35)	17%–56%	17/26 (65)	44%–83%
Localized cancers	4/6 (67)	22%–96%	2/6 (33)	4%–77%	6/6 (100)	12%–188% ^a
Advanced cancers	5/20 (25)	9%–49%	7/20 (35)	15%–59%	11/20 (55)	32%–77%
Rectum and sigmoid colon	5/13 (39)	14%–68%	5/13 (39)	14%–68%	9/13 (69)	39%–91%
From descending colon to cecum	6/13 (46)	19%–75%	4/13 (31)	14%–68%	8/13 (62)	39%–91%
Asymptomatic cases	4/10 (40)	12%–74%	3/10 (30)	7%–65%	6/10 (60)	26%–88%
Symptomatic cases	7/16 (44)	20%–70%	6/16 (38)	15%–65%	11/16 (69)	41%–89%
Adenomas	4/13 (31)	9%–61%	1/13 (8)	2%–36%	4/13 (31)	9%–61%

^aEstimated by normal approximation of Poisson distribution.

Petition, at 13, 19; EX1004 (Lenhard), at 143, 146-47

Demonstrative Exhibit - Not Evidence

Lenhard's Combined Test Reduces False Negatives for CRC Detection

Analysis of Promoter Methylation in Stool: A Novel Method for the Detection of Colorectal Cancer

KONSTANZE LENHARD,* GUIDO T. BOMMER,* SILKE ASUTAY,* ROLF SCHAEFER,*

WOLFGANG KASSEL,†‡§, BERNHARD KRECH,§ ROLF KRECH,§ ROLF KOLLOS,*

*Department of Medicine I, and †Department of Surgery, ‡Institute of Pathology, and §Institute of Radiology, University of Erlangen, Germany

Background & Aims: Detection of tumor-derived DNA alterations in stool is an intriguing new approach with high potential for the noninvasive detection of colorectal cancer (CRC). Because of heterogeneity of tumors, usually multiple markers distributed throughout the human colon are necessary to detect all CRCs. However, the use of markers with high sensitivity and good specificity are needed. We explored the potential of a single epigenetic marker in comparison with fecal occult blood testing (FOBT) for the detection of CRC. **Methods:** Methylation-specific polymerase chain reaction (PCR) was performed to analyze hypermethylated in cancer 1 (HIC1) promoter methylation status in a blinded fashion in stool samples from 28 patients with CRC, 13 with adenomas, and 121 with normal colon. **Results:** Ninety-seven percent of the stool samples contained amplifiable DNA. Forty-two percent of the samples from patients with CRC and 23% of the samples from patients with adenomas were positive for HIC1 promoter methylation. No focal DNA from patients with endoscopically normal colon or hyperplastic polyps. **Conclusions:** The epigenetic marker HIC1 promoter methylation in stool has the potential for the remote detection of CRCs. We postulate that a panel of merely a few genetic and epigenetic markers will be required for the highly sensitive and specific detection of CRCs and adenomas in fecal samples from affected patients.

Colorectal cancer (CRC) is one of the leading causes of cancer-related morbidity and mortality.¹ About 40% of patients die within 5 years of being diagnosed. This mainly is attributable to late presentation with locally advanced or metastatic disease in one third of cases, precluding curative surgery.² The majority of CRCs follow the adenoma-carcinoma sequence, requiring a time period of usually more than 10 years. Detection

of early disease and precancerous adenomatous lesions is a promising new approach for CRC screening. Since there is a strong rationale for screening programs, there is a strong rationale for screening programs. Sigmoidoscopy, colonoscopy, and fecal occult blood (FOBT) alone or in combination with endoscopy, are recommended for screening of the average-risk population.³ However, FOBT, when applied regularly, does not allow for high-throughput screening. Therefore, markers with high sensitivity and good specificity are needed. We explored the potential of a single epigenetic marker in comparison with fecal occult blood testing (FOBT) for the detection of CRC.

Methods: Methylation-specific polymerase chain reaction (PCR) was performed to analyze hypermethylated in cancer 1 (HIC1) promoter methylation status in a blinded fashion in stool samples from 28 patients with CRC, 13 with adenomas, and 121 with normal colon. **Results:** Ninety-seven percent of the stool samples contained amplifiable DNA. Forty-two percent of the samples from patients with CRC and 23% of the samples from patients with adenomas were positive for HIC1 promoter methylation. No focal DNA from patients with endoscopically normal colon or hyperplastic polyps. **Conclusions:** The epigenetic marker HIC1 promoter methylation in stool has the potential for the remote detection of CRCs. We postulate that a panel of merely a few genetic and epigenetic markers will be required for the highly sensitive and specific detection of CRCs and adenomas in fecal samples from affected patients.

Colorectal cancer (CRC) is one of the leading causes of cancer-related morbidity and mortality.¹ About 40% of patients die within 5 years of being diagnosed. This mainly is attributable to late presentation with locally advanced or metastatic disease in one third of cases, precluding curative surgery.² The majority of CRCs follow the adenoma-carcinoma sequence, requiring a time period of usually more than 10 years. Detection

Table 1. Clinicopathologic Data and HIC1 Methylation Status of Patients With CRC

No.	Sex	Age (y)	UICC stage	Localization	Symptoms ^a	HIC1 methylation	FOBT
1	M	71	IV	Sigmoid colon/rectum	1	-	-
2	F	75	III	Sigmoid colon	1,3	-	-
3	M	66	IV	Descending/sigmoid colon	0	-	-
4	M	69	II	Ascending colon	0	+	-
5	M	65	III	Transverse colon	0	+	+
6	M	56	IV	Rectum	1	+	+
7	M	63	IV	Ascending colon	2	-	-
8	F	72	III	Cecum	2	+	+
9	M	74	III	Sigmoid colon/rectum	0	-	+
10	M	68	IV	Rectum	3	+	+
11	M	66	IV	Rectum	1	-	+
12	M	75	III	Cecum	0	-	-
13	M	71	IV	Sigmoid colon	0	+	-
14	M	67	IV	Hepatic flexure	3	+	-
15	F	72	IV	Sigmoid colon	1,2	+	-
16	M	59	II	Rectum	0	+	-
17	M	59	II	Rectum	0	-	+
18	M	53	III	Descending colon	0	-	-
19	F	55	IV	Rectum	2	-	+
20	F	61	IV	Sigmoid colon	2,3	-	-
21	M	61	IV	Rectum	0	-	-
22	M	80	II	Transverse colon	2	+	-
23	F	53	IV	Ascending colon	1,3	-	-
24	M	63	I	Cecum	4	NA	+
25	M	76	III	Transverse colon	2	-	+
26	F	60	IV	Ascending colon	1	+	-

UICC, International Union Against Cancer; M, male; F, female; NA, no amplification.
^a0, no symptoms; 1, change in bowel habits; 2, blood admixed with stool; 3, abdominal pain; 4, anemia.

IPR2024-00459: The Board Found Lenhard Was Not the Only Suggestion in the Art of Combining Blood and Nucleic Acid Tests

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Page: 39
Date: July 9, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Before RYAN H
Administrative Law
JUDGE

FLAX, Adminis

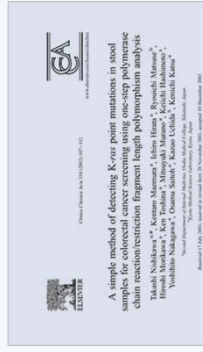
JUDGMENT

Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

FWD

Lenhard unquestionably teaches a combined blood and nucleic acid, dual-portioned, fecal screening test for CRCs, but it is by no means the only incidence or suggestion of such in the prior art of record.

Combining Fecal DNA Tests with FOBT was a Known Strategy to Improve Fecal CRC Tests



Nishikawa

Because *K-ras* point mutations are only associated with 40–50% of colorectal cancers, the detection sensitivity of one-step PCR/RFLP analysis for mutations is low among cancers as a whole. However, the technique is highly specific, noninvasive, and cost-effective, and should provide a more sensitive and specific tool for mass screening of colorectal cancer than is currently available, especially if used in combination with fecal occult blood testing and other methods for detecting genetic abnormalities.



Levin

As noted previously, the most informative data on the performance of sDNA testing is from version 1.0, which has been replaced with version 1.1; the newer version uses the same panel of markers but is reported to have improved quality.^{63,70} Newer versions are currently under evaluation, and are reported to have improved sensitivity, with diminution of specificity. The evolution of tests of this type raises important questions as to how performance of successive iterations should be evaluated and whether large prospective studies of asymptomatic patients with follow-up CSKY among all participants are required. Another question worthy of consideration is whether or not including a sensitive gFOBT or FIT at the time of testing would improve sensitivity without adversely affecting specificity. In a recent retrospective analysis of stool samples from patients with CRC and donor controls, combined results from a standard gFOBT and a panel of DNA markers (APC, BAT26, and L-DNA) resulted in a combined sensitivity for cancer of 93% and specificity of 89%.⁷⁶

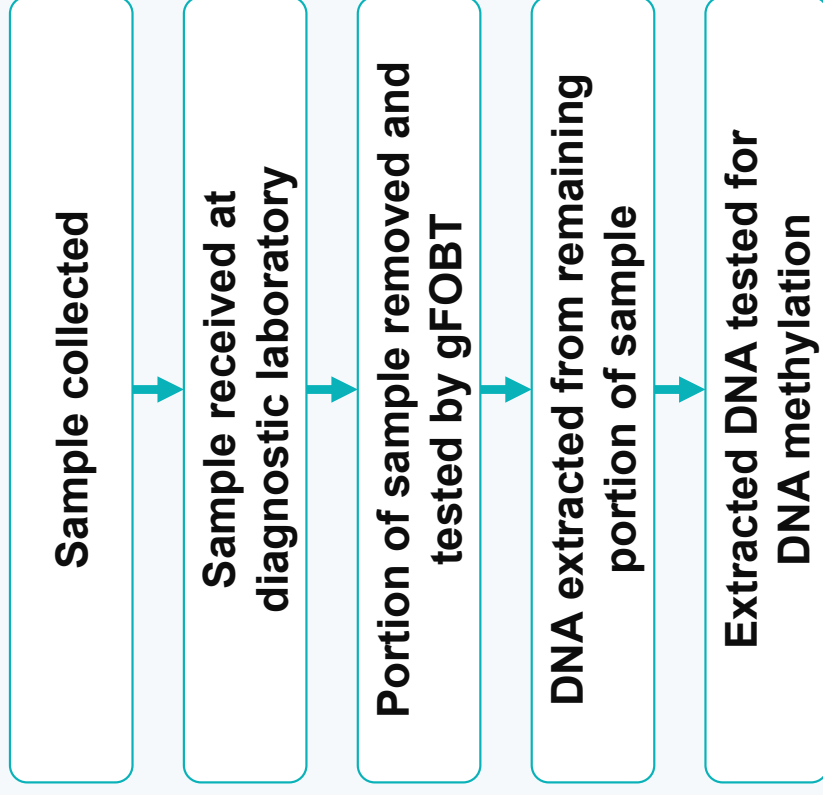
Petition, at 9-10; Reply, at 15-16; EX1011 (Nishikawa), at 112; EX1013 (Levin), at 1578

[illegible]

The treatment of early-stage tumours decreases the overall mortality of colorectal tumour patients. In this retrospective study we determined the sensitivity and the specificity of the faecal occult blood test (FOBT) and the molecular diagnosis (MD). We analysed 57 stool samples from patients with colorectal carcinomas for the presence of occult blood using a standard FOBT and for alterations in the three different tumour relevant markers APC, BAT26 and L-DNA. Stool samples from 44 control donors were analysed to determine the specificity of the applied methods. Twenty-nine (51%; 95% confidence interval (CI): 38–63%) stool samples of the cancer patients gave positive FOBT results. Thirty-seven (65%; CI: 52–76%) samples showed alterations in at least one DNA marker. Sixteen (28%) samples were positive only in the FOBT, and 24 (42%) samples showed a positive result exclusively in MD. The combined application of both methods resulted in a sensitivity of 93% (CI: 83–97%) and an overall specificity of 89% (CI: 76–95%). The combined application of FOBT and MD resulted in an overall sensitivity, which could not be achieved by any of the methods alone and which is in the range of invasive diagnostic methods.

