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Cartridges and instruments for sample analysis

Abstract

Provided herein are instruments and cartridges for processing samples. The cartridges include fluidic circuits in which fluid movement can be regulated by diaphragm valves. In certain cartridges, deformable material providing a diaphragm contacts an interface in the instrument that actuates the diaphragm directly, without intervening actuation layer. Certain cartridges have a plurality of fluidic circuits and fluid distribution channels or pneumatic distribution channels configured to deliver fluids or pneumatic pressure to any of the fluidic circuits, selectively. Certain cartridges have compartments containing on-board reagents. Compartments can be closed by a film attached to a body the cartridge through a heat seal.

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References Cited

U.S. PATENT DOCUMENTS

Patent No.	Issued Date	Patentee Name	U.S. Cl.	CPC
3075740	12/1962	Mcintosh	N/A	N/A
3352643	12/1966	Ando et al.	N/A	N/A
3433257	12/1968	Donald	N/A	N/A
3568692	12/1970	Eric et al.	N/A	N/A
3662517	12/1971	Edward et al.	N/A	N/A
4011357	12/1976	Haase	N/A	N/A
4113665	12/1977	Law et al.	N/A	N/A
4390307	12/1982	Rice	N/A	N/A
4847120	12/1988	Gent	N/A	N/A
4963498	12/1989	Hillman et al.	N/A	N/A
5085757	12/1991	Karger et al.	N/A	N/A
5275645	12/1993	Ternoir et al.	N/A	N/A
5338427	12/1993	Shartle et al.	N/A	N/A
5364759	12/1993	Caskey et al.	N/A	N/A
5376252	12/1993	Ekstroem et al.	N/A	N/A
5387505	12/1994	Wu	N/A	N/A
5453163	12/1994	Yan	N/A	N/A
5482836	12/1995	Cantor et al.	N/A	N/A
5523231	12/1995	Reeve	N/A	N/A
5571410	12/1995	Swedberg et al.	N/A	N/A
5587128	12/1995	Wilding et al.	N/A	N/A
5589136	12/1995	Northrup et al.	N/A	N/A
5635358	12/1996	Wilding et al.	N/A	N/A
5639428	12/1996	Cottingham	N/A	N/A
5675155	12/1996	Pentoney, Jr. et al.	N/A	N/A
5681946	12/1996	Reeve	N/A	N/A
5705628	12/1997	Hawkins	N/A	N/A
5705813	12/1997	Apffel et al.	N/A	N/A
5726026	12/1997	Wilding et al.	N/A	N/A
5741462	12/1997	Nova et al.	N/A	N/A
5750015	12/1997	Soane et al.	N/A	N/A
5770029	12/1997	Nelson et al.	N/A	N/A
5775371	12/1997	Pan et al.	N/A	N/A
5776748	12/1997	Singhvi et al.	N/A	N/A
5830662	12/1997	Soares et al.	N/A	N/A
5842787	12/1997	Kopf-Sill et al.	N/A	N/A
5856174	12/1998	Lipshutz et al.	N/A	N/A
5863502	12/1998	Southgate	422/417	B01L 3/502738
5872010	12/1998	Karger et al.	N/A	N/A
5885470	12/1998	Parce et al.	N/A	N/A
5898071	12/1998	Hawkins	N/A	N/A
5908552	12/1998	Dittmann et al.	N/A	N/A
5922591	12/1998	Anderson et al.	N/A	N/A
5932799	12/1998	Moles	435/288.5	B32B 27/08
5942443	12/1998	Parce et al.	N/A	N/A
5948684	12/1998	Weigl et al.	N/A	N/A

5951262	12/1998	Hartman	N/A	N/A
5971158	12/1998	Yager et al.	N/A	N/A
5994064	12/1998	Staub et al.	N/A	N/A
6001229	12/1998	Ramsey	N/A	N/A
6007690	12/1998	Nelson et al.	N/A	N/A
6007775	12/1998	Yager	N/A	N/A
6010607	12/1999	Ramsey	N/A	N/A
6048100	12/1999	Thrall et al.	N/A	N/A
6056860	12/1999	Amigo et al.	N/A	N/A
6073482	12/1999	Moles	N/A	N/A
6074827	12/1999	Nelson et al.	N/A	N/A
6103199	12/1999	Bjornson et al.	N/A	N/A
6110343	12/1999	Ramsey et al.	N/A	N/A
6120184	12/1999	Laurence et al.	N/A	N/A
6136212	12/1999	Mastrangelo et al.	N/A	N/A
6153389	12/1999	Haarer et al.	N/A	N/A
6168948	12/2000	Anderson et al.	N/A	N/A
6176962	12/2000	Soan et al.	N/A	N/A
6190616	12/2000	Jovanovich et al.	N/A	N/A
6197595	12/2000	Anderson et al.	N/A	N/A
6207031	12/2000	Adourian et al.	N/A	N/A
6235471	12/2000	Kapp et al.	N/A	N/A
6238538	12/2000	Parce et al.	N/A	N/A
6251343	12/2000	Dubrow et al.	N/A	N/A
6280589	12/2000	Manz et al.	N/A	N/A
6319476	12/2000	Victor, Jr. et al.	N/A	N/A
6321791	12/2000	Chow	N/A	N/A
6322683	12/2000	Wolk	N/A	N/A
6326068	12/2000	Kong et al.	N/A	N/A
6342142	12/2001	Ramsey	N/A	N/A
6348318	12/2001	Valkirs	N/A	N/A
6379929	12/2001	Burns et al.	N/A	N/A
6387234	12/2001	Yeung et al.	N/A	N/A
6387707	12/2001	Seul et al.	N/A	N/A
6391622	12/2001	Knapp et al.	N/A	N/A
6403338	12/2001	Knapp et al.	N/A	N/A
6408878	12/2001	Unger et al.	N/A	N/A
6423536	12/2001	Jovanovich et al.	N/A	N/A
6429025	12/2001	Parce	N/A	N/A
6432191	12/2001	Schutt	N/A	N/A
6432290	12/2001	Harrison et al.	N/A	N/A
6454924	12/2001	Jedrzejewski et al.	N/A	N/A
6461492	12/2001	Hayashizaki et al.	N/A	N/A
6489112	12/2001	Hadd et al.	N/A	N/A
6521188	12/2002	Webster	N/A	N/A
6524456	12/2002	Ramsey et al.	N/A	N/A
6527003	12/2002	Webster	N/A	N/A
6531041	12/2002	Cong et al.	N/A	N/A
6531282	12/2002	Dau et al.	N/A	N/A
6532997	12/2002	Bedingham et al.	N/A	N/A
6533914	12/2002	Liu	N/A	N/A
6534262	12/2002	Mckernan et al.	N/A	N/A
6537757	12/2002	Langmore et al.	N/A	N/A
6544734	12/2002	Briscoe et al.	N/A	N/A
6551839	12/2002	Jovanovich et al.	N/A	N/A
6581441	12/2002	Paul	N/A	N/A
6581899	12/2002	Williams	N/A	N/A
6605454	12/2002	Barenburg et al.	N/A	N/A
6613525	12/2002	Nelson et al.	N/A	N/A
6614228	12/2002	Hofmann et al.	N/A	N/A
6618679	12/2002	Loehrlein et al.	N/A	N/A
6620584	12/2002	Chee et al.	N/A	N/A

6623613	12/2002	Mathies et al.	N/A	N/A
6627446	12/2002	Roach et al.	N/A	N/A
6629820	12/2002	Kornelsen	N/A	N/A
6632619	12/2002	Harrison et al.	N/A	N/A
6632655	12/2002	Mehta et al.	N/A	N/A
6660148	12/2002	Shoji et al.	N/A	N/A
6663833	12/2002	Stave et al.	N/A	N/A
6685442	12/2003	Chinn et al.	N/A	N/A
6685678	12/2003	Evans et al.	N/A	N/A
6685809	12/2003	Jacobson et al.	N/A	N/A
6740219	12/2003	Kazumichi et al.	N/A	N/A
6752922	12/2003	Huang et al.	N/A	N/A
6764648	12/2003	Roach et al.	N/A	N/A
6782746	12/2003	Hasselbrink, Jr. et al.	N/A	N/A
6786708	12/2003	Brown et al.	N/A	N/A
6787111	12/2003	Roach et al.	N/A	N/A
6793753	12/2003	Unger et al.	N/A	N/A
6802342	12/2003	Fernandes et al.	N/A	N/A
6803019	12/2003	Bjornson et al.	N/A	N/A
6807490	12/2003	Perlin	N/A	N/A
6824663	12/2003	Boone	N/A	N/A
6829753	12/2003	Lee et al.	N/A	N/A
6833246	12/2003	Balasubramanian	N/A	N/A
6852287	12/2004	Ganesan	N/A	N/A
6870185	12/2004	Roach et al.	N/A	N/A
6883774	12/2004	Nielsen et al.	N/A	N/A
6885982	12/2004	Harris et al.	N/A	N/A
6899137	12/2004	Unger et al.	N/A	N/A
6902706	12/2004	Colin	422/537	B01L 3/502738
6923907	12/2004	Hobbs et al.	N/A	N/A
6929030	12/2004	Unger et al.	N/A	N/A
6951632	12/2004	Unger et al.	N/A	N/A
6953058	12/2004	Fernandes et al.	N/A	N/A
6960437	12/2004	Enzelberger et al.	N/A	N/A
6994986	12/2005	Swartz et al.	N/A	N/A
7005052	12/2005	Shimizu et al.	N/A	N/A
7005292	12/2005	Wilding et al.	N/A	N/A
7005493	12/2005	Huang et al.	N/A	N/A
7015030	12/2005	Fouillet et al.	N/A	N/A
7046357	12/2005	Weinberger et al.	N/A	N/A
7049558	12/2005	Baer et al.	N/A	N/A
7081191	12/2005	Shoji et al.	N/A	N/A
7087380	12/2005	Griffiths et al.	N/A	N/A
7097809	12/2005	Van et al.	N/A	N/A
7105300	12/2005	Parce et al.	N/A	N/A
7118910	12/2005	Unger et al.	N/A	N/A
7142987	12/2005	Eggers	N/A	N/A
7157228	12/2006	Hashmi et al.	N/A	N/A
7169557	12/2006	Rosenblum et al.	N/A	N/A
7170050	12/2006	Turner et al.	N/A	N/A
7198759	12/2006	Bryning et al.	N/A	N/A
7211388	12/2006	Cash et al.	N/A	N/A
7217367	12/2006	Huang et al.	N/A	N/A
7232656	12/2006	Balasubramanian et al.	N/A	N/A
7244559	12/2006	Rothberg et al.	N/A	N/A
7244567	12/2006	Chen et al.	N/A	N/A
7244599	12/2006	Rothberg et al.	N/A	N/A
7244961	12/2006	Jovanovich et al.	N/A	N/A
7258744	12/2006	Sakurada et al.	N/A	N/A
7258774	12/2006	Chou et al.	N/A	N/A
7279146	12/2006	Nassef et al.	N/A	N/A
7282361	12/2006	Hodge	N/A	N/A