Petition, at 9-10; Reply at 15-16; EX1012 (Kutzner), at Abstract, 40

A POSA Would Be Motivated to Apply Known Techniques to Improve Lenhard's Combined Test



POSA would be motivated to incorporate Itzkowitz's sample collection process to facilitate at-home sample collection

POSA would be motivated to replace gFOBT with Vilkin's superior iFOBT to increase patient convenience and improve assay performance

Petition, at pp. 19-24; EX1004 (Lenhard); EX1005 (Vilkin); EX1006 (Itzkowitz)

Demonstrative Exhibit - Not Evidence

Advantages of Using Itzkowitz's At-Home Sample Collection Process for Fecal DNA Tests Were Known

Itzkowitz

Since that time, pilot studies have shown that several technical and conceptual advances could improve fecal DNA testing. First, adding a DNA-stabilizing buffer to the stool immediately on defecation was shown to prevent DNA degradation for several days and enhance the performance of DIA.⁷ Second,

*
*
*

the DNA degradation. This increase in sensitivity for the full version 1 panel was achieved at the expense of a relatively minor decrease in specificity from 94.4% to 89.3%. Thus, even with the original markers, improved DNA preservation and extraction from stool resulted in a better screening test.

Olson

mutant DNA available for the amplification reaction. Despite the apparent stability of the point mutation markers to DNA degradation, it is nevertheless desirable to mitigate loss of DNA if possible. It has recently been shown¹⁰ that to maximize clinical sensitivity of fecal DNA assays, it is important to maximize the recovery of otherwise scarce amounts of human DNA.

Vilkin Teaches Advantages of iFOBT over gFOBT

Vilkin

Performance Characteristics and Evaluation of an Automated-Developed and Quantitative, Immunochromatographic Fecal Occult Blood Screening Test

Alex Vilkin, M.D., Paul Rosen, M.B., B.S., J. Zahar Levi, M.D.,¹ Amal Wakeel, B.Sc.,¹ Eran Masz, M.D.,² Shimon Birkenfeld, M.D.,³ and Yaron Niv, M.D.^{1,2}
¹ Gastroenterology Department, Yehuda Medical Center, Be'er Sheva Hospital, Petach Tikva; ² Tel Aviv University, Sackler School of Medicine, Tel Aviv; ³ Gastroenterology Unit, Chaim Health Services, Tel Aviv, Israel

OBJECTIVES: Guaiac fecal occult blood (gFOBT) screening tests (FOBT) are faulted for low sensitivity and nonspecificity for human hemoglobin (Hb). Automated-developed, immunochromatographic fecal occult blood (iFOBT) is specific, eliminates diet restrictions, and Hb quantification allows selection of a threshold for colonoscopy. Aims were to determine 1) test reproducibility; 2) test stability; 3) intrapatient daily iFOBT variation; 4) test sensitivity and specificity for neoplasia in 500 symptomatic/high-risk patients undergoing colonoscopy; and 5) to correlate fecal Hb measurements with findings.

METHODS: The automated-developed and quantitative iFOBT is human Hb specific, eliminates the need for diet restrictions, and the Hb quantification allows selection of a suitable threshold level for follow-up colonoscopy (5–7, 9–12).

RESULTS: Five iFOBTs re-examined five times in 1 day had no significant measurement changes. Thirty tests re-examined 3 days later had a decay/day of 0.3% ± 0.4 at 4°C (NS), 2.2% ± 1.7 at 20°C (NS), and 3.7% ± 2.4 at 25°C (NS). Intrapatient daily iFOBT variation was 1.1% ± 0.3 (NS). At the recommended 100 ng Hb/mL threshold, all cases of CRC and 20 out of 28 cases of advanced adenoma were detected; evaluated together their sensitivity and specificity were 76.9% and 95.3%.

CONCLUSIONS: Desktop, automated-developed, quantitative iFOBT is now available. Refrigerated OC-Sensor iFOBT is stable for 5 days at 4°C and 20°C and 3 days at 25°C, and at the 100 ng Hb/mL threshold, has high sensitivity, specificity, and negative predictive values for significant neoplasia. Suitability for population CRC screening awaits further evaluation.

(Am J Gastroenterol 2005;100:2519–2525)

The standard guaiac fecal occult blood test (gFOBT) is faulted for its low sensitivity for significant colorectal neoplasia (colorectal cancer (CRC) and advanced adenomatous polyps (AAP)), and low specificity due to nonspecificity for human hemoglobin (Hb). Automated-developed, immunochromatographic fecal occult blood (iFOBT) is human Hb specific, eliminates the need for diet restrictions, and the Hb quantification allows selection of a suitable threshold level for follow-up colonoscopy (5–7, 9–12).

The introduction of central laboratory and office-developed, immunochromatographic fecal occult blood tests (iFOBT) has improved the degree of sensitivity for CRC and AAP. However, for the office-developed tests, the degree of sensitivity for Hb and the occasional experience with more complex office-developed test was not conducive for large-scale screening and maintaining quality control (7–8, 11).

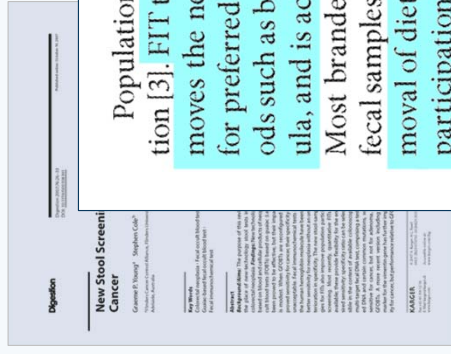
This material may be protected by Copyright law (Title 17 U.S. Code) 2519 Genescopy Exhibit 1005 Page 3

Guaiac fecal occult blood colorectal cancer (CRC) screening tests (FOBT) are faulted for low sensitivity and nonspecificity for human hemoglobin (Hb). Automated-developed, immunochromatographic fecal occult blood (iFOBT) is specific, eliminates diet restrictions, and Hb quantification allows selection of a threshold for colonoscopy. Aims were to determine 1) test reproducibility; 2) test stability; 3) intrapatient daily iFOBT variation; 4) test sensitivity and specificity for neoplasia in 500 symptomatic/high-risk patients undergoing colonoscopy; and 5) to correlate fecal Hb measurements with findings.

The automated-developed and quantitative iFOBT is human Hb specific, eliminates the need for diet restrictions, and the Hb quantification allows selection of a suitable threshold level for follow-up colonoscopy (5–7, 9–12).

The introduction of the instrument-developed, quantitative, fecal occult blood testing allows the physician to choose the optimal fecal Hb threshold level that triggers a follow-up colonoscopy. To validate this premise, we performed

Advantages of iFOBT over gFOBT Were Known in the Art



Young

Population participation is essential for cancer detection [3]. FIT technology simplifies the testing process, removes the need for diet and drug restrictions, provides for preferred and more acceptable stool-sampling methods such as brushes or probes rather than a wooden spatula, and is achieved while collecting fewer fecal samples. Most branded versions of FIT require fewer than three fecal samples, the recommended number for GFOBT. Removal of dietary restrictions has been shown to enhance participation in screening with FIT relative to GFOBT, in one study by 28% [10]. Changing to a brush-sampling method also simplifies the process and enhances participation by 30%. Together, these two advances increase population participation by 66% [10].

* * *

Obviously, FIT's overcome most of the disadvantages presented by GFOBT, are superior to GFOBT in terms of participation as well as performance and should replace GFOBT in two-step screening [14, 16].



Guittet

Evidence in favour of the use of the I-FOBT over the G-FOBT is increasing. I-FOBT tests have no dietary or medication restrictions. These tests have superior sensitivity and specificity, the gain being more important for high risk adenomas than for cancers. They also have a higher compliance rate^{23 26 27} and the automated reading technology allows the choice of the ideal positivity rate. As suggested in recent reviews,^{5 7} it is time to give colorectal cancer screening a new future by using I-FOBT instead of G-FOBT.

Petition, at 20-21; EX1020 (Young), at 29-30; EX1021 (Guittet), at 214

Demonstrative Exhibit - Not Evidence

[illegible]

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:
 - a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;
 - b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and
 - c) in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container.

3. A method of processing a fecal sample, the method comprising:
 - a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising:
 - i) a sealed sealable vessel containing a first portion of a fecal sample and a stabilizing buffer; and
 - ii) a sealed sealable container containing a second portion of a fecal sample and a solution that prevents denaturation or degradation of blood proteins found in a fecal sample,wherein the pair of portions are obtained by the method of claim 1;
 - b) extracting nucleic acid from the first portion of the fecal sample;
 - c) testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid; and
 - d) testing the second portion of the fecal sample for an amount of a blood protein present in the second portion of the fecal sample.

Petition, at 1, 19-24; EX1004 (Lenhard); EX1005 (Vilkin); EX1006 (Itzkowitz)

Demonstrative Exhibit - Not Evidence

Exact's Attack on Motivation to Combine has no Merit

Trials@uspto.gov
571.272.7822

Page: 39
Date: July 9, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,

v.

EXACT SCIENCES CORPORATION,
Patent Owner.

IPR2024-00459
Patent 11,634,781 B2

Before RYAN H. FLAX, DAVID COTTA, and JAMIE T. WISZ,
Administrative Patent Judges.

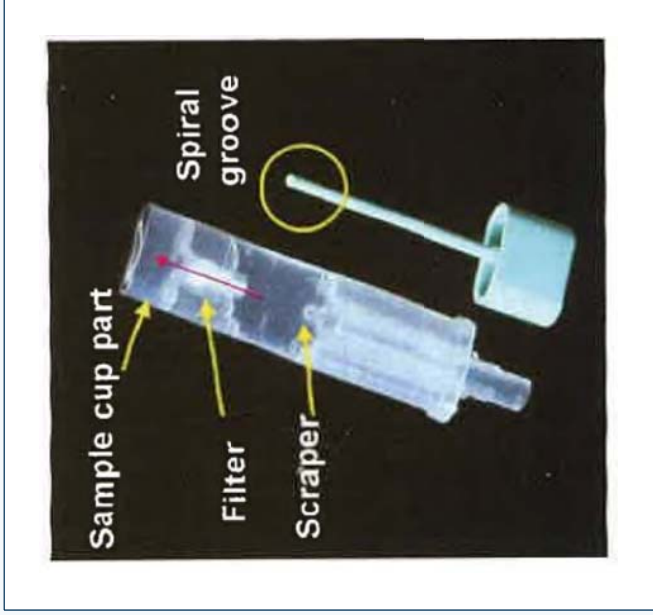
FLAX, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

Each of Exact's arguments on motivation to combine was considered and rejected by the Board in IPR2024-00459

Exact's Single Buffer Argument Has No Merit

As of Priority Date, at home separation was a standard part of the iFOBT workflow.



Vilkin

Fecal Sampling

The fecal test sampling device is shaped like a small test tube with the fecal probe inserted into it and sealing it. The probe has a serrated tip, which is poked into the stool and then pushed back into the tube, past a scraper, and through a membrane into the sample cup. These remove most of the excess feces and leave the stool collected (about 10 mg) into the serrations (Fig. 1). The tip is then put in a closed amount of Hb stabilizing buffer. Each sample tube has a unique bar code and before preparing the sample the patient writes his name and date on the tube. The examinee is requested to prepare three consecutive daily samples during the week before colonoscopy examination. Samples are double-closed in zip-lock bags and kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development.

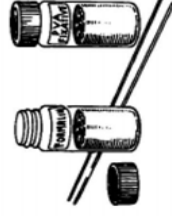
Petition, at 23, 26-27, 38, 40; Reply, at 3; EX1005 (Vilkin), at 2520; EX1086 (Whitney 2nd Decl.) ¶ 67

State of the Art: Partitioning Fecal Sample into Different Buffers to Stabilize Different Biomarkers Prior to Shipment to a Diagnostic Laboratory was Well Known for Decades

Petition, at 6-7; Reply, at 5;
EX1002 (Whitney Decl.) ¶¶ 70, 84; EX1010 (Melvin), at 9-13, 56
Demonstrative Exhibit - Not Evidence

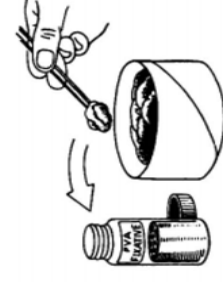
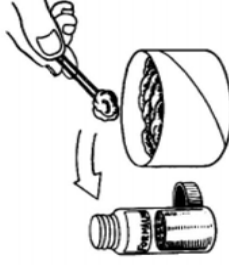
ADAPTED FROM BROOKE AND GOLDMAN, 1949

NOTE: BOTH SOFT AND FORMED SPECIMENS SHOULD BE SUBMITTED BY THIS METHOD. SPECIMENS MUST BE FRESH WHEN PLACED IN VIALS.



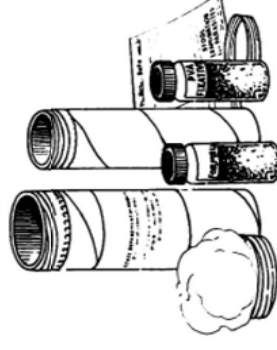
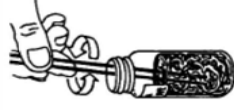
1 THE KIT CONSISTS OF TWO GLASS VIALS (ONE WITH 5% FORMALIN AND ONE WITH PVA-FIXATIVE) AND TWO APPLICATOR STICKS.

2 THE STOOL SHOULD BE PASSED INTO A DRY CONTAINER. URINE SHOULD NOT BE PASSED INTO THE SAME CONTAINER.



3 USING APPLICATOR STICKS, PLACE A QUANTITY OF THE STOOL (ABOUT THE DIAMETER OF A QUARTER) INTO THE VIAL CONTAINING FORMALIN, SCREW CAP ON TIGHTLY.

4 PLACE A SIMILAR QUANTITY INTO THE VIAL CONTAINING THE PVA-FIXATIVE.



5 THOROUGHLY BREAK UP SPECIMEN IN THE PVA-FIXATIVE, USING APPLICATOR STICKS. SCREW CAP ON TIGHTLY AND SHAKE VIGOROUSLY.

6 PACK THE TWO VIALS SO AS TO PROTECT AGAINST BREAKAGE, ENCLOSE APPROPRIATE IDENTIFICATION, AND MAIL OR DELIVER TO YOUR PUBLIC HEALTH LABORATORY.

Exact's Single Buffer Argument Has No Merit

Exact's expert acknowledges that a POSA would preferably use a buffer that had been proven to stabilize their analyte of choice.

Backman Tr.

Q. So a person of skill in the art would preferably use a buffer that had been proven to work in the -- for the preservation of their analyte of choice?

A. Correct.

Q. So a person of skill in the art who was testing for DNA would use a buffer that had been proven to stabilize fecal DNA, right?

THE WITNESS: That would be proven to stabilize DNA. They would certainly use the buffer that is known to stabilize DNA.

Backman Tr.

Q. And if one of skill in the art were testing hemoglobin in a stool sample in their assay, that person would preferably use a buffer that had been proven to stabilize blood proteins?

A. Correct.

Reply, at 3-4; EX1089 (Backman Tr.), 68:17-69:4, 69:22-70:2

Demonstrative Exhibit - Not Evidence

Exact's Single Buffer Argument Has No Merit

As of Priority Date, different buffers were used to stabilize DNA and blood proteins.

 Buffers Optimized to Stabilize DNA	 Buffers Optimized to Stabilize Protein	 Buffers Optimized to Stabilize DNA and Protein
• Olson (EX1022) • Shuber (EX1008) • Itzkowitz (EX1006)	• Vilkin (EX1005) • Grow (EX1041) • Karl (EX1045) • Hirata (EX1070)	NONE REPORTED

Reply, at 3-4; EX1002 (Whitney Decl.) ¶¶ 74-82; EX1068 (Whitney 2nd Decl.) ¶¶ 68-73

Demonstrative Exhibit - Not Evidence

Exact's Single Buffer Argument Has No Merit

Whitney Decl.

degradation of DNA,¹⁰² others were optimized to stabilize proteins.¹⁰³ I am not aware of any disclosure before the Priority Date of a buffer optimized to stabilize *both* fecal DNA and fecal blood proteins and my belief is that there was none. Notably, Dr. Backman does not identify any examples of such optimized buffers in his declaration.

Geneoscopy Expert Duncan Whitney, who developed and optimized DNA stabilizing buffers for Exact before the priority date

Reply, at 4; EX1086 (Whitney 2nd Decl.) ¶ 68

Demonstrative Exhibit - Not Evidence

Exact's Single Buffer Argument Has No Merit

Exact's 1991 Japanese application (Tsuji) does not make use of separate buffers nonobvious

- Does not use a Tris EDTA buffer in any experiments
- Does not disclose that that **any buffer** stabilizes DNA
- Tris and EDTA are only listed in separate laundry lists of possible buffer components

Reply, at 4-5;

EX1068 (Whitney 2nd Decl.), ¶¶ 69-71;

EX2049 (Tsuij), ¶¶ 10-11 and Examples

(19) 日本国特許 (J P)	(12) 公開特許公報 (A)	(11) 特許出願公開番号 特開平5-99923 (49) 公開日 平成5年(1993)4月23日
(54) 【発明の名称】 ヒトヘモグロビンの検出方法	(57) 【要約】 【目的】 糞便を含有する検体液中に存在すると推定されるヒトヘモグロビンを検出する方法、 これに用いる便浴解用緩衝液を提供する。 【構成】 キレート試薬を便浴解するための緩衝液中に添加し、若しヒトヘモグロビン抗体を用いたヒトヘモグロビンの検出を行なう。	
(21) 出願番号 G01N 33/581 33/50 33/53	(22) 出願日 平成3年(1991)10月11日	(73) 特許権者 特願平3-282163 平成3年(1991)10月11日
(51) 国際特許分類 G01N 33/581 33/50 33/53	(52) 特許請求の範囲 1. ヒトヘモグロビンを検出する方法、 これに用いる便浴解用緩衝液を提供する。 2. キレート試薬を便浴解するための緩衝液中に添加し、若しヒトヘモグロビン抗体を用いたヒトヘモグロビンの検出を行なう。	(72) 発明者 Q. So the support of your contribution stabilize human hemoglobin application, right? A. I think
(53) 特許代理人 G01N 33/581 33/50 33/53	(54) 【発明の名称】 ヒトヘモグロビンの検出方法	(57) 【要約】 【目的】 糞便を含有する検体液中に存在すると推定されるヒトヘモグロビンを検出する方法、 これに用いる便浴解用緩衝液を提供する。 【構成】 キレート試薬を便浴解するための緩衝液中に添加し、若しヒトヘモグロビン抗体を用いたヒトヘモグロビンの検出を行なう。

Exact's Single Buffer Argument Has No Merit

Exact provides no evidence that RNAlater stabilizes fecal hemoglobin



RNAlater

RNAlater® for RNA *and* Protein Stabilization

- Simplify sample collection
- No need to freeze sample in liquid nitrogen
- Stabilize both RNA and protein within tissues or cells
- Isolate both RNA and protein from the same sample

RNAlater is an aqueous, nontoxic, tissue and cell collection reagent that stabilizes and protects RNA in intact, unfrozen tissue and cell samples. The solution permeates the cells, stabilizing the RNA inside them. RNAlater

Backman Tr.

Q. Is hemoglobin in feces within tissues or cells?
A. It's -- no, it's -- it's extracellular.

Reply, at 4-5; EX1068 (Whitney 2nd Decl.), ¶ 72; EX2048 (RNAlater); EX1089 (Backman Tr.), 161:21-23

Demonstrative Exhibit - Not Evidence

Exact's Single Buffer Argument Has No Merit

More than 15 years after the Priority Date, despite the purported benefits of using a single buffer, Exact still requires at home sample separation into separate buffers

2009:	Priority Date
2014:	Exact launches Cologuard product, which uses two separate buffers to stabilize blood proteins and DNA
Today:	Exact's Cologuard products continue to use two separate buffers to stabilize blood proteins and DNA
2024:	FDA approves Geneoscopy's original ColoSense product, which uses two separate buffers
2025:	FDA approves new collection kit for Geneoscopy's ColoSense product, which uses a single buffer

Petition, at 10, 66; POR, at 7-8, 63-64; Reply, at 4-5; POSR, at 4; EX1076 (Cologuard Patient Guide); EX2022 (ColoSense Approval Letter); EX2054 (Geneoscopy Press Release)

Exact's Attack on Motivation to Combine Has No Merit



“Our precedent... does not require that the motivation be the best option, only that it be a suitable option from which the prior art does not teach away.”

Gen. Elec. Co. v. Raytheon Techs. Corp., 983 F.3d 1334
(Fed. Cir. 2020), quoting *Par Pharm., Inc. v. Twi Pharms., Inc.*, 773
F.3d 1186, 1197-98 (Fed. Cir. 2014)

Exact's Attack on Motivation to Combine Has No Merit

Sensitivity, not specificity, is of primary importance for fecal CRC assays and improving sensitivity provides sufficient motivation to combine.

- In touting the improved sensitivity of its combined assay, Lenhard does not characterize its 89% specificity as a negative feature
- In Itzkowitz, Exact characterizes version of their fecal DNA test that showed a similar improvement to sensitivity and loss of specificity to Lenhard's combined assay as a "better screening test".
- The specificity of Exact's preferred screening test in Itzkowitz was only 82%
- A POSA would be motivated to improve the specificity of Lenhard's assay by replacing its gFOBT with Vilkin's iFOBT

Itzkowitz

viduals.⁶ By using improved methods for stabilizing DNA during specimen transport, and better extraction of DNA from stool, we now find that the sensitivity for the version 1 marker panel is increased from 52% to 72.5%. This improvement was a direct result of an increase in DIA sensitivity from 3% to 65%, confirming the observations of Olson et al⁷ that the low sensitivity of DIA in the previous multicenter study was as result of the DNA degradation. This increase in sensitivity for the full version 1 panel was achieved at the expense of a relatively minor decrease in specificity from 94.4% to 89.3%. Thus, even with the original markers, improved DNA preservation and extraction from stool resulted in a better screening test.