7312085	12/2006	Chou	N/A	N/A
7312611	12/2006	Harrison et al.	N/A	N/A
7323305	12/2007	Leamon et al.	N/A	N/A
7329388	12/2007	Guzman	N/A	N/A
7361471	12/2007	Gerdes et al.	N/A	N/A
7419578	12/2007	Sakai et al.	N/A	N/A
7438856	12/2007	Jedrzejewski et al.	N/A	N/A
7445926	12/2007	Mathies et al.	N/A	N/A
7473342	12/2008	Ugai et al.	N/A	N/A
7473397	12/2008	Griffin et al.	N/A	N/A
7486865	12/2008	Foquet et al.	N/A	N/A
7488603	12/2008	Gjerde et al.	N/A	N/A
7501237	12/2008	Solus et al.	N/A	N/A
7526741	12/2008	Lee et al.	N/A	N/A
7531076	12/2008	Hayashizaki et al.	N/A	N/A
7537886	12/2008	Nazarenko et al.	N/A	N/A
7575865	12/2008	Leamon et al.	N/A	N/A
7584240	12/2008	Eggers	N/A	N/A
7589184	12/2008	Hogan et al.	N/A	N/A
7595200	12/2008	Bedingham et al.	N/A	N/A
7645580	12/2009	Barber et al.	N/A	N/A
7691614	12/2009	Senapathy	N/A	N/A
7704735	12/2009	Facer et al.	N/A	N/A
7718442	12/2009	Davis et al.	N/A	N/A
7744737	12/2009	James et al.	N/A	N/A
7745207	12/2009	Jovanovich et al.	N/A	N/A
7749365	12/2009	Nguyen et al.	N/A	N/A
7749737	12/2009	Mcbride et al.	N/A	N/A
7763453	12/2009	Clemmens et al.	N/A	N/A
7766033	12/2009	Mathies et al.	N/A	N/A
7785458	12/2009	Shimizu et al.	N/A	N/A
7785770	12/2009	Spencer et al.	N/A	N/A
7790368	12/2009	Fukuzono	N/A	N/A
7799553	12/2009	Mathies et al.	N/A	N/A
7803281	12/2009	Davies et al.	N/A	N/A
7817273	12/2009	Bahatt et al.	N/A	N/A
7832429	12/2009	Young et al.	N/A	N/A
7863357	12/2010	Madabhushi et al.	N/A	N/A
7867713	12/2010	Nasarabadi	N/A	N/A
7885770	12/2010	Gill et al.	N/A	N/A
7892856	12/2010	Grate et al.	N/A	N/A
7942160	12/2010	Jeon et al.	N/A	N/A
7943305	12/2010	Korlach et al.	N/A	N/A
7959875	12/2010	Zhou et al.	N/A	N/A
7976789	12/2010	Kenis et al.	N/A	N/A
7976795	12/2010	Zhou et al.	N/A	N/A
7998708	12/2010	Handique et al.	N/A	N/A
8007746	12/2010	Unger et al.	N/A	N/A
8018593	12/2010	Tan et al.	N/A	N/A
8053192	12/2010	Bignell et al.	N/A	N/A
RE43122	12/2011	Harrison et al.	N/A	N/A
8142635	12/2011	Shimizu et al.	N/A	N/A
8221990	12/2011	Mori et al.	N/A	N/A
8222023	12/2011	Battrell et al.	N/A	N/A
8268263	12/2011	Campbell et al.	N/A	N/A
8283165	12/2011	Hogan et al.	N/A	N/A
8313941	12/2011	Takayama et al.	N/A	N/A
8337777	12/2011	Nurse et al.	N/A	N/A
8388908	12/2012	Blaga, I et al.	N/A	N/A
8398642	12/2012	Weekes	N/A	N/A
8420318	12/2012	Mathies et al.	N/A	N/A
8431384	12/2012	Hogan et al.	N/A	N/A

8501305	12/2012	Barlow	N/A	N/A
8512538	12/2012	Majlof et al.	N/A	N/A
8551714	12/2012	Jovanovich et al.	N/A	N/A
8557518	12/2012	Jovanovich et al.	N/A	N/A
8562918	12/2012	Jovanovich et al.	N/A	N/A
8584703	12/2012	Kobrin et al.	N/A	N/A
8672532	12/2013	Jovanovich et al.	N/A	N/A
8748165	12/2013	Vangbo	N/A	N/A
8763642	12/2013	Vangbo	N/A	N/A
8815521	12/2013	Taylor et al.	N/A	N/A
8841116	12/2013	Mathies et al.	N/A	N/A
8894946	12/2013	Nielsen et al.	N/A	N/A
9012236	12/2014	Jovanovich et al.	N/A	N/A
9121058	12/2014	Jovanovich et al.	N/A	N/A
9291284	12/2015	Penterman et al.	N/A	N/A
9341284	12/2015	Vangbo	N/A	N/A
9592501	12/2016	Jarvius et al.	N/A	N/A
9663819	12/2016	Jovanovich et al.	N/A	N/A
9752185	12/2016	Boronkay et al.	N/A	N/A
10208332	12/2018	Eberhart et al.	N/A	N/A
10525467	12/2019	Nielsen et al.	N/A	N/A
10690627	12/2019	Kindwall et al.	N/A	N/A
2001/0012612	12/2000	Petersen et al.	N/A	N/A
2001/0041357	12/2000	Fouillet et al.	N/A	N/A
2002/0003895	12/2001	Some	N/A	N/A
2002/0022261	12/2001	Anderson et al.	N/A	N/A
2002/0022587	12/2001	Ferguson et al.	N/A	N/A
2002/0025529	12/2001	Quake et al.	N/A	N/A
2002/0025576	12/2001	Northrup et al.	N/A	N/A
2002/0042125	12/2001	Petersen et al.	N/A	N/A
2002/0047003	12/2001	Bedingham et al.	N/A	N/A
2002/0048536	12/2001	Bergh et al.	N/A	N/A
2002/0051992	12/2001	Bridgham et al.	N/A	N/A
2002/0054833	12/2001	Qu et al.	N/A	N/A
2002/0055167	12/2001	Pourahmadi et al.	N/A	N/A
2002/0058332	12/2001	Quake et al.	N/A	N/A
2002/0068357	12/2001	Mathies et al.	N/A	N/A
2002/0098097	12/2001	Singh	N/A	N/A
2002/0110900	12/2001	Jovanovich et al.	N/A	N/A
2002/0115201	12/2001	Berenburg et al.	N/A	N/A
2002/0119480	12/2001	Weir et al.	N/A	N/A
2002/0119482	12/2001	Nelson et al.	N/A	N/A
2002/0137039	12/2001	Gessner	N/A	N/A
2002/0139084	12/2001	Tobolka	N/A	N/A
2002/0151089	12/2001	Chapman et al.	N/A	N/A
2002/0157951	12/2001	Foret et al.	N/A	N/A
2002/0160361	12/2001	Loehrlein et al.	N/A	N/A
2002/0187560	12/2001	Pezzuto	422/504	B01L 3/502707
2003/0008308	12/2002	Enzelberger et al.	N/A	N/A
2003/0019753	12/2002	Ogle et al.	N/A	N/A
2003/0021734	12/2002	Vann et al.	N/A	N/A
2003/0029724	12/2002	Derand et al.	N/A	N/A
2003/0070677	12/2002	Handique et al.	N/A	N/A
2003/0087425	12/2002	Eggers	N/A	N/A
2003/0087446	12/2002	Eggers	N/A	N/A
2003/0087455	12/2002	Eggers	N/A	N/A
2003/0088657	12/2002	Eggers	N/A	N/A
2003/0095897	12/2002	Grate	N/A	N/A
2003/0104466	12/2002	Knapp et al.	N/A	N/A
2003/0129755	12/2002	Sadler et al.	N/A	N/A
2003/0162304	12/2002	Dority et al.	N/A	N/A
2003/0175706	12/2002	Zhang	N/A	N/A

2003/0197139	12/2002	Williams	N/A	N/A
2003/0198573	12/2002	Forood et al.	N/A	N/A
2003/0215369	12/2002	Eggers et al.	N/A	N/A
2003/0217923	12/2002	Harrison et al.	N/A	N/A
2004/0003997	12/2003	Anazawa et al.	N/A	N/A
2004/0013536	12/2003	Hower et al.	N/A	N/A
2004/0014091	12/2003	Duck et al.	N/A	N/A
2004/0018611	12/2003	Ward et al.	N/A	N/A
2004/0021068	12/2003	Staats	N/A	N/A
2004/0022676	12/2003	Hamilton et al.	N/A	N/A
2004/0037739	12/2003	Mcneely et al.	N/A	N/A
2004/0038385	12/2003	Langlois et al.	N/A	N/A
2004/0053290	12/2003	Terbrueggen et al.	N/A	N/A
2004/0063217	12/2003	Webster et al.	N/A	N/A
2004/0072278	12/2003	Chou et al.	N/A	N/A
2004/0086427	12/2003	Childers et al.	N/A	N/A
2004/0086870	12/2003	Tyvoll et al.	N/A	N/A
2004/0101966	12/2003	Davis et al.	N/A	N/A
2004/0115838	12/2003	Quake	N/A	N/A
2004/0132170	12/2003	Storek et al.	N/A	N/A
2004/0146452	12/2003	Fujieda et al.	N/A	N/A
2004/0151629	12/2003	Pease et al.	N/A	N/A
2004/0185484	12/2003	Costa et al.	N/A	N/A
2004/0197845	12/2003	Hassibi et al.	N/A	N/A
2004/0200724	12/2003	Fujii et al.	N/A	N/A
2004/0209354	12/2003	Mathies et al.	N/A	N/A
2004/0217004	12/2003	Hayashizaki et al.	N/A	N/A
2004/0219533	12/2003	Davis et al.	N/A	N/A
2004/0224380	12/2003	Chou et al.	N/A	N/A
2005/0026181	12/2004	Davis et al.	N/A	N/A
2005/0026300	12/2004	Samper et al.	N/A	N/A
2005/0042656	12/2004	Davis et al.	N/A	N/A
2005/0047967	12/2004	Chuang et al.	N/A	N/A
2005/0053952	12/2004	Hong et al.	N/A	N/A
2005/0142663	12/2004	Parthasarathy et al.	N/A	N/A
2005/0161326	12/2004	Morita et al.	N/A	N/A
2005/0161669	12/2004	Jovanovich et al.	N/A	N/A
2005/0181394	12/2004	Steemers et al.	N/A	N/A
2005/0201901	12/2004	Grossman et al.	N/A	N/A
2005/0221373	12/2004	Enzelberger et al.	N/A	N/A
2005/0224134	12/2004	Yin et al.	N/A	N/A
2005/0224352	12/2004	Harrison et al.	N/A	N/A
2005/0241941	12/2004	Parce et al.	N/A	N/A
2005/0250199	12/2004	Anderson et al.	N/A	N/A
2005/0255000	12/2004	Yamamoto et al.	N/A	N/A
2005/0255003	12/2004	Summersgill et al.	N/A	N/A
2005/0255007	12/2004	Yamada et al.	N/A	N/A
2005/0266582	12/2004	Modlin et al.	N/A	N/A
2005/0287572	12/2004	Mathies et al.	N/A	N/A
2006/0014177	12/2005	Hogan et al.	N/A	N/A
2006/0027456	12/2005	Harrison et al.	N/A	N/A
2006/0040300	12/2005	Dapprich et al.	N/A	N/A
2006/0057209	12/2005	Chapman et al.	N/A	N/A
2006/0073484	12/2005	Mathies et al.	N/A	N/A
2006/0076068	12/2005	Young et al.	N/A	N/A
2006/0140051	12/2005	Kim et al.	N/A	N/A
2006/0163143	12/2005	Chirica et al.	N/A	N/A
2006/0177832	12/2005	Brenner	N/A	N/A
2006/0186043	12/2005	Covey et al.	N/A	N/A
2006/0210994	12/2005	Joyce	N/A	N/A
2006/0210998	12/2005	Kettliz et al.	N/A	N/A
2006/0260941	12/2005	Tan et al.	N/A	N/A

2006/0263789	12/2005	Kincaid	N/A	N/A
2006/0266645	12/2005	Chen et al.	N/A	N/A
2006/0292032	12/2005	Hataoka et al.	N/A	N/A
2007/0015179	12/2006	Klapperich et al.	N/A	N/A
2007/0017812	12/2006	Bousse	N/A	N/A
2007/0020654	12/2006	Blume et al.	N/A	N/A
2007/0031865	12/2006	Willoughby	N/A	N/A
2007/0034025	12/2006	Pant et al.	N/A	N/A
2007/0105163	12/2006	Grate et al.	N/A	N/A
2007/0122819	12/2006	Wu et al.	N/A	N/A
2007/0175756	12/2006	Nguyen et al.	N/A	N/A
2007/0183935	12/2006	Clemmens et al.	N/A	N/A
2007/0184463	12/2006	Molho et al.	N/A	N/A
2007/0184547	12/2006	Handique et al.	N/A	N/A
2007/0196241	12/2006	Kimura	422/400	B41J 2/17566
2007/0202531	12/2006	Grover et al.	N/A	N/A
2007/0218485	12/2006	Davis et al.	N/A	N/A
2007/0237686	12/2006	Mathies et al.	N/A	N/A
2007/0238109	12/2006	Min et al.	N/A	N/A
2007/0248958	12/2006	Jovanovich et al.	N/A	N/A
2007/0263049	12/2006	Preckel et al.	N/A	N/A
2007/0292941	12/2006	Handique et al.	N/A	N/A
2007/0297947	12/2006	Sommers et al.	N/A	N/A
2008/0014576	12/2007	Jovanovich et al.	N/A	N/A
2008/0014589	12/2007	Link et al.	N/A	N/A
2008/0047836	12/2007	Strand et al.	N/A	N/A
2008/0057572	12/2007	Petersen	435/306.1	B01L 7/52
2008/0064610	12/2007	Lipovsek et al.	N/A	N/A
2008/0124723	12/2007	Dale et al.	N/A	N/A
2008/0131904	12/2007	Parce et al.	N/A	N/A
2008/0138809	12/2007	Kapur et al.	N/A	N/A
2008/0160630	12/2007	Liu et al.	N/A	N/A
2008/0179255	12/2007	Jung et al.	N/A	N/A
2008/0179555	12/2007	Landers et al.	N/A	N/A
2008/0217178	12/2007	Ben-Asouli et al.	N/A	N/A
2008/0237146	12/2007	Harrison et al.	N/A	N/A
2008/0241844	12/2007	Kellogg	N/A	N/A
2008/0242560	12/2007	Gunderson et al.	N/A	N/A
2008/0257437	12/2007	Fernandes et al.	N/A	N/A
2008/0262474	12/2007	Kain et al.	N/A	N/A
2008/0262747	12/2007	Kain et al.	N/A	N/A
2008/0281090	12/2007	Lee et al.	N/A	N/A
2008/0302732	12/2007	Soh et al.	N/A	N/A
2008/0311585	12/2007	Gao et al.	N/A	N/A
2009/0004494	12/2008	Blenke et al.	N/A	N/A
2009/0011959	12/2008	Costa et al.	N/A	N/A
2009/0020427	12/2008	Tan et al.	N/A	N/A
2009/0023603	12/2008	Selden et al.	N/A	N/A
2009/0026082	12/2008	Rothberg et al.	N/A	N/A
2009/0035770	12/2008	Mathies et al.	N/A	N/A
2009/0053799	12/2008	Chang-Yen et al.	N/A	N/A
2009/0056822	12/2008	Young et al.	N/A	N/A
2009/0060797	12/2008	Mathies et al.	N/A	N/A
2009/0084679	12/2008	Harrison et al.	N/A	N/A
2009/0087850	12/2008	Eid et al.	N/A	N/A
2009/0092970	12/2008	Williams et al.	N/A	N/A
2009/0134069	12/2008	Handique	N/A	N/A
2009/0137413	12/2008	Mehta et al.	N/A	N/A
2009/0148933	12/2008	Battrell et al.	N/A	N/A
2009/0178934	12/2008	Jarvius et al.	N/A	N/A
2009/0181411	12/2008	Battrell et al.	N/A	N/A
2009/0183990	12/2008	Shoji et al.	N/A	N/A

2009/0233325	12/2008	Mori et al.	N/A	N/A
2009/0253181	12/2008	Vangbo et al.	N/A	N/A
2009/0269504	12/2008	Liao	N/A	N/A
2009/0286327	12/2008	Cho et al.	N/A	N/A
2009/0311804	12/2008	McBrady et al.	N/A	N/A
2009/0314970	12/2008	McAvoy et al.	N/A	N/A
2009/0314972	12/2008	McAvoy et al.	N/A	N/A
2009/0325182	12/2008	Bannasch et al.	N/A	N/A
2009/0325183	12/2008	Lao et al.	N/A	N/A
2009/0325276	12/2008	Battrell et al.	N/A	N/A
2010/0010472	12/2009	Moore	N/A	N/A
2010/0011845	12/2009	Laugharn, Jr.	73/64.53	B01F 31/87
2010/0028513	12/2009	Balce	N/A	N/A
2010/0034986	12/2009	Kodas et al.	N/A	N/A
2010/0035252	12/2009	Rothberg et al.	N/A	N/A
2010/0068723	12/2009	Jovanovich et al.	N/A	N/A
2010/0075858	12/2009	Davis et al.	N/A	N/A
2010/0092948	12/2009	Davis et al.	N/A	N/A
2010/0093068	12/2009	Williams et al.	N/A	N/A
2010/0111770	12/2009	Hwang et al.	N/A	N/A
2010/0129810	12/2009	Greiner et al.	N/A	N/A
2010/0137143	12/2009	Rothberg et al.	N/A	N/A
2010/0165784	12/2009	Jovanovich et al.	N/A	N/A
2010/0172898	12/2009	Doyle et al.	N/A	N/A
2010/0173392	12/2009	Davis et al.	N/A	N/A
2010/0173398	12/2009	Peterman	N/A	N/A
2010/0178210	12/2009	Hogan et al.	N/A	N/A
2010/0197507	12/2009	Rothberg et al.	N/A	N/A
2010/0209957	12/2009	Hogan et al.	N/A	N/A
2010/0210008	12/2009	Strand et al.	N/A	N/A
2010/0218623	12/2009	Eggers et al.	N/A	N/A
2010/0221726	12/2009	Zenhausern et al.	N/A	N/A
2010/0228513	12/2009	Roth et al.	N/A	N/A
2010/0233696	12/2009	Joseph et al.	N/A	N/A
2010/0243916	12/2009	Maurer et al.	N/A	N/A
2010/0248363	12/2009	Hogan et al.	N/A	N/A
2010/0266432	12/2009	Pirk et al.	N/A	N/A
2010/0285578	12/2009	Selden et al.	N/A	N/A
2010/0285606	12/2009	Phillips et al.	N/A	N/A
2010/0285975	12/2009	Mathies et al.	N/A	N/A
2010/0291666	12/2009	Collier et al.	N/A	N/A
2010/0303687	12/2009	Blaga	156/247	F16K 99/0015
2010/0304355	12/2009	Shuler et al.	N/A	N/A
2010/0304986	12/2009	Chen et al.	N/A	N/A
2011/0003301	12/2010	Raymond et al.	N/A	N/A
2011/0005932	12/2010	Jovvanovich et al.	N/A	N/A
2011/0008785	12/2010	Tan et al.	N/A	N/A
2011/0008813	12/2010	Dilleen et al.	N/A	N/A
2011/0014606	12/2010	Steinmetzer et al.	N/A	N/A
2011/0027913	12/2010	Bau et al.	N/A	N/A
2011/0038758	12/2010	Akaba et al.	N/A	N/A
2011/0039303	12/2010	Jovanovich	536/23.1	B01L 3/50273
2011/0041935	12/2010	Zhou et al.	N/A	N/A
2011/0045505	12/2010	Warthoe et al.	N/A	N/A
2011/0053784	12/2010	Unger et al.	N/A	N/A
2011/0070578	12/2010	Bell et al.	N/A	N/A
2011/0124049	12/2010	Li et al.	N/A	N/A
2011/0126910	12/2010	May	N/A	N/A
2011/0127222	12/2010	Chang-Yen et al.	N/A	N/A
2011/0136179	12/2010	Bin/Lee et al.	N/A	N/A
2011/0137018	12/2010	Chang-Yen et al.	N/A	N/A
2011/0171086	12/2010	Prins et al.	N/A	N/A

2011/0172403	12/2010	Harrold	N/A	N/A
2011/0186466	12/2010	Kurowski et al.	N/A	N/A
2011/0189678	12/2010	Mcbride et al.	N/A	N/A
2011/0195495	12/2010	Selden et al.	N/A	N/A
2011/0206576	12/2010	Woudenberg et al.	N/A	N/A
2011/0207140	12/2010	Handique et al.	N/A	N/A
2011/0212440	12/2010	Viovy et al.	N/A	N/A
2011/0212446	12/2010	Wang et al.	N/A	N/A
2011/0223605	12/2010	Bienvenue et al.	N/A	N/A
2011/0229897	12/2010	Bell et al.	N/A	N/A
2011/0229898	12/2010	Bell et al.	N/A	N/A
2011/0256530	12/2010	Hogan	N/A	N/A
2011/0275058	12/2010	Zhou et al.	N/A	N/A
2011/0312614	12/2010	Selden et al.	N/A	N/A
2012/0055798	12/2011	Selden et al.	N/A	N/A
2012/0100522	12/2011	Saghbini et al.	N/A	N/A
2012/0128549	12/2011	Zhou et al.	N/A	N/A
2012/0181460	12/2011	Eberhart et al.	N/A	N/A
2012/0230888	12/2011	Asogawa et al.	N/A	N/A
2012/0240127	12/2011	Brittenham et al.	N/A	N/A
2012/0267247	12/2011	Tan et al.	N/A	N/A
2012/0279638	12/2011	Zhou et al.	N/A	N/A
2012/0290648	12/2011	Sharkey	N/A	N/A
2012/0308987	12/2011	Hogan et al.	N/A	N/A
2012/0309637	12/2011	Schumm et al.	N/A	N/A
2012/0315635	12/2011	Vangbo et al.	N/A	N/A
2012/0322666	12/2011	Pham et al.	N/A	N/A
2013/0020932	12/2012	Tanaka et al.	N/A	N/A
2013/0053255	12/2012	Vangbo et al.	N/A	N/A
2013/0074944	12/2012	Van	N/A	N/A
2013/0084565	12/2012	Landers et al.	N/A	N/A
2013/0105017	12/2012	Zhou et al.	N/A	N/A
2013/0115607	12/2012	Nielsen et al.	N/A	N/A
2013/0118900	12/2012	Reimitz	204/600	B01L 3/502738
2013/0139895	12/2012	Vangbo	137/15.01	B01L 3/502738
2013/0203634	12/2012	Jovanovich et al.	N/A	N/A
2013/0209326	12/2012	Williams et al.	N/A	N/A
2013/0210126	12/2012	Williams	435/303.1	C12M 23/42
2013/0210129	12/2012	Selden et al.	N/A	N/A
2013/0213810	12/2012	Tan et al.	N/A	N/A
2013/0217026	12/2012	Egan et al.	N/A	N/A
2013/0224846	12/2012	Jovanovich et al.	N/A	N/A
2013/0230906	12/2012	Martinelli	435/283.1	G01N 1/28
2013/0240140	12/2012	Kurowski et al.	N/A	N/A
2013/0260380	12/2012	Hall et al.	N/A	N/A
2013/0287645	12/2012	Shaike et al.	N/A	N/A
2013/0344475	12/2012	Jovanovich et al.	N/A	N/A
2014/0030456	12/2013	Collins	428/335	B01L 3/545
2014/0045704	12/2013	Jovanovich et al.	N/A	N/A
2014/0065628	12/2013	Van et al.	N/A	N/A
2014/0065689	12/2013	Hogan et al.	N/A	N/A
2014/0073043	12/2013	Holmes	N/A	N/A
2014/0161686	12/2013	Bort et al.	N/A	N/A
2014/0170645	12/2013	Jovanovich et al.	N/A	N/A
2014/0246618	12/2013	Zhou et al.	N/A	N/A
2014/0370519	12/2013	Vangbo et al.	N/A	N/A
2015/0021502	12/2014	Vangbo	N/A	N/A
2015/0050721	12/2014	Asogawa et al.	N/A	N/A
2015/0024436	12/2014	Jovanovich et al.	N/A	N/A
2015/0136602	12/2014	Jovanovich et al.	N/A	N/A
2015/0136604	12/2014	Nielsen et al.	N/A	N/A
2015/0352548	12/2014	Deshpande	422/502	B01L 3/545

2016/0016140	12/2015	Jovanovich et al.	N/A	N/A
2016/0053314	12/2015	Jovanovich et al.	N/A	N/A
2016/0096176	12/2015	Jarvius et al.	N/A	N/A
2016/0116439	12/2015	Kindwall et al.	N/A	N/A
2016/0367981	12/2015	Wunderle et al.	N/A	N/A
2017/0002399	12/2016	Eberhart et al.	N/A	N/A
2017/0197213	12/2016	Nielsen et al.	N/A	N/A