Reply, at 8-10; EX1004 (Lenhard); EX1006 (Itzkowitz), at 111, 116; EX1005 (Vilkin), at 2519, 2524

Exact's Attack on Motivation to Combine Has No Merit

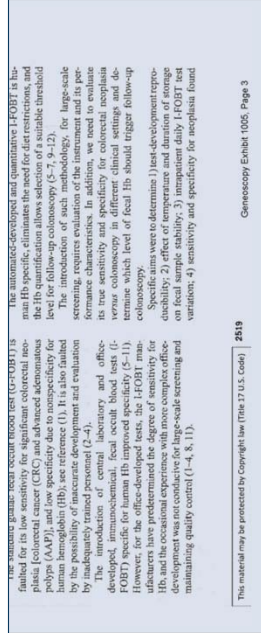
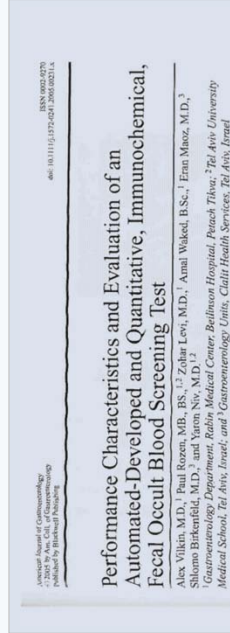
- Vilkin does not require fecal collection on three consecutive days

Vilkin

Specific aims were to determine 1) test-development reproducibility; 2) effect of temperature and duration of storage on fecal sample stability; 3) intrapatient daily I-FOBT test variation; 4) sensitivity and specificity for neoplasia found in persons also undergoing colonoscopy; and 5) to correlate fecal Hb levels with clinical findings.

At present, we will continue with collecting three annual fecal tests, as we have confirmed the additive clinical value of repeated occult blood testing in this high-risk population. This is in contrast to the annual 2-day, average-risk population I-FOBT collection, as routinely used in Japan, United States, and Australia and 1-day biennial testing as performed in Italy (11, 12, 16–18).

The decision on the number of fecal samples to be obtained and optimal fecal Hb threshold chosen for screening an average risk population will also involve an evaluation of cost-benefit. This will require a prospective colonoscopy



Reply, at 10-12; EX1005 (Vilkin), 2519-20, 2524

Demonstrative Exhibit - Not Evidence

Exact's Attack on Motivation to Combine Has No Merit

- By the priority date, the iFOBT used in Vilkin was being used to test single samples without at home refrigeration.

Van Rossum

The OC-Sensor test consisted of a single sampling tube and written instructions. The sampling tube, filled with stabilizing buffer, had an integrated fecal probe. Participants were instructed to scrape different parts of the surface of their defecation with the probe. The amount of feces that can be inserted into the sample bottle is regulated to approximately 10 mg.¹⁴ Participants were instructed to return the test as soon as possible because lasting exposition to room temperature might result in degradation of hemoglobin in the sampling solution.¹³ If the test could not be returned immediately, storage in a refrigerator was advised. In the laboratory, tests were

GASTROENTEROLOGY 2008;135:92-99

Random Comparison of Guaiac and Immunochemical Fecal Occult Blood Tests for Colorectal Cancer in a Screening Population

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Background & Aims: Despite very performance guaiac-based fecal occult blood tests (G-FOBT) are not frequently implemented for colorectal cancer screening. Immunochemical fecal occult blood tests (i-FOBT) are more sensitive but more expensive. We compared G-FOBT and i-FOBT in a screening population.

Methods: We conducted a population-based study on a random sample of 20,623 individuals 50–75 years of age, randomized to either G-FOBT or i-FOBT. The positivity rate difference was 1.1% (95% CI, 0.5%–1.7%). The specificity difference was 1.1% (95% CI, 0.5%–1.7%). The sensitivity difference was 1.1% (95% CI, 0.5%–1.7%). The specificity difference was 1.1% (95% CI, 0.5%–1.7%). The sensitivity difference was 1.1% (95% CI, 0.5%–1.7%).

To demonstrate that i-FOBTs have improved diagnostic performance, the tests should be compared with G-FOBTs in a randomized design. In the present study, we performed a randomized design and the specific i-FOBT used (Infomax) was compared with the G-FOBT used (Hemoccult). The results of the present study show that i-FOBTs have a higher sensitivity than G-FOBTs. The specificity of i-FOBTs was not significantly different from G-FOBTs. The results of the present study show that i-FOBTs have a higher sensitivity than G-FOBTs. The specificity of i-FOBTs was not significantly different from G-FOBTs.

Conclusions: In the present study, we aimed to randomly compare the test performance parameters of the Hemoccult i-FOBT (Infomax) and the Hemoccult G-FOBT (Hemoccult) in a screening population. The results of the present study show that i-FOBTs have a higher sensitivity than G-FOBTs. The specificity of i-FOBTs was not significantly different from G-FOBTs.

doi:10.1053/j.gastro.2008.03.040

Gastroenterology Exhibit 1090, Page 1

Reply, at 11-12; EX1090 (Van Rossum), at 83
Demonstrative Exhibit - Not Evidence

Exact's Attack on Motivation to Combine Has No Merit

Equal sensitivity for adenomas would not discourage Lenhard's combined test

Levin

- As of the priority date, cancer detection was of primary importance in fecal CRC assays.
- The 2008 American Cancer Society guidelines confirms that adenoma screening is not the primary goal of fecal DNA tests, which “primarily are effective at identifying CRC.”
- In Itzkowitz, Exact assesses performance of versions its fecal DNA assay based solely on their ability to detect cancer, never testing for adenoma detection.

Reply, at 8; EX1086 (Whitney 2nd Decl.) ¶¶ 26-29, 79-81; EX1006 (Itzkowitz); EX1013 (Levin), at 1572-73

Individuals and health care professionals should also understand that screening tests for CRC broadly fall into 2 categories. In one category are the fecal tests (ie, gFOBT, FIT, and sDNA), which are tests that primarily are effective at identifying CRC. Some premalignant adenomatous polyps may be detected, providing an opportunity for polypectomy and the prevention of CRC, but the opportunity for prevention is both limited and incidental and is not the primary goal of CRC screening with these tests. In the second category are the partial or full structural exams (ie, FSIG, CSPY, DCBE, and CTC)⁴⁴ which are tests that are effective at detecting cancer and premalignant adenomatous polyps. These tests differ in complexity and accuracy for the detection of CRC and advanced neoplasia. When performed properly, each of these structural exams has met the standard of detecting at least half of prevalent or incident cancers at the time of testing.

Exact's Attack on Motivation to Combine Has No Merit

A POSA would not have been dissuaded from using Lenhard's combined test by cost and complexity.

- Using Itzkowitz's sample collection process and replacing Lenhard's gFOBT with Vilkin's iFOBT increases patient convenience by facilitating at-home sample collection.
- The iFOBT sample collection process was known to be more convenient for patients than the corresponding gFOBT process.
- iFOBT tests were well established in the art and relatively inexpensive (under \$30, compared to over \$400 for fecal DNA tests).

Reply, at 12-14; EX1086 (Whitney 2nd Decl.) ¶¶ 102-04; EX1020 (Young), at 29, 31; EX1013 (Levin), at 1576, 1578

Demonstrative Exhibit - Not Evidence

Young

Population participation is essential for cancer detection [3]. FIT technology simplifies the testing process, removes the need for diet and drug restrictions, provides for preferred and more acceptable stool-sampling methods such as brushes or probes rather than a wooden spatula, and is achieved while collecting fewer fecal samples. Most branded versions of FIT require fewer than three fecal samples, the recommended number for GFOBT. Removal of dietary restrictions has been shown to enhance participation in screening with FIT relative to GFOBT, in one study by 28% [10]. Changing to a brush-sampling method also simplifies the process and enhances participation by 30%. Together, these two advances increase population participation by 66% [10].

Levin

block the peroxidase reaction. In addition, because globin is degraded by digestive enzymes in the upper gastrointestinal tract, FIT also are more specific for lower gastrointestinal bleeding, thus improving their specificity for CRC. Finally, the sample collection for some variants of FIT are less demanding of patients than gFOBT, requiring fewer samples or less direct handling of stool.

Ground III: **Shuber and Vilkin**

Claims 1-4, 14-19

IPR2024-00459: The Board Found the Narrower Claims of the '781 Patent Obvious Over Shuber and Vilkin

Trinks@uspto.gov 571.272.7822 UNITED STATES PATENT AND TRADEMARK OFFICE BEFORE THE PATENT TRIAL AND APPEAL BOARD GENEOSCOPY, INC., Petitioner, v. EXACT SCIENCES CORPORATION, Patent Owner. IPR2024-00459 Patent 11,634,781 B2 Before RYAN H. FLAX, DAVID COTTA, and JAMIE T. WISZ, <i>Administrative Patent Judges.</i> FLAX, <i>Administrative Patent Judge.</i> JUDGMENT Final Written Decision Determining All Challenged Claims Unpatentable 35 U.S.C. § 318(a)	FWD The ordinarily skilled artisan would have had good reason to combine the methods of Shuber and Vilkin to achieve a better CRC screening method than either method provided individually.
	FWD When combined, Shuber and Vilkin teach or suggest each step and element of independent claim 1, and of dependent claims 2–20 (adding the relevant disclosures of Kanaoka and Derks). As discussed above, Shuber

EX1087 (FWD), at 67-68; Reply, at 14

Demonstrative Exhibit - Not Evidence

United States Patent

Lawgave

(54) **FECAL SAMPLE PROCESSING AND ANALYSIS FOR COMBINING DETECTION OF BLOOD**

(71) Applicant: **Karl Schenck Corporation, Madison, WI (US)**

(72) Inventor: **Jean Leunig, Denmark (CI)**

(73) Assignee: **Karl Schenck Corporation, Madison, WI (US)**

(*) Notice: Subject to any disclaimer, the term of this patent, which will extend to the term of any subsequent patent issuing on or derived from or relating to this invention, shall be extended by 3 years, pursuant to 35 U.S.C. 146(b) for 6 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **18779,045**

(22) Filed: **Mar. 7, 2023**

(65) **Prior Publication Data**

(66) **US 2023/031377 A1 Oct. 5, 2023**

Related U.S. Application Data

(65) Continuation of Application No. 17,936,335, filed on Feb. 28, 2022, now Pat. No. 11,643,281, which is a continuation of Application No. 16,842,466, filed on Jan. 27, 2017, which is a continuation of Application No. 15,010,456, filed on Jan. 29, 2016, now Pat. No. 10,010,456, filed on Jan. 29, 2016, now Pat. No. 13,147,570, filed as application No. 2013/013,475, which is a continuation of Application No. 12,000,610 on Feb. 3, 2010, now abandoned.

(66) Provisional application No. 61/149,581, filed on Feb. 3, 2009.