FOREIGN PATENT DOCUMENTS

Patent No.	Application Date	Country	CPC
1109597	12/1994	CN	N/A
1146017	12/1996	CN	N/A
1354692	12/2001	CN	N/A
1593338	12/2004	CN	N/A
101004423	12/2006	CN	N/A
101312759	12/2007	CN	N/A
101389406	12/2008	CN	N/A
101495236	12/2008	CN	N/A
101553306	12/2008	CN	N/A
102459565	12/2011	CN	N/A
102740976	12/2011	CN	N/A
102803147	12/2011	CN	N/A
102906573	12/2012	CN	N/A
103173346	12/2012	CN	N/A
105873681	12/2015	CN	N/A
2056951	12/1970	DE	N/A
2056951	12/1970	DE	N/A
0 459 241	12/1993	EP	N/A
0 637 999	12/1994	EP	N/A
0 527 905	12/1994	EP	N/A
1 065 378	12/2001	EP	N/A
1 411 340	12/2003	EP	N/A
1 411 340	12/2003	EP	N/A
1 658 890	12/2007	EP	N/A
2 345 739	12/2010	EP	N/A
2 345 739	12/2010	EP	N/A
H 10206384	12/1997	JP	N/A
2003-536058	12/2002	JP	N/A
2004-025159	12/2003	JP	N/A
2004-108285	12/2003	JP	N/A
2004-180594	12/2003	JP	N/A
2005-323519	12/2004	JP	N/A
2005-337415	12/2004	JP	N/A
2005-345463	12/2004	JP	N/A
2007-155491	12/2006	JP	N/A
2007-198765	12/2006	JP	N/A
2008-513022	12/2007	JP	N/A
2008-513022	12/2007	JP	N/A
2008-851022	12/2007	JP	N/A
9604547	12/1995	WO	N/A
9852691	12/1997	WO	N/A
9853300	12/1997	WO	N/A
9853300	12/1998	WO	N/A
9936766	12/1998	WO	N/A
9940174	12/1998	WO	N/A
0040712	12/1999	WO	N/A
0060362	12/1999	WO	N/A
0061198	12/1999	WO	N/A
0101025	12/2000	WO	N/A
0113127	12/2000	WO	N/A
0138865	12/2000	WO	N/A
01/41930	12/2000	WO	N/A
0101025	12/2000	WO	N/A

0185341	12/2000	WO	N/A
0224949	12/2001	WO	N/A
0241995	12/2001	WO	N/A
0243615	12/2001	WO	N/A
0243615	12/2002	WO	N/A
03062462	12/2002	WO	N/A
03085379	12/2002	WO	N/A
03085379	12/2002	WO	N/A
2004038363	12/2003	WO	N/A
2004062804	12/2003	WO	N/A
2004080597	12/2003	WO	N/A
2004098757	12/2003	WO	N/A
2004038363	12/2003	WO	N/A
2005072858	12/2004	WO	N/A
2005075081	12/2004	WO	N/A
2005121308	12/2004	WO	N/A
2005123950	12/2004	WO	N/A
2004098757	12/2005	WO	N/A
2007002579	12/2006	WO	N/A
2007064635	12/2006	WO	N/A
2007074289	12/2006	WO	N/A
2007075292	12/2006	WO	N/A
2007082480	12/2006	WO	N/A
2007084425	12/2006	WO	N/A
2008012104	12/2007	WO	N/A
2008024319	12/2007	WO	N/A
2008030631	12/2007	WO	N/A
2008024319	12/2007	WO	N/A
2008039875	12/2007	WO	N/A
2008012104	12/2007	WO	N/A
2008115626	12/2007	WO	N/A
2008115626	12/2007	WO	N/A
2009008236	12/2008	WO	N/A
2009015296	12/2008	WO	N/A
2007002579	12/2008	WO	N/A
2009108260	12/2008	WO	N/A
2009129415	12/2008	WO	N/A
2009108260	12/2008	WO	N/A
2010130762	12/2009	WO	N/A
2010041174	12/2009	WO	N/A
2010041231	12/2009	WO	N/A
WO-2010040758	12/2009	WO	B01L 3/502738
2010042784	12/2009	WO	N/A
2010041231	12/2009	WO	N/A
2010109392	12/2009	WO	N/A
2010130762	12/2009	WO	N/A
2010141921	12/2009	WO	N/A
2011003941	12/2010	WO	N/A
2011011172	12/2010	WO	N/A
2011012621	12/2010	WO	N/A
2011034621	12/2010	WO	N/A
2011048521	12/2010	WO	N/A
2011056215	12/2010	WO	N/A
2011084703	12/2010	WO	N/A
2011094577	12/2010	WO	N/A
2011106315	12/2010	WO	N/A
2011034621	12/2010	WO	N/A
2011084703	12/2010	WO	N/A
2012024657	12/2011	WO	N/A
2012024658	12/2011	WO	N/A
2012136333	12/2011	WO	N/A
WO-2013064683	12/2012	WO	B01L 3/502738

2013130910	12/2012	WO	N/A
2014014587	12/2013	WO	N/A
2014055936	12/2013	WO	N/A
2015/073999	12/2014	WO	N/A
WO-2015063347	12/2014	WO	B01L 3/502738
2015/078998	12/2014	WO	N/A

OTHER PUBLICATIONS

First Examination Report dated Oct. 9, 2018, issued in Application No. 14861199.9. cited by applicant
International Preliminary Report on Patentability, issued in PCT Application No. PCT/US14/66008, dated May 24, 2016. cited by applicant
International Search Report and Written Opinion, issued in PCT Application No. PCT/US14/66008, dated Mar. 3, 2015. cited by applicant
CN Search Report issued in Application No. 201480071855.1, dated Apr. 12, 2017. cited by applicant
CN First Office Action issued in Application No. 201480071855.1, dated Apr. 20, 2017. cited by applicant
CN Supplemental Search Report issued in Application No. 201480071855.1, dated Feb. 4, 2018. cited by applicant
CN Second Office Action issued in Application No. 201480071855.1, dated Feb. 11, 2018. cited by applicant
EP Search Report and Written Opinion issued in Application No. EP14861199.9, dated Oct. 18, 2017. cited by applicant
Office Action issued in U.S. Appl. No. 15/117,053, dated May 7, 2018. cited by applicant
Office Action issued in U.S. Appl. No. 15/173,894, dated Jan. 23, 2018. cited by applicant
International Search Report and Written Opinion issued in Application No. PCT/US2016/037711 dated Sep. 16, 2016. cited by applicant
International Preliminary Report of Patentability issued in Application No. PCT/US2016/037711 dated Dec. 19, 2017. cited by applicant
International Preliminary Report of Patentability issued in Application No. PCT/US15/28510 dated Dec. 1, 2016. cited by applicant
CN Third Office Action issued in Application No. 201480071855.1, Global Dossier date of Aug. 13, 2018. cited by applicant
European search report with written opinion dated Jul. 12, 2017 for EP14861199. cited by applicant
Notice of allowance dated Jun. 9, 2017 for U.S. Appl. No. 14/824,333. cited by applicant
Notice of allowance dated Jun. 12, 2017 for U.S. Appl. No. 14/804,675. cited by applicant
Notice of allowance dated Jun. 22, 2017 for U.S. Appl. No. 14/824,333. cited by applicant
Amendment and Request for Correction of Inventorship mailed Jan. 10, 2008 in U.S. Appl. No. 10/750,533. cited by applicant
Anderson, et al. A miniature integrated device for automated multistep genetic assays. Nucleic Acids Research. 2000;28:e60. cited by applicant
Armani, et al. Re-configurable fluid circuits by PDMS elastomer micromachining. Proceedings of IEEE Micro Electro Mechanical Systems: MEMS. 1999; 222-227. cited by applicant
Au et al., Microvalves and Micropumps for BioMEMS, Micromachines 2011, 2(2), 179-220, May 24, 2011. cited by applicant
Bennett, et al. Toward the 1,000 dollars human genome. Pharmacogenomics, 6 (4) 373-382. (Jun. 2005). cited by applicant
Bings, et al. Microfluidic Devices Connected to Fused-Silica Capillaries with Minimal Dead Dead Volume. Analytical Chemistry. 1999;71(15):3292-3296. cited by applicant
Blazej, et al. Microfabricated bioprocessor for integrated nanoliter-scale Sanger DNA sequencing. Proc. Natl. Acad. Sci. USA 2006;103:7240-7245. cited by applicant
Blazej, et al. Polymorphism Ratio Sequencing: A New Approach for Single Nucleotide Polymorphism Discovery and Genotyping. Genome Research. 2003;13:287-293. cited by applicant
Branton, et al. The potential and challenges of nanopore sequencing. Nat Biotechnol. Oct. 2008. 26(10):1146-53. doi: 10.1038/nbt.1495. cited by applicant
Brenner, et al. Gene expression analysis by massively parallel signature sequencing (MPSS) on microbead arrays. Nature Biotechnology, 18: 630-634 (2000). cited by applicant
Buchholz, et al. The use of light scattering for precise characterization of polymers for DNA sequencing by capillary electrophoresis. Electrophoresis. 2001;22:4118-4128. cited by applicant
CAPLUS abstract of Krohkin et al. Modified silica as a stationary phase for ion chromatography. Journal of Chromatography A. 1995;706:93-8. cited by applicant
Chan, et al. Microfabricated Polymer Devices for Automated Sample Delivery of Peptides for Analysis by Electrospray Ionization Tandem Mass Spectrometry. Analytical Chemistry. 1999;71(20):4437-4444. cited by applicant
Chiem, et al. Microchip systems for immunoassay: an integrated immunoreactor with electrophoretic separation for serum theophylline determination. Clinical Chemistry. 1998;44(3):591-598. cited by applicant
Chiem, et al. Room temperature bonding of micromachined glass devices for capillary electrophoresis. Sensors and Actuators. 2000;B63(3):147-152. cited by applicant
Chinese office action dated Jan. 31, 2011 for CN 200580035911.7. (In Chinese with English translation). cited by applicant

Chinese office action dated Jul. 8, 2011 for CN 200580035911.7. (In Chinese with English translation). cited by applicant
Coleman, et al. A sequential injection microfluidic mixing strategy. Microfluidics and Nanofluidics. 2005;319-327. cited by applicant
Zhang, et al. Microfabricated Devices for Capillary Electrophoresis-Electrospray Mass Spectrometry. Analytical Chemistry. 1999;71(15):3258-3264. cited by applicant
Curcio, et al. Continuous Segmented-Flow Polymerase Chain Reaction for High-Throughput Miniaturized DNA Amplification. Analytical Chemistry. 2003;75(1):1-7. cited by applicant
Datasheet Cycle Sequencing, Retrieved from the internet, URL:http//answers.com/topic/cycle sequencing. Printed Sep. 3, 2010, pp. 1-2. cited by applicant
Diehl et al. BEAMing: single-molecule PCR on microparticles in water-in-oil emulsions. Nature Methods 3(7):551-559 (2006). cited by applicant
Doherty, et al. Sparsely Cross-linked “Nanogel” Matrices as Fluid, Mechanically Stablized Polymer Networks for High-Throughput Microchannel DNA Sequencing. Analytical Chemistry. 2004;76:5249-5256. cited by applicant
Doherty, et al. Sparsely cross-linked “nanogels” for microchannel DNA sequencing. Electrophoresis. 2003;24(24):4170-4180. cited by applicant
Dorfman, et al. Contamination-Free Continuous Flow Microfluidic Polymerase Chain Reaction for Quantitative and Clinical Applications. Analytical Chemistry. 2005;77(11):3700-3704. cited by applicant
Doyle, et al. Self-Assembled Magnetic Matrices for DNA Separation Chips. Science. 2000;295:2237. cited by applicant
Dressman, et al. Transforming single DNA molecules into fluorescent magnetic particles for detection and enumeration of genetic variations. Proc Natl Acad Sci USA. 2003;100(15):8817-8822. cited by applicant
Eid, et al. Real-time DNA sequencing from single polymerase molecules. Science. Jan. 2, 2009;323(5910):133-8. doi: 10.1126/science.1162986. Epub Nov. 20, 2008. cited by applicant
Emrich, et al. Microfabricated 384-Lane Capillary Array Electrophoresis Bioanalyzer for Ultrahigh-Throughput Genetic Analysis. Analytical Chemistry. 2002;74(19):5076-5083. cited by applicant
Ericson, et al. Electroosmosis- and Pressure-Driven Chromatography in Chips Using Continuous Beds. Analytical Chemistry. 2000;72(1):81-87. cited by applicant
Erratum for Margulies, et al. Genome sequencing in microfabricated high-density picolitre reactors. Nature. 2005;437(7057):376-80. cited by applicant
European search report and search opinion dated Jun. 6, 2011 for Application No. 10011511.2. cited by applicant
European search report and search opinion dated Jun. 22, 2016 for EP Application No. 11818879.6. cited by applicant
European search report and search opinion dated Aug. 17, 2011 for Application No. 08799648.4. cited by applicant
European search report and search opinion dated Sep. 11, 2013 for EP Application No. 10784213. cited by applicant
European search report dated Jul. 13, 2016 for EP Application No. 09714332.5. cited by applicant
European search report dated Oct. 29, 2012 for EP Application No. 07853470.8. cited by applicant
European search report dated Dec. 18, 2009 for Application No. 03808583.3. cited by applicant
European search report dated Sep. 1, 2010 for Application No. 5804847.1. cited by applicant
Ewing, et al. Base-Calling of Automated Sequencer Traces Using Phred. I. Accuracy Assessment. Genome Research. 1998;8:175-185. cited by applicant
Ewing, et al. Base-Calling of Automated Sequencer Traces Using Phred. II. Error probabilities. Genome Research. 1998;8:186-194. cited by applicant
Figeys, et al. A Microfabricated Device for Rapid Protein Identification by Microelectrospray Ion Trap Mass Spectrometry. Analytical Chemistry. 1997;69(16):3153-3160. cited by applicant
Figeys, et al. An Integrated Microfluidics-Tandem Mass Spectrometry System for Automated Protein Analysis. Analytical Chemistry. 1998;70(18):3728-3734. cited by applicant
Figeys, et al. Microfabricated Device Coupled with an Electrospray Ionization Quadrupole Time-of-Flight Mass Spectrometer: Protein Identifications Based on Enhanced-Resolution Mass Spectrometry and Tandem Mass Spectrometry Data. Rapid Communications In Mass Spectrometry. 1998; 12:1435-1444. cited by applicant
Figeys, et al. Nanoflow Solvent Gradient Delivery from a Microfabricated Device for Protein Identifications by Electrospray Ionization Mass Spectrometry. Analytical Chemistry. 1998;70(18):3721-3727. cited by applicant
Francis, et al. Flow analysis based on a pulsed flow of solution: theory, instrumentation and applications. Talanta. 2002;58(6):1029-1042. cited by applicant
Fuentes, et al. Detecting minimal traces of DNA using DNA covalently attached to superparamagnetic nanoparticles and direct PCR-ELISA. Biosens Bioelectron. Feb. 15, 2006;21(8):1574-80. Epub Aug. 29, 2005. cited by applicant
Fuller, et al. The challenges of sequencing by synthesis. Nat Biotechnol. Nov. 2009;27(11):1013-23. doi: 10.1038/nbt.1585. Epub Nov. 6, 2009. Ghadessy, et al. Directed evolution of polymerase function by compartmentalized selfreplication. Proc Natl Acad Sci USA. 2001;98:4552-4557. cited by applicant
Ghadessy, et al. Directed evolution of polymerase function by compartmentalized self-replication. Proc Natl Acad Sci USA. 2001;98:4552-4557. cited by applicant
Giddings, et al. A software system for data analysis in automated DNA sequencing. Genome Research. 1998;8:644-665. cited by applicant
Goll, et al. Microvalves with bistable buckled polymer diaphragms. Journal of Micromechanics and Microengineering. 1996;6:77-79. cited by applicant