(59) **Foreign Application Priority Data**

(60) **Feb. 3, 2010 (WO) PCT/0201000180**

(51) **Int. Cl.**

C12G 1/6886

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(10) Patent No.: **US 11,970,746 B2**
(45) Date of Patent: ***Apr. 30, 2024**

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,437,975 A 3/1984 Gillespie et al.
4,482,211 A 4/1982 Gillespie et al.
4,582,610 A 1/1988 Price et al.
4,859,610 A 8/1989 Price et al.
5,137,906 A 12/1989 Maguire et al.
5,198,965 A 1/1993 Maguire et al.
5,241,639 A 1/1993 Maguire et al.
5,241,640 A 1/1993 Maguire et al.
6,411,716 B2 10/2001 Maguire et al.
7,195,278 B2 12/2004 Maguire et al.
7,271,427 B1 10/2005 Maguire et al.
8,291,225 B2 10/2014 Maguire et al.
11,654,381 B2 1/2020 Maguire et al.
11,845,599 A 1/2021 Maguire et al.
2002/0187,476 A1 12/2002 Maguire et al.
2003/0095,248 A1 5/2003 Maguire et al.
2004/0095,248 A1 5/2004 Maguire et al.
2004/0095,248 A1 5/2004 Maguire et al.
2005/0087,543 A1 5/2005 Maguire et al.

1. A method for sample without further processing, comprising:
a) collecting a sample wherein the human subject is in a sealable fecal sample container;
b) in a sealable fecal sample container;
c) in a sealable fecal sample container;
d) in a sealable fecal sample container;
e) in a sealable fecal sample container;
f) in a sealable fecal sample container;
g) in a sealable fecal sample container;
h) in a sealable fecal sample container;
i) in a sealable fecal sample container;
j) in a sealable fecal sample container;
k) in a sealable fecal sample container;
l) in a sealable fecal sample container;
m) in a sealable fecal sample container;
n) in a sealable fecal sample container;
o) in a sealable fecal sample container;
p) in a sealable fecal sample container;
q) in a sealable fecal sample container;
r) in a sealable fecal sample container;
s) in a sealable fecal sample container;
t) in a sealable fecal sample container;
u) in a sealable fecal sample container;
v) in a sealable fecal sample container;
w) in a sealable fecal sample container;
x) in a sealable fecal sample container;
y) in a sealable fecal sample container;
z) in a sealable fecal sample container;

FOREIGN

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1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:
 - a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;
 - b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and
 - c) in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container.

- Petition, at 1, 37-41; EX1008 (Shuber); EX1005 (Vilkin)
Demonstrative Exhibit - Not Evidence

Shuber's Fecal DNA Assay

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:

- a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;
- b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and

3. A method of processing a fecal sample, the method comprising:

- a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising:
 - i) a sealed sealable vessel containing a first portion of a fecal sample and a stabilizing buffer; and
- b) extracting nucleic acid from the first portion of the fecal sample;
- c) testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid; and

Shuber

In any of the aspects of the invention described herein, including the examples, a sample (e.g., a stool sample) may be directly deposited into a container (e.g., a sealable container) that already contains stabilization solution. The amount of solution may be sufficient to cover the sample or a portion thereof. Alternatively, stabilization solution may be added to a container when (e.g., at the same time, immediately after, or within minutes, hours, or a day) a biological sample (e.g., a stool sample) is deposited in the container. The amount of solution added may be sufficient to cover the entire sample or at least a portion thereof (e.g., 10%, 25%, 50%, or more). In one embodiment, an amount of solution sufficient to fill the container may be added. In some embodiments, a container may be between about 25 mls and about 1,000 mls (e.g., between about 50 mls and about 500 mls, between about 100 mls and about 400 mls, or about 250 mls). However, smaller or larger containers may be used. A container with sample and stabilization solution may be sealed for storage/shipping.

In one aspect of the invention, a stabilization solution may be particularly useful when samples are not refrigerated or frozen or when there is a risk that a sample may not be maintained at a sufficiently low temperature to preserve indicia of disease. For example, a stabilization solution may be particularly useful if a sample is obtained at a remote location and mailed or delivered to a testing center. However, stabilization solutions also may be useful to preserve samples that are being processed on-site at a medical center.

Petition, at 16-17, 37-41; EX1008 (Shuber), at 10:12-14, 29:8-19

Demonstrative Exhibit - Not Evidence

Shuber's Fecal DNA Assay

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:

- a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;
- b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and

3. A method of processing a fecal sample, the method comprising:

- a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising:
 - i) a sealed sealable vessel containing a first portion of a fecal sample and a stabilizing buffer; and
- b) extracting nucleic acid from the first portion of the fecal sample;
- c) testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid; and

Shuber

Recovery of DNA from stool

The sample preparation methodology used to recover DNA from stool was previously reported (Ahluquist DA, Skoletsky JE, Boynton KA, et al. Colorectal cancer screening by detection of altered human DNA in stool: Feasibility of a multi-target assay panel. Gastroenterology 2000; 119:1219-1227; Whitney D, Skoletsky J, Moore K, et al. Enhanced Retrieval of DNA from Human Fecal Samples Results in Improved Performance of Colorectal Cancer Screening Assay. J Mol. Diagn. 2004; 6 (4), 386-395). Stool aliquots were weighed and combined with Exact buffer A (1:7 (w/v) ratio), and homogenized on an Exactor (Exact Sciences). After homogenization, a 4-g stool equivalent (~32 mls) of each sample was centrifuged to remove all particulate matter. The supernatants were then treated with 20u1 TE

buffer (0.01 mol/L Tris [pH 7.4] and 0.001 mol/L EDTA) containing RNase A (2.5 mg/mL), and incubated at 37°C for 1 hour. Total nucleic acid was then precipitated (first adding 1/10 volume 3 mol/L NaAc, then an equal-volume of isopropanol). Genomic DNA was pelleted by centrifugation, the supernatant removed, and the DNA resuspended in TE.

In certain embodiments, methods of the invention are used to preserve a sample for analysis using a nucleic acid integrity assay along with a mutation detection assay (e.g., a multiple mutation panel assay), a hypermethylation assay, or both.

Petition, at 16-17, 37-41, 45; EX1008 (Shuber), at 7:19-21, 15:18-31

Demonstrative Exhibit - Not Evidence

Vilkin's Automated iFOBT

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:

a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;

c) in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container.

3. A method of processing a fecal sample, the method comprising:

a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising:

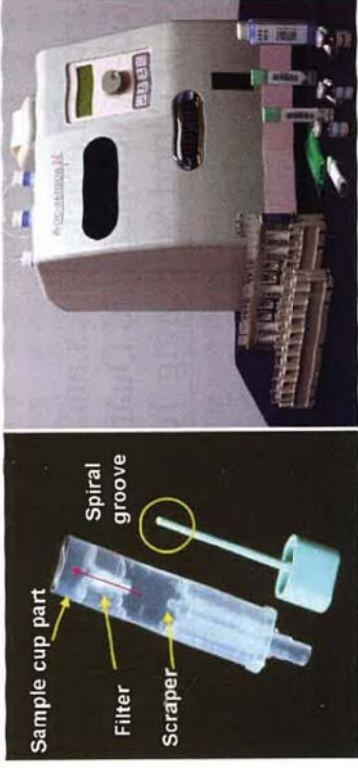
ii) a sealed sealable container containing a second portion of a fecal sample and a solution that prevents denaturation or degradation of blood proteins found in a fecal sample,

d) testing the second portion of the fecal sample for an amount of a blood protein present in the second portion of the fecal sample.

Petition, at 14-15, 37-41; EX1005 (Vilkin), at 2520

Demonstrative Exhibit - Not Evidence

Vilkin



Fecal Sampling

The fecal test sampling device is shaped like a small test tube with the fecal probe inserted into it and sealing it. The probe has a serrated tip, which is poked into the stool and then pushed back into the tube, past a scraper, and through a membrane into the sample cup. These remove most of the excess feces and leave the stool collected (about 10 mg) into the serrations (Fig. 1). The tip is then put in a closed amount of Hb stabilizing buffer. Each sample tube has a unique bar code and before preparing the sample the patient writes his name and date on the tube. The examinee is requested to prepare three consecutive daily samples during the week before colonoscopy examination. Samples are double-closed in zip-lock bags and kept in the refrigerator until returned to the developing laboratory where they are also kept at 4°C until development.

Both Kutzner and Lenhard Experimentally Demonstrate Improved Sensitivity in Combined Assay



Kutzner

This is one of the first studies, which evaluate and directly compare the potential of the two non-invasive methods MD and FOBT in the diagnosis of colorectal carcinomas. The combined application of the two methods together led to a significantly higher sensitivity than the application of any of the methods alone. Regarding the low cost and the little technical expense of the FOBT, we suggest that MD and FOBT should complement rather than replace each other.



Lenhard

more adenomas (31% vs. 8%, $P = .14$). In addition, specificity of the HIC1 assay was higher (97.9% vs. 89.9%, $P = .102$). The combination of both assays resulted in increased detection rates for CRCs (65%; 95% CI, 44%–83%). Although the combined test detected all localized cancers, no increase in the sensitivity for adenoma was seen.

Petition, at 13, 39; Reply at 15-16;
EX1012 (Kutzner), at 40; EX1004 (Lenhard), at 147

Demonstrative Exhibit - Not Evidence

Combining a Fecal DNA Test with a FOBT was a Strategy Worth Trying With a Reasonable Expectation of Success



“[W]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions...it is likely the product not of innovation, but of ordinary skill and common sense.”

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007)

Reply, at 16;
EX1013 (Levin), at 1578

Demonstrative Exhibit - Not Evidence



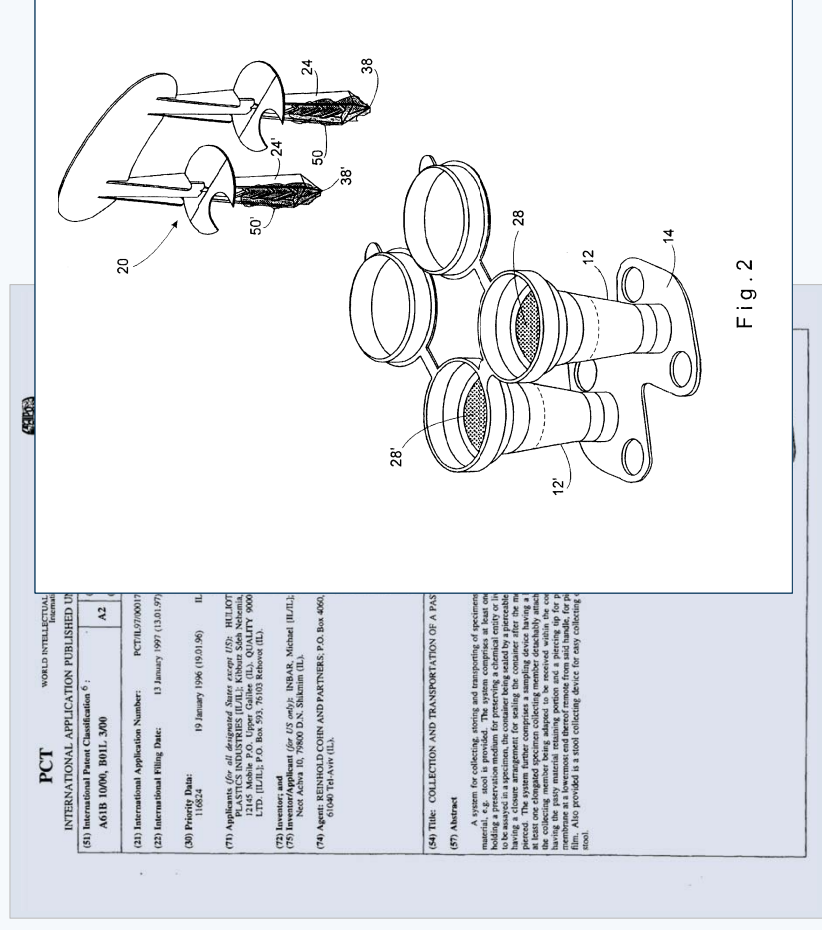
Levin

required. Another question worthy of consideration is whether or not including a sensitive gFOBT or FIT at the time of testing would improve sensitivity without adversely affecting specificity. In a recent retrospective analysis of stool samples from patients with CRC and donor controls, combined results from a standard gFOBT and a panel of DNA markers (APC, BAT26, and L-DNA) resulted in a combined sensitivity for cancer of 93% and specificity of 89%.⁷⁶