Grodzinski, et al. Microfluidic System Integration in Sample Preparation Chip-Sets—a Summary. Conf. Proc. IEEE Eng. Med. Biol. Soc. 2004;4:2615-2618. cited by applicant
Grover, et al. An integrated microfluidic processor for single nucleotide polymorphism-based DNA computing. Lab on a Chip. 2005;5(10):1033-1040. cited by applicant
Grover, et al. Development and multiplexed control of latching pneumatic valves using microfluidic logical structures. Lab on a chip. 2006;6:623-631. cited by applicant
Grover, et al. Monolithic membrane valves and diaphragm pumps for practical large-scale integration into glass microfluidic devices. Sensors and Actuators. 2003;B89:315-323. cited by applicant
Grover, et al. Practical Valves and Pumps for Large-Scale Integration into Microfludic Analysis Devices. Micro Total Analysis Systems. 2002;1:136-138. cited by applicant
Hansen, et al. A robust and scalable microfluidic metering method that allows protein crystal growth by free interface diffusion. Proc Natl Acad Sci USA. 2002;99(26):16531-16536. cited by applicant
Harrison, et al. Micromachining a Miniaturized Capillary Electrophoresis-Based Chemical Analysis System on a Chip. Science. 1993;261(5123):895-897. cited by applicant
Hayes, et al. EDGE: A Centralized Resource for the Comparison, Analysis, and Distribution of Toxicogenomic Information. Molecular Pharmacology. 2005;67(4):1360-1368. cited by applicant
Heath, et al. PCR primed with VNTR core sequences yields species specific patterns and hypervariable probes. Nucleic Acids Res. Dec. 11, 1993;21(24):5782-5. cited by applicant
Holland, et al. Point-of-care molecular diagnostic systems—past, present and future. Curr Opin Microbiol. Oct. 2005;8(5):504-9. cited by applicant
Hultman, et al. Bidirectional Solid-Phase Sequencing of In Vitro-Amplified Plasmid DNA. BioTechniques. 1991;10(1):84-93. cited by applicant
International Preliminary Report for corresponding PCT Application No. PCT/CA2000/01421 dated Feb. 14, 2002. cited by applicant
International Preliminary Report for corresponding PCT Application No. PCT/US2005/018678 dated Nov. 13, 2007. cited by applicant
International Preliminary Report for corresponding PCT Application No. PCT/US2005/033347 dated Mar. 20, 2007. cited by applicant
International Preliminary Report for corresponding PCT Application No. PCT/US2007/007381 dated Sep. 23, 2008. cited by applicant
International Preliminary Report for corresponding PCT Application No. PCT/US2007/002721 dated Aug. 5, 2008. cited by applicant
International Preliminary Report for corresponding PCT Application No. PCT/US2007/061573 dated Aug. 26, 2008. cited by applicant
International search report and written opinion dated Jan. 5, 2012 for PCT Application No. PCT/US2011/048527. cited by applicant
International search report and written opinion dated Jan. 29, 2016 for PCT Application No. PCT/US2015/056764. cited by applicant
International search report and written opinion dated Mar. 8, 2013 for PCT/US2012/061223. cited by applicant
International search report and written opinion dated Mar. 24, 2011 for PCT Application No. PCT/US2010/058227. cited by applicant
International search report and written opinion dated Apr. 30, 2012 for PCT/US2012/021217. cited by applicant
International search report and written opinion dated Jun. 9, 2011 for PCT Application No. PCT/US2011/030973. cited by applicant
International search report and written opinion dated Jul. 22, 2013 for PCT Application No. US2013/028462. cited by applicant
International search report and written opinion dated Sep. 1, 2010 for PCT Application No. PCT/US2010/040490. cited by applicant
International search report and written opinion dated Oct. 26, 2011 for PCT Application No. PCT/US11/38180. cited by applicant
International search report and written opinion dated Oct. 26, 2015 for PCT/US2015/028510. cited by applicant
Yu, et al. Towards stationary phases for chromatography on a microchip: Molded porous polymer monoliths prepared in capillaries by photoinitiated in situ polymerization as separation media for electrochromatography. Electrophoresis. 2000;21:120-127. cited by applicant
International search report dated Oct. 6, 2010 for PCT Application No. PCT/US10/37545. cited by applicant
International search report dated Apr. 5, 2001 for PCT Application No. PCT/CA2000/01421. cited by applicant
International search report dated May 14, 2010 for PCT Application No. PCT/US2009/006640. cited by applicant
International search report dated Jul. 11, 2008 for PCT Application No. PCT/US07/61573. cited by applicant
International search report dated Jul. 30, 2010 for PCT Application No. PCT/US2010/36464. cited by applicant
International search report dated Aug. 18, 2009 for PCT Application No. PCT/US09/00419. cited by applicant
International search report dated Aug. 23, 2006 for PCT Application No. PCT/US2005/033347. cited by applicant
International search report dated Aug. 26, 2004 PCT Application No. PCT/US2003/41466. cited by applicant

International search report dated Sep. 25, 2007 for PCT Application No. PCT/US2007/002721. cited by applicant
Zhang, et al. A Microdevice with Integrated Liquid Junction for Facile Peptide and Protein Analysis by Capillary Electrophoresis/Electrospray Mass Spectrometry. Analytical Chemistry. 2000;72(5):1015-1022. cited by applicant
International written opinion dated Oct. 6, 2010 for PCT Application No. PCT/US10/37545. cited by applicant
International written opinion report dated Jul. 30, 2010 for PCT Application No. PCT/US2010/36464. cited by applicant
Jacobson, et al. Electrokinetic Focusing in Microfabricated Channel Structures. Anal. Chem., 1997, 69 (16), pp. 3212-3217. cited by applicant
Japanese office action dated May 11, 2012 for Application No. 2008-553535 (English translation). cited by applicant
Japanese office action dated May 27, 2011 for Application No. 2007-532553 (in Japanese with English translation). cited by applicant
Japanese office action dated Jul. 28, 2011 for Application No. 2008-553535 (in Japanese with English translation). cited by applicant
Japanese Office Action dated Dec. 21, 2010 for Application No. JP2001-540363 (in Japanese with English translation). cited by applicant
Japanese Office Action dated Apr. 27, 2010 for Application No. JP2001-540363 (in Japanese with English translation). cited by applicant
Ju, et al. Fluorescence energy transfer dye-labeled primers for DNA sequencing and analysis. Proc. Natl. Acad. Sci. USA. 1995;92:4347-4351. cited by applicant
Kan, et al. A novel thermogelling matrix for microchannel DNA sequencing based on poly-Nalkoxyalkylaclylamide copolymers. Electrophoresis. 2003;24(24):4161-4169. cited by applicant
Koh, et al. Integrating Polymerase Chain Reaction, Valving, and Electrophoresis in a Plastic Device for Bacterial Detection. Analytical Chemistry. 2003;75(17):4591-4598. cited by applicant
Kopp, et al. Chemical Amplification Continuous-Flow PCR on a Chip. Science. 1998;280:1046-1048. cited by applicant
Lagally, et al. Fully integrated PCR-capillary electrophoresis microsystem for DNA analysis. Lab on a Chip. 2001;1(2):102-107. cited by applicant
Lagally, et al. Integrated Portable Genetic Analysis Microsystem for Pathogen/Infectious Disease Detection. Analytical Chemistry. 2004;76:3162-3170. cited by applicant
Lagally, et al. Monolithic integrated microfluidic DNA amplification and capillary electrophoresis analysis system. Sensors and Actuators. 2000; B63(3):138-146. cited by applicant
Lagally, et al. Single-Molecule DNA Amplification and Analysis in an Integrated Microfluidic Device. Analytical Chemistry. 2001;73(3): 565-570. cited by applicant
Lai et al., Design and dynamic characterization of “single-stroke” peristaltic PDMS micropumps, Lab Chip. Jan. 21, 2011; 11(2): 336-342, Published online Oct. 19, 2010. cited by applicant
Lazar, et al. Subattomole-Sensitivity Microchip Nanoelectrospray Source with Time-of-Flight Mass Spectrometry Detection. Analytical Chemistry. 1999;71(17):3627-3631. cited by applicant
Li, et al. Integration of Microfabricated Devices to Capillary Electrophoresis-Electrospray Mass Spectrometry Using a Low Dead Volume Connection: Application to Rapid Analyses of Proteolytic Digests. Analytical Chemistry. 1999;71(15):3036-3045. cited by applicant
Li, et al. Rapid and sensitive separation of trace level protein digests using microfabricated devices coupled to a quadrupole-time-of-flight mass spectrometer. Electrophoresis. 2000;21:198-210. cited by applicant
Li, et al. Separation and Identification of Peptides from Gel-Isolated Membrane Proteins Using a Microfabricated Device for Combined Capillary Electrophoresis/Nanoelectrospray Mass Spectrometry. Analytical Chemistry. 2000;72(3):599-609. cited by applicant
Licklider, et al. A Micromachined Chip-Based Electrospray Source for Mass Spectrometry. Analytical Chemistry. 2000;72(2):367-375. cited by applicant
Lisec, et al. A bistable pneumatic microswitch for driving fluidic components. Sensors and Actuators. 1996;A54:746-749. cited by applicant
Liu, et al. Automated parallel DNA sequencing on multiple channel microchips. Proc. Natl. Acad. Sci. USA. 2000;97(10):5369-5374. cited by applicant
Liu, et al. Optimization of High-Speed DNA Sequencing on Microfabricated Capillary Electrophoresis Channels. Analytical Chemistry. 1999;71:566-573. cited by applicant
Lund-Olesen, et al. Capture of DNA in microfluidic channel using magnetic beads: Increasing capture efficiency with integrated microfluidic mixer. Journal of Magnetism and Magnetic Materials 311 (2007): 396-400. cited by applicant
Mamanova, et al. FRT-seq: amplification-free, strand-specific transcriptome sequencing. Nat Methods. Feb. 2010;7(2):130-2. doi: 10.1038/nmeth.1417. Epub Jan. 17, 2010. cited by applicant
Melin, et al. A Passive 2-Dimensional Liquid Sample Micromixer. 7th International Conference on Miniaturized Chemical and Biochemical Analysis Systems. 2003;167-170. cited by applicant
Metzker, M. Sequencing technologies—the next generation. Nat Rev Genet. Jan. 2010;11(1):31-46. doi: 10.1038/nrg2626. Epub Dec. 8, 2009. cited by applicant
MillGat pump user manual, version 2.12, published 2005, pp. 1-28. cited by applicant
Mitra, et al. Digital genotyping and haplotyping with polymerase colonies. Proc Natl Acad Sci USA. 2003.100(10):15926-5931. cited by applicant

Norris, et al. Fully-integrated, multiplexed STR-based human identification using a single microfluidic chip and automated instrument. Available at http://www.promega.com/geneticidproc/ussymp20proc/oralpresentations/landersbienvenue.pdf. Accessed Jun. 2, 2010. cited by applicant
Notice of allowance dated Jan. 31, 2017 for U.S. Appl. No. 14/552,389. cited by applicant
Notice of allowance dated Feb. 19, 2013 for U.S. Appl. No. 12/845,650. cited by applicant
Notice of allowance dated Apr. 25, 2013 for U.S. Appl. No. 12/815,685. cited by applicant
Notice of allowance dated May 3, 2010 for U.S. Appl. No. 11/670,866. cited by applicant
Notice of allowance dated May 5, 2015 for U.S. Appl. No. 13/202,884. cited by applicant
Notice of allowance dated Jun. 9, 2011 for U.S. Appl. No. 12/831,949. cited by applicant
Notice of allowance dated Jun. 25, 2014 for U.S. Appl. No. 13/656,503. cited by applicant
Notice of allowance dated Jul. 8, 2013 for U.S. Appl. No. 13/717,585. cited by applicant
Notice of allowance dated Nov. 12, 2014 for U.S. Appl. No. 13/967,957. cited by applicant
Notice of allowance dated Nov. 22, 2013 for U.S. Appl. No. 13/590,965. cited by applicant
Notice of allowance dated Dec. 7, 2012 for U.S. Appl. No. 12/795,515. cited by applicant
Obeid, et al. Microfabricated Device for DNA and RNA Amplification by Continuous-Flow Polymerase Chain Reaction and Reverse Transcription-Polymerase Chain Reaction with Cycle Number Selection. Analytical Chemistry. 2003; 75(2): 288-295. cited by applicant
Ocvirk, et al. High Performance Liquid Chromatography Partially Integrated onto a Silicon Chip. Analytical Methods and Instrumentation. 1995;2:74-82. cited by applicant
Ocvirk, et al. Optimization of confocal epifluorescence microscopy for microchip-based Miniaturized total analysis systems. The Analyst. 1998;123:1429-1434. cited by applicant
Office action dated Jan. 13, 2017 for U.S. Appl. No. 14/253,622. cited by applicant
Office action dated Jan. 17, 2014 for U.S. Appl. No. 13/656,503. cited by applicant
Office action dated Jan. 22, 2013 for U.S. Appl. No. 12/845,650. cited by applicant
Office action dated Feb. 14, 2017 for U.S. Appl. No. 14/804,675. cited by applicant
Office action dated Feb. 28, 2013 for U.S. Appl. No. 13/113,968. cited by applicant
Office action dated Mar. 19, 2009 for U.S. Appl. No. 11/670,866. cited by applicant
Office action dated Mar. 24, 2010 for U.S. Appl. No. 11/670,866. cited by applicant
Office action dated Mar. 24, 2015 for U.S. Appl. No. 13/202,884. cited by applicant
Office action dated Mar. 30, 2012 for U.S. Appl. No. 12/795,515. cited by applicant
Office action dated Apr. 1, 2014 for U.S. Appl. No. 13/202,884. cited by applicant
Office action dated Apr. 15, 2015 for U.S. Appl. No. 13/896,581. cited by applicant
Office action dated May 22, 2012 for U.S. Appl. No. 12/526,015. cited by applicant
Office action dated May 30, 2014 for U.S. Appl. No. 13/656,503. cited by applicant
Office action dated Jul. 1, 2016 for U.S. Appl. No. 14/253,622. cited by applicant
Office action dated Jul. 26, 2012 for U.S. Appl. No. 12/845,650. cited by applicant
Office action dated Aug. 9, 2016 for U.S. Appl. No. 14/500,846. cited by applicant
Office action dated Aug. 23, 2012 for U.S. Appl. No. 13/287,398. cited by applicant
Office action dated Aug. 24, 2012 for U.S. Appl. No. 12/026,510. cited by applicant
Office action dated Aug. 29, 2012 for U.S. Appl. No. 12/605,217. cited by applicant
Office action dated Sep. 11, 2014 for U.S. Appl. No. 13/967,957. cited by applicant
Office action dated Sep. 15, 2014 for U.S. Appl. No. 13/886,068. cited by applicant
Office action dated Oct. 29, 2013 for U.S. Appl. No. 13/202,884. cited by applicant
Office action dated Nov. 14, 2012 for U.S. Appl. No. 12/526,015. cited by applicant
Office action dated Dec. 29, 2016 for U.S. Appl. No. 14/824,333. cited by applicant
Office action dates Jan. 15, 2014 for U.S. Appl. No. 12/321,594. cited by applicant
Office action dates Feb. 27, 2013 for U.S. Appl. No. 13/590,965 . cited by applicant
Office action dates Sep. 19, 2012 for U.S. Appl. No. 12/321,594. cited by applicant
Office action dates Dec. 7, 2012 for U.S. Appl. No. 13/590,051. cited by applicant
Office Action Final dated Feb. 6, 2008 issued in U.S. Appl. No. 11/139,018. cited by applicant
Office Action mailed Apr. 27, 2007 in U.S. Appl. No. 11/139,018. cited by applicant
Office Action mailed Jul. 2, 2007 in U.S. Appl. No. 10/540,658. cited by applicant
Office Action mailed Jul. 12, 2007 in U.S. Appl. No. 10/750,533. cited by applicant
Oh, et al. A review of microvalves. J. Micromech. Microeng. 2006; 16:R13-R39. cited by applicant
Ohori, et al. Partly disposable three-way mirovalve for a medical micro total analysis system (muTAS). Sensors and Actuators. 1998;A64(1): 57-62. cited by applicant
Oleschuk, et al. Trapping of Bead-Based Reagents within Microfluidic Systems: On-Chip Solid-Phase Extraction and Electrochromatography. Analytical Chemistry. 2000;72:585-590. cited by applicant
Olsen, et al. Immobilization of DNA Hydrogel Plugs In Microfluidic Channels. Analytical Chemistry. 2002;74:1436-1441. cited by applicant
Paegel, et al. High-throughput DNA sequencing with a 96-lane capillary array electrophoresis bioprocessor. Proc Natl Acad Sci USA. 2002;99:574-579. cited by applicant

Paegel, et al. Microchip Bioprocessor for Integrated Nanovolume Sample Purification and DNA Sequencing. Analytical Chemistry. 2002;74(19):5092-5098. cited by applicant
Paegel, et al. Microfluidic devices for DNA sequencing: sample preparation and electrophoretic analysis. Current Opinion in Biotechnology. 2003;14(1):42-50. cited by applicant
Paegel, et al. Turn Geometry for Minimizing Band Broadening in Microfabricated Capillary Electrophoresis Channels. Analytical Chemistry. 2000;72:3030-3037. cited by applicant
PCT Notification of Transmittal of the International Search Report and The Written Opinion of the International Searching Authority, or the Declaration, mailed Jun. 17, 2008, Application No. PCT/US2007/082568. cited by applicant
Peoples, et al. Microfluidic Immunoaffinity Separations for Bioanalysis. J. Chromat. B. 2008;866:14-25 (available online Aug. 30, 2007). cited by applicant
Peterson, et al. Enzymatic Microreactor-on-a-Chip: Protein Mapping Using Trypsin Immobilized on Porous Polymer Monoliths Molded in Channels of Microfluidic Devices. Analytical Chemistry. 2002;74:4081-4088. cited by applicant
Ramsey, et al. Generating Electrospray from Microchip Devices Using Electroosmotic Pumping. Analytical Chemistry. 1997;69(6):1174-1178. cited by applicant
Rohr, et al. Porous polymer monoliths: Simple and efficient mixers prepared by direct polymerization in the channels of microfluidic chips. Electrophoresis. 2001;22:3959-3967. cited by applicant
Rye, et al. High-sensitivity two-color detection of double-stranded DNA with a confocal fluorescence gel scanner using ethidium homodimer and thiazole orange. Nucleic Acids Research. 1991;19(2):327-333. cited by applicant
Scherer, et al. High-Pressure Gel Loader for Capillary Array Electrophoresis Microchannel Plates. Biotechniques. 2001;31(5):1150-1154. cited by applicant
Schomburg, et al. Design Optimization of Bistable Microdiaphragm Valves. Sensors and Actuators. 1998;A64:259-264. cited by applicant
Seifar, et al. Capillary electrochromatography with 1.8-mum ODS-modified porous silica particles. Journal of Chromatography. 1998; A808:71-77. cited by applicant
Shaikh, et al. A modular microfluidic architecture for integrated biochemical analysis. Proc Natl Acad Sci U S A. Jul. 12, 2005;102(28):9745-50. Epub Jun. 28, 2005. cited by applicant
Shendure, et al. Next-generation DNA sequencing. Nat Biotechnol. Oct. 26, 2008(10):1135-45. doi: 10.1038/nbt1486. cited by applicant
Simpson, et al. High-throughput genetic analysis using microfabricated 96-sample capillary array electrophoresis microplates. Proc Natl Acad Sci USA. 1998;95:2256-2261. cited by applicant
Simpson, et al. Microfabrication Technology for the Production of Capillary Array Electrophoresis Chips. Biomedical Microdevices. 1998;1:7-26. cited by applicant
Soper, et al. Sanger DNA Sequencing Reactions Performed in a Solid-Phase Nanoreactor Directly Coupled to Capillary Gel Electrophoresis. Analytical Chemistry. 1998;70:4036-4043. cited by applicant
Spiering, et al. Novel microstructures and technologies applied in chemical analysis techniques. 1997 International Conference on Solid-State Sensors and Actuators. 1997;1:511-514. cited by applicant
Stevens, et al. Bacterial Separation and Concentration from Complex Sample Matrices: a Review. Crit. Rev. Microbiol. 2004;30(1):7-24. cited by applicant
Takao, et al. A Pneumatically Actuated Full In-Channel Microvalve with MOSFET-Like Function in Fluid Channel Networks. Journal of Microelectromechanical Systems. 2002;11(5):421-426. cited by applicant
Takao, et al. Microfluidic Integrated Circuits for Signal Processing Using Analogous Relationship Between Pneumatic Microvalve and MOSFET. Journal of Microelectromechanical Systems. 2003;12(4):497-505. cited by applicant
Tanaka et al., An active valve incorporated into a microship using a high strain electroactive polymer, Sensors and Actuators B 184 (2013) 163-169, Apr. 20, 2013. cited by applicant
Thomas, et al. Application of Genomics to Toxicology Research. Environmental Health Perspectives. 2002;110(6):919-923. cited by applicant
Tice, et al. Formation of Droplets and Mixing in Multiphase Microfluidics at Low Values of the Reynolds and the Capillary Numbers. Langmuir. 2003;19:9127-9133. cited by applicant
Todd Thorsen, et al., “Microfluidic Large-Scale Integration”, www.sciencemag.org, Science, vol. 298, Oct. 18, 2002, pp. 580-584. cited by applicant
Unger, et al. Monolithic microfabricated valves and pumps by multilayer soft lithography. Science. Apr. 7, 2000;288(5463):113-6. cited by applicant
U.S. Appl. No. 10/540,658 Office Action Final dated Feb. 19, 2008. cited by applicant
U.S. Appl. No. 61/709,417, filed Oct. 4, 2012. cited by applicant
Unpublished U.S. Appl. No. 14/032,173, filed Sep. 10, 2013. cited by applicant
Unpublished U.S. Appl. No. 14/474,047, filed Aug. 29, 2014. cited by applicant
Van Der Moolen, et al. A Micromachined Injection Device for CZE: Application to Correlation CZE. Analytical Chemistry. 1997;69(20):4220-4225. cited by applicant
Van Der Moolen, et al. Correlation Capillary Zone Electrophoresis, a Novel Technique to Decrease Detection Limits. Chromatographia. 1995;40(7/8):368-374. cited by applicant
Van Ness, et al. Isothermal Reactions for the Amplification of Oligonucleotides. Proc. Nat. Acad. Sci. USA. 2003;100 (8):4504-4509. cited by applicant