Ground VI: **Inbar, Vilkin, and Shuber**

Claims 1-4, 14-19

Inbar Discloses a Device For Separating Fecal Samples into Separate Buffers



The system of the present invention is suitable for collecting, storing and transporting of any pasty material, for example, stools, food samples, e.g. soft cheese, yogurt, various spreads; soil samples, e.g. mud samples; and many others. With appropriate preservation media, the samples may be stored for a lengthy period of time prior to assaying for the chemical entity or living matter. The composition of the medium depends on the type of entity which should be preserved and subsequently assayed: for example, if the entity is a chemical substance, the medium will have a composition which ensure that the substance is preserved in a manner to avoid its deterioration; if the assayed entity is microorganism or any other living matter, the medium will be designed so as to maintain such microorganisms or other living matter in a viable condition. A system for

Demonstrative Exhibit - Not Evidence

Grounds II, IV, and VII:

Ground I, III, and VI Prior Art with Kanaoka

Claims 12 and 13

IPR2024-00459: The Board Found Narrower RNA Claims of the '781 Patent Obvious Over Ground I and III Art Combined With Kanaoka

FWD

Having considered the arguments and evidence presented at trial, we find Petitioner has shown by a preponderance of the evidence that claims 1–9, 11, and 14–20 are unpatentable as obvious over Lenhard, Vilkin, and Itzkowitz, that claims 12 and 13 are unpatentable as obvious over this same prior art combination adding Kanaoka's disclosed techniques of using RNA as a CRC biomarker,

FWD

Having considered the arguments and evidence presented at trial, we find Petitioner has shown by a preponderance of the evidence that claims 1–9, 11, and 14–20 are unpatentable as obvious over Shuber and Vilkin, claims 12 and 13 are unpatentable as obvious over Shuber, Vilkin, and Kanaoka,

FWD

persuaded. As Dr. Whitney identifies, adding another biomarker to the Lenhard-Vilkin-Itzkowitz combined teachings,¹⁶ specifically COX-2 RNA, would have been attractive to the ordinarily skilled artisan because Kanaoka discloses its process works (high sensitivity and specificity) and also that COX-2 was effectively combined with iFOBT in a complementary way (each detects certain CRC the other does not). Ex. 1002 ¶¶ 225–226;

EX1087 (FWD), at 56, 57, 69; Reply, at 18-19

Demonstrative Exhibit - Not Evidence

Kanaoka Discloses mRNA as a Known Fecal Biomarker that Complements iFOBT

Kanaoka

'746 Patent

12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the human gene.

13. The method of claim 12, wherein measuring an amount of RNA expressed from the human gene comprises reverse transcriptase polymerase chain reaction (RT-PCR).

[0021] Further, the present invention is a tumor marker detecting method for diagnosing colon cancer, comprising the following processes in addition to the process described above:

[0022] b) a process to extract RNA from the obtained sample for extracting RNA;

[0023] c) a process to reverse transcribe the extracted RNA to give cDNA;

[0024] d) a process to amplify the obtained cDNA; and,

[0025] e) a process to detect the amplified cDNA.

* * *

[0067] Among three COX-2 negative colon cancer cases, one was positive in the immunological fecal occult blood test, and 2 were negative.

[0068] COX-2 was detected in 3 among 5 colon cancer cases negative to the immunological fecal occult blood test,

* * *

[0076] Further, since the method of the present invention needs smaller amount of feces for detection and has higher detection sensitivity compared to the detection of the gene mutation of APC, K-ras, or p53, it can save largely the time and effort needed for the detection.

Petition, at 16, 35-37, 48-49, 65-66;
EX1007 (Kanaoka) ¶¶ 21-25, 67-68, 76

Demonstrative Exhibit - Not Evidence

A POSA Would Have a Reasonable Expectation of Stabilizing RNA Biomarkers Without Freezing

Nechvatal

to the bacterial constituents of the same human subject. In conclusion, this study suggests that preserving fecal samples at room temperature for a duration of 5 days, in a medium suitable for DNA and RNA analysis is feasible. With development of a suitable collection and shipping device, preservation of fecal samples in RNAlater may greatly facilitate self-collection and delivery of stool samples for comprehensive epidemiologic studies of molecular markers for intestinal bacteria, human cancer, and other human factors.

Backman Tr.

Q. Do you provide any data that would contradict Nechvatal's conclusion?

A. No, I don't.

Petition, at 36; Reply, at 19-21; EX1002 (Whitney Decl.) ¶ 223; EX1086 (Whitney 2nd Decl.) ¶¶ 120-124; EX1024 (Nechvatal), at 131; EX1089 (Backman Tr.), at 167:12-14

Buffers for Preserving RNA Were Known in the Art by the Priority Date

RNA^{later}

RNA^{later}® for RNA and Protein Stabilization

- Simplify sample collection
- No need to freeze sample in liquid nitrogen
- Stabilize both RNA and protein within tissues or cells
- Isolate both RNA and protein from the same sample

RNA^{later} is an aqueous, nontoxic, tissue and cell collection reagent that stabilizes and protects RNA in intact, unfrozen tissue and cell samples. The solution permeates the cells, stabilizing the RNA inside them. RNA^{later} treated samples can be stored at room temperature (25°C) for up to one week, at 4°C for up to one month, or at -20°C (or lower) indefinitely. Intact protein can be recovered from RNA^{later}-stabilized samples for use in downstream applications such as Western blotting or 2D gel analysis. Thus, RNA^{later} is the ideal companion to the PARIS™ (Protein And RNA Isolation System) Kit, a kit specifically engineered for the isolation of both protein and RNA from the same experimental sample. (See "RNAi: Get the Whole Story")

Backman Tr.

Q. Were buffers for preserving RNA known in the art in 2009?

THE WITNESS: There were -- there were buffers that would preserve RNA.

Petition, at 36; Reply, at 19-21; EX1002 (Whitney Decl.) ¶ 223; EX1086 (Whitney 2nd Decl.) ¶¶ 120-124; EX1089 (Backman Tr.), at 42:6-11; EX2048 (RNA^{later})

Demonstrative Exhibit - Not Evidence

Exact's Expert Admits that the RNA Claims of the '746 Patent Would Be Practiced Using Buffers Known in the Art

Q. The '78- -- sorry. The '746 patent disclosure does not disclose any buffers that were not already known in the art, does it?

A. I don't think so.

Q. And it doesn't disclose any new buffers or preserving RNA, does it?

THE WITNESS: It doesn't.

Backman
Tr.

Q. So to practice claim 12 of the '746 patent in 2009, a person of ordinary skill in the art would have had to use buffers already known in the art, right?

THE WITNESS: They would have to use a -- an appropriate buffer.

BY MR. JONES:

Q. That was already -- a buffer that was already known in the art?

THE WITNESS: They -- they wouldn't use buffers stated in the claims because no new specific buffer is mentioned in the claims.

How they would develop the buffer exactly, I believe that's outside of the scope of the -- of this -- of this patent.

Practically, they would -- they -- they would use a buffer that was available, known in prior art, designed their own, mix existing components. They -- they would certainly have to use a buffer.

BY MR. JONES:

Q. Were buffers for preserving RNA known in the art in 2009?

THE WITNESS: There were -- there were buffers that would preserve RNA.

Backman
Tr.

Alleged Secondary Considerations

IPR2024-00459: The Board Found that Exact Did Not Prove the Nearly Identical Claims of the '781 Patent had the Necessary Nexus to Exact's Cologuard Product

FWD

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571.272.7822

Paper 39
Date: July 9, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENEOSCOPY, INC.,
Petitioner,
v.

EXACT SCIENCES CORPORATION,
Patent Owner.

IPR2024-00459
Patent 11,634,781 B2

Before RYAN H. FLAX, DAVID COTTA, and JAMIE T. WISZ,
Administrative Patent Judges.

FLAX, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

Thus, even though aspects of the Cologuard product appear to embody claims of the '781 patent, the product has a multitude of features not covered by the '781 patent's claims, some of which are critical unclaimed elements according to Patent Owner. Accordingly, Cologuard is not coextensive with the challenged claims, and no nexus between the product and the challenged claims is shown on this record.

FWD

Where a party is not entitled to a presumption of nexus, it bears the burden of showing that the success of the product is “a direct result of unique characteristics of the claimed invention.” *Fox Factory, Inc.*, 944 F.3d at 1373–74. Patent Owner does not show here that success is the “direct result of unique characteristics of the claimed invention.” For each of the alleged objective indicia, we address whether the evidence supports the existence of a nexus even absent a presumption.

Reply, at 21; EX1087 (FWD), at 29-30

Demonstrative Exhibit - Not Evidence

Exact Has Burden To Prove Nexus Between the Asserted Claims and Cologuard's Success



“In order to accord substantial weight to secondary considerations in an obviousness analysis, the evidence of secondary considerations must have a ‘nexus’ to the claims, *i.e.*, there must be ‘a legally and factually sufficient connection’ between the evidence and the patented invention.”

“The patentee bears the burden of showing that a nexus exists.”

Fox Factory, Inc. v. SRAM, LLC,
944 F.3d 1366, 1373 (Fed. Cir. 2019)

Reply, at 22

Demonstrative Exhibit - Not Evidence

62

Presumption of Nexus Requires Coextensiveness



“[P]resuming nexus is appropriate ‘when the patentee shows that the asserted objective evidence is tied to a specific product and that **product ‘embodies the claimed features, and is coextensive with them.’**”

Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1373 (Fed. Cir. 2019)

“[T]o meet the coextensiveness requirement, what we do require is that the patentee demonstrate that the **product is essentially the claimed invention.**”

Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1374 (Fed. Cir. 2019)

Reply, at 22

Not Coextensive If Product Embodies Features Claimed by Other Patents



“A patent claim is **not coextensive** with a product that includes a ‘critical’ unclaimed feature that is **claimed by a different patent** and that **materially impacts the product’s functionality**.”

Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1375 (Fed. Cir. 2019)

“Where a product embodies claims from two patents, a **presumption of nexus can be appropriate only if the claims of both patents generally cover the same invention**.”

Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1377 (Fed. Cir. 2019)

Reply, at 22-23

Exact Admits that Cologuard Embodies Over 60 Unrelated Patents Directed to Distinct Inventions

8/9/24, 2:41 PM
EXACT SCIENCES
Patents and Trademarks | Exact Sciences

PATENTS & TRADEMARKS

Trademarks

QUARTS, COLOGUARD, EXACT, EXACT SCIENCES, BE SEEN GET SCREENED, and COINE are trademarks of Exact Sciences Corporation. MicroAmp® and Applied Biosystems® are registered trademarks of Life Technologies Corporation (Thermo Scientific). MicroLab® is a registered trademark of Hamilton Robotics. ELx808™ is trademark of Biotek® Instruments Inc. Titer Top® is a registered trademark of Diversified Biotech. Paraflin® is a registered trademark of Pecheney Plastic Packag

Patents

The Cologuard® test and its use are covered by one or more of the following patent associated pending patent applications, or non-U.S. international equivalents: U.S. 8,361,720, 8,673,555, 8,715,937, 8,722,330, 8,916,344, 8,969,046, 8,980,107, 8,993,341, 8,999,176, 9,000,146, 9,024,006, 9,057,098, 9,121,070, 9,121,071, 9,127,318, 9,163,278, 9,169,975, 9,211,112, 9,212,392, 9,290,797, 9,315,853, 9,376,721, 9,399,800, 9,631,228, 9,637,792, 9,657,330, 9,750,482, 9,783,856, 9,803,249, 9,845,491, 9,856,515, 9,982,308, 10,000,817, 10,047,390, 10,093,987, 10,106,844, 10,138,524, 10,144,953, 10,196,676, 10,253,358, 10,253,358, 10,265,054, D849,266, 10,435,753, 10,450,614, 10,486,158, 10,519,510, 10,590,489, 10,604,793, 10,626,465, 10,702,250, 10,704,083, 10,808,286, 10,822,639, 10,870,893, 10,889,867, 10,894,256, 11,634,781, 11,845,991, and 11,970,746. This product and its use are also covered by patents pending in the U.S. and around the world.

Dye compounds in the Cologuard® test are sold under license from Biosearch Technologies, Inc. and may be protected by U.S. and world-wide patents or patent

https://www.exactsciences.com/patents-and-trademarks
Genomecopy Exhibit 1084, Page 1
114

Cologuard Website

Patents

The Cologuard® test and its use are covered by one or more of the following patents, associated pending patent applications, or non-U.S. international equivalents: U.S. 8,361,720, 8,673,555, 8,715,937, 8,722,330, 8,916,344, 8,969,046, 8,980,107, 8,993,341, 8,999,176, 9,000,146, 9,024,006, 9,057,098, 9,121,070, 9,121,071, 9,127,318, 9,163,278, 9,169,511, 9,211,112, 9,212,392, 9,290,797, 9,315,853, 9,376,721, 9,399,800, 9,631,228, 9,637,792, 9,657,330, 9,750,482, 9,783,856, 9,803,249, 9,845,491, 9,856,515, 9,982,308, 10,000,817, 10,047,390, 10,093,987, 10,106,844, 10,138,524, 10,144,953, 10,196,676, 10,253,358, 10,253,358, 10,265,054, D849,266, 10,435,753, 10,450,614, 10,486,158, 10,519,510, 10,590,489, 10,604,793, 10,626,465, 10,702,250, 10,704,083, 10,808,286, 10,822,639, 10,870,893, 10,889,867, 10,894,256, 11,634,781, 11,845,991, and 11,970,746. This product and its use are also covered by patents pending in the U.S. and around the world.

Petition, at 67-68; Reply, at 22; EX1026 (Cologuard Website), at 1

Demonstrative Exhibit - Not Evidence

Exact Admits that Cologuard Embodies Over 60 Unrelated Patents Directed to Distinct Inventions

Unclaimed in '781 Patent	Claimed By U.S. Patent Nos.
Cologuard's DNA stabilizing buffer	6,551,777; 8,722,330
Cologuard's DNA isolation methods	6,268,136; 6,406,857; 8,993,341; 8,999,176; 9,000,146; 9,057,098; 9,163,278; 9,169,511; 9,657,330; 9,631,228; 9,845,491; 9,856,515; 10,047,390; 10,822,639
Cologuard's DNA markers	8,673,555; 8,969,046; 9,121,070; 9,127,318; 9,163,278; 9,169,511; 9,399,800; 9,783,856; 9,803,249; 9,845,491; 10,435,753
Cologuard's methods of preparing DNA	9,315,853; 10,144,953; 10,704,083
Cologuard's methods of testing for methylated DNA	8,916,344; 9,637,792; 10,519,510; 10,590,489; 10,808,286
Cologuard's methods of detecting DNA mutations	8,361,720; 8,715,937; 9,024,006; 9,121,071; 9,212,392; 9,290,797; 9,376,721; 10,000,817; 10,106,844; 10,590,489
Cologuard's control molecules	9,212,392; 10,106,844; 10,138,524; 10,253,358; 10,889,867
Use of stool in CRC screening	5,741,650; 5,952,178; 6,303,304; 6,586,177
Cologuard's collection and storage container	9,211,112; 9,750,482; 10,265,054; 10,486,158; 10,702,250; 10,894,256

Petition, at 67-68; Reply, at 22; EX1002 (Whitney Decl.) ¶ 344; EX1026 (Cologuard Website), at 1

Cologuard Includes Critical Features Not Claimed by '781 Patent

Device Description

Cologuard utilizes a multi-targeted approach to detect DNA and hemoglobin markers associated with CRC, as well as pre-malignant colorectal neoplasia (i.e., AA). Three independent categories of biomarkers are targeted and provide an additive association with CRC and pre-malignant colorectal neoplasia

Device Description

Cologuard utilizes a multi-target approach to detect DNA and hemoglobin markers associated with CRC, as well as pre-malignant colorectal neoplasia (i.e., AA). Three independent categories of biomarkers are targeted and provide an additive association with CRC and pre-malignant colorectal neoplasia

* * *

The third category of biomarker is non-DNA based and detects hemoglobin, which can be associated with colonic bleeding. Results from the methylation, mutation, and hemoglobin assays are combined in the laboratory analysis to determine a positive or negative reportable result or no result.

Cologuard is designed to analyze patients' stool for the presence of 11 molecular markers, including hemoglobin and DNA markers, which may indicate the presence of colorectal cancer or advanced adenomas. Because cellular exfoliation of DNA into stool occurs continuously, Cologuard can detect pre-malignant neoplasia at early onset of abnormality.

Patent Owner's Assertions About Significance of Unclaimed Features in ColoGuard Precludes Presumption of Nexus



“In light of the patentee’s own assertions about the significance of the unclaimed features, no reasonable fact finder could conclude that these features are insignificant.”

Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1375 (Fed. Cir. 2019)

Exact Asserts Significance of Unclaimed Features

Multitarget Stool DNA Testing for Colorectal-Cancer Screening

Thomas F. Imperiale, M.D., David F. Basshoff, M.D., Steven H. Johnston, M.D., Theodore B. Jensen, M.D., Philip Levin, Ph.D., Graham F. Lilgard, Ph.D., David A. Ahlquist, M.D., and Barry M. Berger, M.D.

ABSTRACT

BACKGROUND An accurate, noninvasive test could improve the effectiveness of colorectal-cancer screening.

METHODS We used a noninvasive, multitarget stool DNA test with a fecal immunochromatographic test (FIT) in persons at average risk for colorectal cancer. The DNA test includes quantitative molecular assays for KRAS mutations, aberrant AIMP4 and BMP3 methylation, and β -actin, plus a hemoglobin immunoassay. Results were generated with the use of a logistic-regression algorithm, with values of 185 or more considered to be positive. Persons with more than 100 ng of hemoglobin per milligram of buffer were considered to be positive. Tests were processed independently of colonoscopy findings.

RESULTS Of 10,999 participants who could be evaluated, 65 (0.7%) had colorectal cancer. Of 1757 (16%) had advanced precancerous lesions. The sensitivity of the multitarget stool DNA test for colorectal cancer was 92.3% and 73.8% for advanced precancerous lesions. The sensitivity for detecting colorectal cancer was 92.3% with DNA testing and 73.8% with FIT ($P=0.002$). The sensitivity for detecting advanced precancerous lesions was 42.4% with DNA testing and 23.8% with FIT ($P<0.0001$). The rate of detection of colorectal cancer was 1.0% with DNA testing and 0.7% with FIT ($P=0.004$). The rates of detection of advanced precancerous lesions were 42.4% and 5.1%, respectively ($P<0.0001$). Specificities with DNA testing and FIT were 86.6% and 94.9%, respectively, among participants with nonadvanced or negative findings ($P<0.0001$) and 89.8% and 96.4%, respectively, among those with negative results from colonoscopy ($P<0.0001$). The numbers of persons who had negative results and no detectable colorectal cancer were 154 with colonoscopy, 169 with DNA testing, and 208 with FIT.

CONCLUSIONS In asymptomatic persons at average risk for colorectal cancer, multitarget stool DNA testing was more sensitive than FIT for colorectal cancer and advanced precancerous lesions. (Funded by Exact Sciences; ClinicalTrials.gov number, NCT01397792)

DISCUSSION

We compared a multitarget stool DNA test with a commercial FIT among patients at average risk for colorectal cancer. The sensitivity of the DNA test for the detection of both colorectal cancer (92.3%) and advanced precancerous lesions (42.4%) exceeded that of FIT by an absolute difference of nearly 20 percentage points. This difference may be attributed to the DNA marker and algorithm components of the test, since the test performance of the hemoglobin immunoassay component of the DNA test was nearly identical to that of FIT.

Exact Asserts Significance of Unclaimed Features

PATENT Attorney Docket No.: EXCT-31029 US-A-CON		Response to Final Office Action, '278 Patent	
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE			
In re Application of: Janelle J. Bruinsma Serial No.: 1445082 Filed: 12/31/2014 Examiner: [redacted] Entitled: ISOLATION OF NUCLEIC ACID	Co-Applicant: VAN ENGELAND, ZOU, and VAN AMENDMENT UNDER 37 C.F.R. § 1.312 FINAL OFFICE ACTION MAILED AND REQUEST FOR AFTER-FINAL CONSIDERATION	The references cited in making the rejection, including SHUBER, ZOU, and VAN ENGELAND, demonstrate that there has been a long-felt need for a way to screen for colorectal cancers based on stool DNA testing. However, even in possession of the methods and markers disclosed in the art cited by the Examiner, as stated by VAN ENGELAND, other workers in the field have failed. In contrast, Applicants have been able to meet this need and succeed where others had failed by using a particular combination of markers and methods for extracting the marker DNA, as described in the instant application. The embodiments as claimed herein addressed this long-felt need and succeeded where others had failed, as evidenced by first-ever FDA approval for the product containing these components.	
VIA EFS WEB Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450			
CERTIFICATE OF EFS WEB TRANSMISSION NUMBER I hereby certify that this correspondence (along with any referred to as being incorporated by reference) has been transmitted to the Patent and Trademark Office filing system in accordance with 37 C.F.R. 1.156(a)(4). Dated: July 21, 2015. By: [redacted] Muz.Ashish [redacted] Attorney			
This communication is an After Final Amendment under the Final Office Communication mailed July 6, 2015, with a request for reconsideration of the rejection of Claims 1-16 under 37 C.F.R. § 1.116, and is filed with a Request for After-Final Consideration respectfully request entry of this amendment. The Commissioner is hereby authorized to charge any fee for this application, including fees due under 37 C.F.R. §§ 1.16 and 1.156, including any required extension of time fees, or credit any overpayment of fees. This communication is being filed in accordance with 37 C.F.R. § 1.156(a)(4). 4302, referencing Attorney Docket No.: EXCT-31029 US-3-C (which is a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME under 37 C.F.R. § 1.136(a)(3)). Amendments to the Claims are reflected in the Listing of Claims. Remarks begin on page 5.			
-1-		Genescopy Exhibit 1086, Page 1	

Petition, at 68; Reply, at 24-25; EX1029 (Response to Final Office Communication, '278 Patent), at 9

Demonstrative Exhibit - Not Evidence

Exact Has Not Shown Cologuard's Purported Success Is the Direct Result of the Unique Characteristics of the Challenged Claims



“A finding that a presumption of nexus is inappropriate does not end the inquiry into secondary considerations. To the contrary, the patent owner is still afforded an opportunity to prove nexus by showing that the evidence of secondary considerations is the ‘**direct result of the unique characteristics of the claimed invention.**’”

Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1373-74 (Fed. Cir. 2019)

- Exact has not proven that “diagnostic accuracy and patient uptake” are unique characteristics of the challenged claims.