Vazquez, et al. Electrophoretic Injection within Microdevices. Analytical Chemistry. 2002;74:1952-1961. cited by applicant
Veenstra, et al. The design of an in-plane compliance structure for microfluidical systems. Sensors and Actuators. 2002;B81:377-383. cited by applicant
Waller, et al. Quantitative Immunocapture PCR Assay for Detection of Campylobacter jejuni in Foods. Applied Environmental Microbiology. 2000; 66(9):4115-4118. cited by applicant
Weimer, et al. Solid-Phase Capture of Proteins, Spores, and Bacteria. Applied Environmental Microbiology. 2001;67(3):1300-1307. cited by applicant
Wen, et al. Microfabricated isoelectric focusing device for direct electrospray ionization-mass spectrometry. Electrophoresis. 2000;21:191-197. cited by applicant
Wikipedia brochure for defining stocahstic process. Sep. 2, 2009. cited by applicant
Williams, et al. Amplification of complex gene libraries by emulsion PCR. Nature Methods. 2006;3(7):545-50. cited by applicant
Woolley, et al. Functional Integration of PCR Amplification and Capillary Electrophoresis in a Microfabricated DNA Analysis Device. Analytical Chemistry. 1996;68(23):4081-4086. cited by applicant
Wright, et al. Behavior and Use of Nonaqueous Media without Supporting Electrolyte in Capillary Electrophoresis and Capillary Electrochromatography. Analytical Chemistry. 1997;69(16):3251-3259. cited by applicant
Xiang, et al. An Integrated Microfabricated Device for Dual Microdialysis and On-Line ESI-Ion Trap Mass Spectrometry for Analysis of Complex Biological Samples. Analytical Chemistry. 1999;71(8):1485-1490. cited by applicant
Xue, et al. Integrated Multichannel Microchip Electrospray Ionization Mass Spectrometry: Analysis of Peptides from On-Chip Tryptic Digestion of Melittin. Rapid Communications in Mass Spectrometry. 1997; 11:1253-1256. cited by applicant
Xue, et al. Multichannel Microchip Electrospray Mass Spectrometry. Analytical Chemistry. 1997;69(3):426-430. cited by applicant
Yang, et al. A MEMS thermopneumatic silicone rubber membrane valve. Sensors and Actuators. 1998;A64(1):101-108. cited by applicant
Yu, et al. Preparation of Monolithic Polymers with Controlled Porous Properties for Microfluidic Chip Applications Using Photoinitiated Free Radial Polymerization. Journal of Polymer Science. 2002;40:755-769. cited by applicant
Krsek, et al. Comparison of different methods for the isolation and purification of total community DNA from soil. Journal of Microbiological Methods 39.1 (1999): 1-16. cited by applicant
Co-pending U.S. Appl. No. 15/154,086, filed May 13, 2016. cited by applicant
International search report and written opinion dated Mar. 3, 2015 for PCT Application No. PCT/US2014/066008. cited by applicant
Co-pending U.S. Appl. No. 14/659,108, filed Mar. 16, 2015. cited by applicant
CN Search Report issued in Application No. 201480071855.1, dated Apr. 12, 17. cited by applicant
CN Supplemental Search Report issued in Application No. 201480071855.1, dated Feb. 4, 18. cited by applicant
EP Search Report and Written Opinion issued in Application No. EP14861199.9, dated Oct. 18, 17. cited by applicant
Bings, et al. Microfluidic Devices Connected to Fused-Silica Capillaries with Minimal Dead Dead vol. Analytical Chemistry. 1999;71(15):3292-3296. cited by applicant

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Background/Summary

CROSS-REFERENCE TO RELATED APPLICATIONS (1) This application is a divisional of U.S. application Ser. No. 16/258,412, filed Jan. 25, 2019, which is a divisional of U.S. application Ser. No. 15/037,039, filed May 16, 2016, now U.S. Pat. No. 10,191,071, which is a nationalization of PCT Application No. PCT/US14/66008, filed Nov. 17, 2014, which claims the benefit of and priority to U.S. Provisional Application No. 61/905,804 filed Nov. 18, 2013 and U.S. Provisional Application No. 61/981,678, filed Apr. 14, 2014, each of which is incorporated herein by reference in its entirely.

STATEMENT AS TO FEDERALLY SPONSORED RESEARCH
(1) None.
BACKGROUND OF THE INVENTION
(2) One barrier to the broad adoption of rapid DNA-based human identification is the consumable cost. A low-cost cartridge using small amounts of reagents would reduce this barrier. Previous approaches have focused on automation and manufacturing process improvement to reduce the cost to make a given cartridge.
(3) Versions of systems including sample cartridges and fluidic systems for sample extraction and analysis are described in, for example, U.S. Pat. No. 6,190,616 (Jovanovich et al.); U.S. Pat. No. 6,551,839 (Jovanovich et al.); U.S. Pat. No. 6,870,185 (Jovanovich et al.); U.S. Pat. No. 7,244,961 (Jovanovich et al.); U.S. Pat. No. 7,445,926 (Mathies et al.); U.S. Pat. No. 7,799,553 (Mathies et al.); U.S. Pat. No. 8,173,417 (Tan et al.); U.S. Pat. No. 8,206,974 (Tan et al.); U.S. Pat. No. 8,394,642 (Jovanovich et al.); U.S. Pat. No. 8,425,861 (Selden et al.); U.S. Pat. No. 8,431,340 (Jovanovich et al.); U.S. Pat.

No. 8,720,036 (Selden et al.) and U.S. Pat. No. 8,858,770 (Tan et al.); US patent applications 2009/0178934 (Jarvius); 2009/0253181; 2011/0039303 (Jovanovich et al.); 2011/0126911 (Kobrin et al.); 2011/0220502 (Selden et al.); 2012/0181460 (Eberhart et al.); 2013/0139895 (Vangbo) and 2013/0115607 (Nielsen et al.); and International Patent Application WO/US2013/130910.

SUMMARY OF THE INVENTION

(4) Fluidic devices are provided, for example in the form of a cartridge, for sample extraction and analyte reaction and analysis.

(5) Provided herein is a cartridge comprising one or more fluidic circuits that each comprise at least one diaphragm valve; wherein the cartridge comprises: (a) a body comprising (i) a surface comprising a valve seat in fluidic communication with a valve inlet and a valve outlet and (ii) at least one port in fluidic communication with the fluidic circuit; and (b) a layer of deformable material covering the valve seat and the at least one port, wherein a portion of the layer of deformable material functions as a diaphragm which, in combination with the valve seat, forms a diaphragm valve, and wherein the diaphragm, when actuated (for example, by being moved into contact with the valve seat or by being moved out of contact with the valve seat), regulates fluid flow across the diaphragm valve, and comprising at least one conduit through the layer of deformable material, each conduit communicating with a port; and wherein the cartridge is configured to engage a cartridge interface, putting the deformable material in direct contact with a surface of cartridge interface, putting the diaphragm in communication with a source of positive and/or negative pressure that actuates the diaphragm (e.g., pneumatically or mechanically) and putting the at least one port in communication with a fluid or pneumatic line through the conduit, wherein the layer of deformable material optionally functions as a gasket sealing the at least one port against leakage. In one embodiment the fluidic circuit further comprises a reaction chamber formed in the body, optionally covered with a film of heat conductive material (e.g., a metal film). In another embodiment the fluidic circuit further comprises a chamber configured to receive a sample comprising a biological material, said chamber optionally comprising a close tab. An example of such an instrument and cartridge is shown in FIGS. **1-5**.

(6) Also provided herein is an instrument comprising: (a) at least one cartridge interface comprising: (i) an engagement unit configured to receive a removably insertable cartridge and to engage a received cartridge with a manifold assembly and, optionally, a thermal regulator, wherein the cartridge comprises at least one fluidic circuit comprising at least one fluid channel, at least one exit port; and at least one diaphragm valve comprising a valve seat configured to regulate fluid flow in the at least one fluidic circuit; and a layer of deformable material covering the valve seat and the at least one port, wherein the deformable material functions as a diaphragm in the diaphragm valve and comprises at least one conduit through the layer, each conduit communicating with a port; and (ii) a manifold assembly comprising an engagement surface configured to directly contact the deformable layer of a received cartridge and having a plurality of transmission channels communicating with ports on the engagement surface; wherein engaging a cartridge with the manifold assembly: (A) puts the diaphragm in communication with a first port on the engagement surface configured to transmit positive or negative pressure to the diaphragm, and (B) puts the exit ports in communication with second ports on the engagement surface configured to transmit fluid into or out of a fluidic circuit through the transmission channels; and (iii) a thermal regulator which, when engaged with a received cartridge, puts a heat pump (e.g., a thermoelectric heater, e.g., a Peltier device) in thermal contact with a thermal cycling chamber in the cartridge or a heating element in thermal contact with a chamber in the cartridge. In one embodiment the instrument of further comprises any of: (b) a pneumatic pressure source configured to deliver positive or negative pneumatic pressure to a transmission channel of the manifold assembly; (c) a pump configured to move liquid into or out of a transmission channel of the manifold assembly; (d) a source of reagents in fluid communication with a transmission channel of the manifold assembly; (e) an analysis module configured to perform at least one analysis (e.g., electrophoresis) on a fluid received from the cartridge; and (f) a control module comprising executable code that, when executed, controls operation of the instrument.

(7) Also provided herein is a cartridge comprising a first layer and a deformable layer: (a) wherein the first layer comprises: (i) a first side contacting the deformable layer, wherein the first side comprises a plurality of fluidic circuits, each fluidic circuit comprising at least one fluidic channel; and (ii) a second side comprising at least one fluidic distribution channel, which fluidic distribution channel is covered by a cover layer; (iii) a plurality of vias in the first layer, each via configured to put the fluidic distribution channel in communication with a fluidic channel; and (iv) optionally, at least one via in the first layer configured to put the fluidic distribution channel in communication with a port on a side of the first layer configured to engage a source of fluid; and (b) optionally comprising an actuation layer comprising at least one actuation circuit configured to actuate a diaphragm against a valve seat in the first side. An example of such a cartridge is shown in FIGS. **6** and **9**.

(8) Also provided herein is a cartridge comprising a first layer, a second layer and a deformable layer sandwiched there between: (a) wherein the first layer comprises: (i) a first side contacting the deformable layer, wherein the first side comprises a plurality of fluidic circuits, each fluidic circuit comprising at least one fluidic channel and at least one valve seat; (ii) a second side comprising at least one pneumatic distribution channel, which pneumatic distribution channel is optionally covered by a cover layer; (iii) at least one via in the first layer configured to put a pneumatic distribution channel in communication with the deformable layer; and (iv) optionally, at least one via in the first layer configured to put a pneumatic distribution channel in communication with a port on a side of the first layer configured to engage in a source of pneumatic pressure; (b) wherein portions of the deformable layer, in combination with valve seats in the first layer form diaphragm valves; and (c) wherein the actuation layer comprises at least one actuation circuit comprising at least one branch channel, wherein each branch channel is configured to actuate a diaphragm against a valve seat in a different fluidic

circuit and further comprises a valve seat; and wherein positive or negative pressure applied to a pneumatic distribution channel transmits pressure through the via to actuate a diaphragm portion of the deformable layer into or out of contact with the valve seat in the branched channel, wherein closing the control valve inhibits actuation the diaphragm valve in the fluidic circuit. An example of such a configuration is shown in FIG. **10**A-B.

(9) Also provided herein is a cartridge comprising: (a) a body comprising a polymer and comprising at least one functional feature on a surface of the body and configured to transmit fluid (e.g., a port, a via, a fluid channel, a chamber, a valve inlet and valve outlet and/or a valve seat); and (b) a layer of deformable material thermally bonded to the body and covering the functional feature (optionally, wherein at least one portion of the layer comprises a permanent deformation), and wherein application of positive or negative pressure to at least one portion of the layer actuates the deformable material into or out of contact with a functional feature on the surface of the body; and wherein the cartridge is configured to engage a cartridge interface configured to supply positive or negative pressure to the at least one portion of the layer. In one embodiment the cartridge further comprises a fluid-filled chamber in the body, wherein the chamber has an opening sealed closed with a heat seal material. In another embodiment the deformable material comprises a heat seal material. In another embodiment the deformable material comprises a material selected from polypropylene, polyethylene, polystyrene, cycloolefin co-polymer (COC), mylar, polyacetate and a metal. An example of valves in such a cartridge is shown in FIGS. **7**, **8**, **13**, and **14** (seal not shown in all figures).