Reply, at 23-26

Demonstrative Exhibit - Not Evidence

Exact Has Not Shown Cologuard's Purported Success Is the Direct Result of the Unique Characteristics of the Challenged Claims

Unclaimed in '781 Patent		Claimed By U.S. Patent Nos.
Cologuard's DNA stabilizing buffer		6,551,777; 8,722,330
Cologuard's DNA isolation methods		6,268,136; 6,406,857; 8,993,341; 8,999,176; 9,000,146; 9,057,098; 9,163,278; 9,169,511; 9,657,330; 9,631,228; 9,845,491; 9,856,515; 10,047,390; 10,822,639
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Petition, at 67-68; Reply, at 22; EX1002 (Whitney Decl.) ¶ 344; EX1026 (Cologuard Website), at 1

Exact Has Attributed Cologuard's Sensitivity to Unclaimed Features

Exact's Extensive Post-Priority R&D and Marketing Efforts Contributed Significantly to the Patient Uptake of Cologuard

- Even after obtaining FDA approval in 2014, it took Cologuard “many years to gain widespread recognition and adoption.”
- Exact Sciences spent **over \$3.6 billion** dollars on its Cologuard products **between 2009 and 2023**.
- Between **2009 and 2023**, Exact Sciences spent **over \$290 million** in research and development for Cologuard.
- Between **2009 and 2023**, Exact Sciences spent **over \$3 billion** in sales and marketing of Cologuard.

Reply, at 25; EX2019 (Declaration of Peter Wood, Exact Sciences' Vice President of Screening Portfolio Strategy) ¶ 13

Exact's Extensive Marketing Efforts Contributed Significantly to Cologuard's Commercial Success

Forbes Article

So Exact adopted a similar strategy, running direct-to-consumer (DTC) marketing tests in five cities shortly after Cologuard's launch. "We ran targeted TV commercials in these five markets and compared them to the five control markets. These markets grew cumulatively 10% per week over the five control markets. After 9 weeks, we were up 100% compared to the control markets." Concludes Conroy: "The Board - and our investors - did not need more proof than that in order for us to really ramp up investment in DTC - \$28 million in 2016."

Reply, at 25-26; EX1091 (Forbes Article Quoting Kevin Conroy, CEO of Exact Sciences), at 6

Demonstrative Exhibit - Not Evidence

Exact Represented to the Patent Office that Cologuard's Success Was Attributable to Exact's Later Invention

Response to Final Office Action, '278 Patent

PATENT
Attorney Docket No.: EXCT-100000-000000
IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Date of Application of: Amended Petition
Serial No.: 14/16,082
Filed: 12/31/2013
Entitled: ISOLATION OF NUCLEIC ACID

AMENDMENT UNDER 37 C.F.R. § 1.116 AFTER
FINAL OFFICE ACTION MAILED JULY 6, 2015
REQUEST FOR AFTER-FINAL CONSIDERATION UNDER AFCP 2.0

VIA FIRST CLASS MAIL
P.O. Box 1450
Alexandria, Virginia 22311-1450

CERTIFICATE OF MAILING
I hereby certify that the communication, including any fee, enclosed in a sealed envelope, was mailed to the United States Patent and Trademark Office on the date indicated below, and that the communication was received by the United States Patent and Trademark Office on the date indicated below.
Date: 12/31/2013
By: [Signature]

This communication is an After-Final Amendment under 37 C.F.R. § 1.116, responsive to the Final Office Communication mailed July 6, 2015, with response due on or before October 6, 2015, and is filed with a Request for After-Final Consideration under AFCP 2.0. Applicants respectfully request entry of this amendment.

The Commissioner is hereby authorized to charge any fees during the entire pendency of this application, including fees due under 37 C.F.R. §§ 1.16 and 1.17 that may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 96-4062, referencing Attorney Docket No. EXCT-100000-000000. This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. § 1.136(a)(3).

Amendments to the Claims are reflected in the Listing of Claims beginning on page 2.

Remarks begin on page 5.

-1-

Continuity Guideline 100E, Page 1

Petition, at 68; Reply, at 24-25;
EX1029 (Response to Final Office
Communication, '278 Patent), at 9;
FWD, at 29

The references cited in making the rejection, including SHUBER, ZOU, and VAN ENGELAND, demonstrate that there has been a long-felt need for a way to screen for colorectal cancers based on stool DNA testing. However, even in possession of the methods and markers disclosed in the art cited by the Examiner, as stated by VAN ENGELAND, other workers in the field have failed. In contrast, Applicants have been able to meet this need and succeed where others had failed by using a particular combination of markers and methods for extracting the marker DNA, as described in the instant application. The embodiments as claimed herein addressed this long-felt need and succeeded where others had failed, as evidenced by first-ever FDA approval for the product containing these components.

FWD

components.” Ex. 1086, 9. The fact that other patented inventions (of the '278 patent), not at issue in this proceeding, met the long-felt need and were the reason for success (of Cologuard) supports our giving little weight to Patent Owner’s arguments on long-felt need and failures of others/success of Patent Owner.

Demonstrative Exhibit - Not Evidence

Challenged Claims

'746 Patent, Cl. 1*

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:
 - a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject;
 - b) in a sealable vessel, combining a first portion of the fecal sample with a stabilizing buffer, and sealing the sealable vessel; and
 - c) in a sealable container, combining a second portion of the fecal sample with a solution that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container.

* Patent Owner Statutorily Disclaimed claim 1 of the '746 patent, prior to institution of the IPR (See: EX 2041)

EX1001, EX1030

Demonstrative Exhibit - Not Evidence

'781 Patent, Cl. 1

1. A method of processing a freshly-collected fecal sample without freezing, the method comprising:
 - a) collecting a fecal sample from a human subject, wherein the fecal sample is collected at home by the human subject by defecation directly into a sealable collection vessel;
 - b) removing a portion of the fecal sample to a separate sealable container to produce a removed portion and a remaining portion of the fecal sample;
 - c) combining the removed portion of the fecal sample in the separate sealable container with a buffer that prevents denaturation or degradation of blood proteins found in a fecal sample, and sealing the sealable container; and
 - d) combining the remaining portion of the fecal sample in the sealable collection vessel with a stabilizing buffer, and sealing the sealable collection vessel.

'746 Patent, Cl. 3

3. A method of processing a fecal sample, the method comprising:

- a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising:
 - i) a sealed sealable vessel containing a first portion of a fecal sample and a stabilizing buffer; and
 - ii) a sealed sealable container containing a second portion of a fecal sample and a solution that prevents denaturation or degradation of blood proteins found in a fecal sample,wherein the pair of portions are obtained by the method of claim 1;
- b) extracting nucleic acid from the first portion of the fecal sample;
- c) testing nucleic acid extracted from the first portion of the fecal sample for an amount of a human nucleic acid; and
- d) testing the second portion of the fecal sample for an amount of a blood protein present in the second portion of the fecal sample.

'781 Patent, Cl. 3

3. A method of processing a fecal sample, the method comprising:

- a) obtaining a pair of portions of a fecal sample collected from a human subject, the pair of portions comprising:
 - i) a sealed sealable container containing a removed portion of a fecal sample and a buffer; and
 - ii) a sealed sealable collection vessel containing a remaining portion of a fecal sample and a stabilizing buffer,the pair of portions obtained by the method of claim 1;
- b) testing the removed portion of the fecal sample for an amount of a blood protein present in the removed portion;
- c) extracting nucleic acid from the remaining portion of the fecal sample; and
- d) testing the nucleic acid for an amount of a human nucleic acid.

EX1001, EX1030

Demonstrative Exhibit - Not Evidence

'746 Patent, Cl. 4

4. The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene.

'781 Patent, Cl. 4

4. The method of claim 3, wherein testing the nucleic acid comprises determining expression from a human gene.

'746 Patent, Cl. 12

12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the human gene.

'781 Patent, Cl. 12

12. The method of claim 4, wherein determining expression from the human gene comprises measuring an amount of RNA expressed from the gene.

'746 Patent, Cl. 13

13. The method of claim 12, wherein measuring an amount of RNA expressed from the human gene comprises reverse transcriptase polymerase chain reaction (RT-PCR).

'781 Patent, Cl. 13

13. The method of claim 12, wherein measuring an amount of RNA expressed from the gene comprises reverse transcriptase polymerase chain reaction (RT-PCR).

'746 Patent, Cl. 14

14. The method of claim **3**, wherein testing for an amount of a blood protein present in the second portion comprises testing for a concentration of hemoglobin in the second portion, wherein a concentration of hemoglobin is indicative of a presence of blood in the fecal sample.

'781 Patent, Cl. 14

14. The method of claim **3**, wherein testing for an amount of a blood protein in the removed portion comprises testing for a concentration of hemoglobin in the removed portion.

'746 Patent, Cl. 15

15. The method of claim 14, wherein testing for the concentration of hemoglobin comprises immunochemical detection of hemoglobin.

'781 Patent, Cl. 15

15. The method of claim 14, wherein testing for the concentration of hemoglobin comprises immunochemical detection of hemoglobin.

'746 Patent, Cl. 16

16. The method of claim 14, wherein the second portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the second portion is at least 5 ng/ml.

'781 Patent, Cl. 16

16. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 5 ng/ml.

'746 Patent, Cl. 17

17. The method of claim 14, wherein the second portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the second portion is at least 10 ng/ml.

'781 Patent, Cl. 17

17. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 10 ng/ml.

'746 Patent, Cl. 18

18. The method of claim 14, wherein the second portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the second portion is at least 20 ng/ml.

'781 Patent, Cl. 18

18. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 20 ng/ml.

'746 Patent, Cl. 19

19. The method of claim 14, wherein the second portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the second portion is at least 50 ng/ml.

'781 Patent, Cl. 19

19. The method of claim 14, wherein the removed portion of the fecal sample is considered positive for the presence of blood when the concentration of hemoglobin detected in the removed portion is at least 50 ng/ml.



ORAL ARGUMENT FOR IPR2024-01330

U.S. Patent No. 11,970,746

Petitioner's Hearing Demonstratives

November 20, 2025

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a true and correct copy of the foregoing **PETITIONER'S DEMONSTRATIVES** was served on November 17, 2025 via the delivery method indicated to the attorneys of record for the Patent Owner as follows:

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Dated: November 17, 2025

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