(10) Also provided herein is a device comprising the aforementioned cartridge and a ram configured to actuate a diaphragm of a diaphragm valve on the body.

(11) Also provided herein is a device comprising a cartridge and a clamping device: (a) wherein the cartridge comprises: (i) a body comprising: (A) at least one fluidic circuit comprising: (I) at least one functional feature on a surface of the body and configured to transmit fluid (e.g., a port, a fluid channel, a chamber, a valve inlet and valve outlet and/or a valve seat), wherein the functional feature optionally comprises a ridge on the surface of the body; and (II) at least one compartment containing a liquid, wherein the compartment communicates with the functional feature through one or more vias in the body; and (ii) a layer of deformable material covering the functional feature; and (b) wherein the clamping device, when engaged with the cartridge, applies sufficient pressure to the deformable material to deform the deformable material against the cartridge body and seal against movement of liquid from the compartment and through the at least one functional feature; and wherein removing the clamping device releases pressure to the deformable material, allowing the seal to open (e.g., through an elastic response of the deformable material or through application of positive or negative pressure against the seal). In one embodiment the clamping device comprises a mechanical clamp or a vacuum seal. An example of such a cartridge is shown in FIGS. **6** and **11**.

(12) Also provided herein is a cartridge comprising: (a) a fluidics layer comprising a surface having at least one diaphragm valve comprising a valve seat (e.g., a recessed valve seat); (b) a deformable layer mated to the surface, wherein a portion of the deformable layer functions as a diaphragm which, when actuated, is configured to move into or out of contact with the valve seat; and wherein the portion of the deformable layer functioning as a diaphragm comprises a boss positioned on a side of the deformable layer opposite of a side that contacts the valve seat; and (c) optionally comprising: a rigid substrate mated with the deformable layer and comprising apertures exposing the bosses and configured to receive a ram that contacts the boss and actuates the diaphragm, e.g., by application of mechanical pressure; or configured to engage an interface comprising apertures exposing the bosses and configured to receive a ram that contacts the boss and actuates the diaphragm, e.g., by application of mechanical pressure. An example of such a cartridge is shown in FIGS. **15** A and B.

(13) Also provided herein is a cartridge comprising: (a) a base comprising: (I) a central barrel comprising a pump chamber and movable syringe, (II) a base floor comprising a port station comprising a floor port; and (III) a channel fluidically connecting the barrel chamber to the port in the floor; and (b) a turret configured to revolve around the central barrel and comprising a plurality of turret chambers, each turret chamber comprising a turret chamber aperture in a chamber floor of the turret chamber and facing the base floor, wherein positioning a turret chamber at the port station puts the turret chamber aperture in fluid communication with the barrel chamber through the floor port, and wherein the floor closes a turret chamber aperture when the turret chamber is positioned at at least one position other than the port station; and wherein at least one turret chamber further comprises a channel communicating between the floor port and an exit port. An example of such a cartridge is shown in FIG. **17**.

(14) Also provided herein is a instrument comprising a cartridge interface and a removable cartridge engaged therewith: (a) wherein the interface comprises a base and one or more hollow bore pins for delivering fluid to a port in the cartridge, wherein the pin is biased against the base by the cartridge and protrudes through an aperture in the base; and wherein the pin comprises a home lead-in configured to put the pin in a home position after the bias is released by removal of the cartridge; and a tapered end configured to mate with a guide in the cartridge; and (b) wherein the cartridge comprises a fluidic circuit comprising a port and a pin guide communicating with the port, wherein the pin guide comprises a mating cone configured to mate with a tapered end of the pin and a pin guide lead-in configured to guide the pin into the mating cone when the cartridge exerts a bias against the tapered end of the pin during engagement with the interface. An example of such a combination is shown in FIG. **18**.

(15) Also provided herein is a cartridge comprising: (a) a body comprising at least one puncturing element, at least one fluidic channel and at least one flange; and (b) a reagent reservoir comprising at least one fluidically isolated, fluid filled compartment; a breakable seal in a wall of the compartment and a breakable tab attached to an outside wall of the compartment; wherein the cartridge is configured such that when the reagent reservoir is engaged with the body: (i) the puncturing elements punctures the breakable seal, putting the compartment in fluidic communication with the channel; and

(ii) the flange exerts a force against the breakable tab, breaking the tab and forming a vent in the compartment. An example of such an embodiment is shown in FIG. **12**.

(16) Also provided herein is a fluidic device comprising one or more diaphragm valves, each diaphragm valve configured to regulate fluid flow in a fluidic channel, wherein the fluidic device comprises a fluidics layer, an actuation element and a deformable membrane, wherein each diaphragm valve comprises: a) a diaphragm comprised in the deformable membrane; b) a valve seat comprised in the fluidics layer and recessed from a surface of the fluidics layer that contacts the deformable membrane so that the diaphragm does not close the diaphragm valve unless positive pressure is exerted on the diaphragm; and c) a valve inlet and a valve outlet comprised in the fluidics layer and in fluid communication with a fluidic channel; and d) a ram configured to actuate the diaphragm; wherein the deformable membrane comprises a plastic material adhered to the fluidics layer through a heat activated adhesive, thermal fusion, chemical bonding or a pressure sensitive adhesive, and wherein the deformable membrane is configured such that pressure on the deformable membrane presses the membrane against the valve seat, thereby closing the valve and wherein the valve can be opened by releasing pressure of the ram against the deformable membrane or by pushing liquid through the valve. In one embodiment the deformable membrane is not an elastomeric material, e.g., is not PDMS. In another embodiment the deformable membrane comprises a laminate comprising the plastic material and a deformable, space-filling material, wherein pressure against the space-filling material causes the space filling material to fill the valve chamber sufficiently so that of the plastic material closes the valve. In another embodiment the deformable material has a durometer value of between 10 to 80 Shore D. In another embodiment the deformable material has a thickness sufficient such that the mechanical pressure is applied the deformable material sufficiently fills the valve chamber to form a seal between the plastic material in a valve seat to close the valve. In another embodiment the deformable, space-filling material comprises a solid foam. In another embodiment the deformable material is attached to the plastic material through an adhesive. In another embodiment the deformable material is pressed into contact with the plastic layer through an interface device. In another embodiment the fluidics layer comprises a polymer, e.g., a thermoplastic.

(17) Also provided herein is a fluidic device comprising one or more diaphragm valves, each diaphragm valve configured to regulate fluid flow one or more fluidic channels, wherein the fluidic device comprises a fluidics layer, an actuation element and a deformable membrane, wherein each diaphragm valve comprises: a) a diaphragm comprised in the deformable membrane; b) a valve seat comprised in the fluidics layer and recessed from a surface of the fluidics layer that contacts the deformable membrane so that the diaphragm does not close the diaphragm valve unless positive pressure is exerted on the diaphragm; and c) a valve inlet and a valve outlet comprised in the fluidics layer and in fluid communication with a fluidic channel; and d) a ram comprised as an actuation element having a forked end comprising tines, wherein the end has a surface complying with the valve seat and wherein the tines are compliant to lateral pressure whereby pressure by the ram on the diaphragm and against the valve seat closes the valve. Embodiments are shown in FIGS. **29-32**.

(18) Also provided herein is a fluidic device comprising a sample input, a sample output and a waste chamber, all fluidically connected through fluid channels wherein the waste chamber comprises a material that degrades nucleic acid. In one embodiment the material that degrades nucleic acid comprises a hypochlorite salt. In another embodiment the material that degrades nucleic acid comprises an enzyme such as an exonuclease or an endonuclease.

(19) Also provided herein is a fluidic device comprising a fluidic circuit comprising sample input, a reaction chamber and a sample output, wherein the reaction chamber comprises a solid substrate, e.g., solid phase extraction material, for retaining analyte from a sample. In one embodiment the solid substrate comprises a material that binds nucleic acid. In another embodiment the solid substrate comprises Whatman FTA paper, a carboxylated material, a sponge-like material, a polymer membrane, or glass particles. In another embodiment the solid substrate binds a predetermined amount of material. Embodiments are shown in FIGS. **22-28**.

(20) Also provided herein is a method comprising 1. A method comprising: (a) providing a reaction mixture comprising: (I) a sample comprising mammalian (e.g., human) DNA, (II) reagents for amplifying short tandem repeats (STRs) in the mammalian DNA (e.g., labeled primers, nucleotides and polymerase) and (III) a mammalian-specific probe selected to be amplified in the reaction and including a label that is distinguishable from the labeled primers; (b) performing an STR reaction comprising amplifying STRs in the sample and the mammalian specific probe; (c) detecting an amount of amplified mammalian specific probe in the reaction, e.g., over time, e.g., performing real-time PCR; and (d) optionally, stopping the STR reaction based on the amount of amplified mammalian specific probe detected. In one embodiment the labels are fluorescent labels and the distinguishable label has a wavelength above or below the highest or lowest wavelength of labeled primers. In another embodiment the mammalian specific probe further comprises a quencher such as a Black Hole Quencher® or a TaqMan® probe.

INCORPORATION BY REFERENCE

(21) All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Description

BRIEF DESCRIPTION OF THE DRAWINGS

(1) The novel features of the disclosure are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present disclosure will be obtained by reference to the following detailed description that

sets forth illustrative claims, in which the principles of the disclosure are utilized, and the accompanying drawings of which:
(2) FIG. **1** shows an instrument **101** comprising an interface adapted to engage a cartridge, including a cartridge interface **103** and a cartridge **200** inserted into a slot **107**. The embodiment shown contains four cartridge-receiving subassemblies and Peltier device **109**.
(3) FIG. **2** shows cartridge **200**, which is insertable into instrument **101**. The cartridge includes a body **201**. It further includes elastic layer **203** attached to a surface of the body. Layer **203** provides a diaphragm for a diaphragm valve on a surface of body **201**, as well as ports **215** communicating with fluidic channels in body **201**. The cartridge also includes cover sheet **205** that seals a chamber in the body and/or functions to transmit heat to or from the chamber. For example, when the cartridge is engaged with the interface, the chamber can function as a thermal cycling chamber and cover sheet **205** can be in contact with a source of thermal energy, such as a Peltier device **109**. The cartridge also includes a slot **207** adapted for receiving a sample. Aperture **209** and notch **225** are alignment features configured to align cartridge **200** with cartridge interface **103**. The cartridge also includes a closable cap **211**.
(4) FIG. **3** shows a cutaway view of cartridge **200**. Reaction chamber **301** is in thermal contact with the cover sheet **205** which can be sealed to the body. Cartridge **200** includes diaphragm valve **303**. Diaphragm valve **303** includes recessed valve seat **305** defining a valve chamber. Valve inlet **306** and valve outlet **307** are configured as vias through body **201** and communicate with fluidic channels in the body. Deformable layer **203** includes a portion functioning as a diaphragm **311**. Putting diaphragm **311** into contact with valve seat **305** closes diaphragm valve **303**. Deformable layer **203** also comprises port **309** that communicates with a fluidic conduit in the cartridge. When the cartridge is engaged with a cartridge interface, deformable layer **203** functions as a gasket that seals around port **309**.
(5) FIG. **4** shows from one aspect an exploded view of a cartridge **200** and an assembly **401** of a cartridge interface. The cartridge includes body **201**, cover sheet **205**, and deformable layer **203**. The body includes, on one side, fluidic channel **213** and reaction chamber **301**. Fluidic channels communicate through apertures in body **201** with a face covered by deformable layer **203**. The deformable layer **203** includes ports **215** configured to align with ports **403** on the interface assembly **401** and an area **311** positioned to function as a diaphragm in a diaphragm valve. Fluidic lines **405** connect to interface assembly **401** and transmit fluids to port **403** which connects to cartridge **201**. Pneumatic line **407** also connects to interface assembly **401** and transmits positive or negative pneumatic pressure to port **409** which actuates diaphragm for **311**.
(6) FIG. **5** shows from another aspect an exploded view of a cartridge of this disclosure and an assembly **401** of a cartridge interface. Body **201** includes a valve body with valve seat **305** with apertures **306** and **307** which is covered by deformable layer **203**. Interface assembly (**401**) includes pneumatic line **407** that, when engaged with deformable layer **203**, transmits positive or negative pressure to actuate diaphragm **311**. Interface assembly **401** also includes fluid lines **405** communicating through passages in interface **401** with apertures **215** in the deformable layer **203** to allow movement of fluids into, through an out of fluidic circuits in the cartridge.
(7) FIG. **6** shows cartridge **601** comprising a plurality of sample receptacles **607** and comprising reagent chambers in piece **905**, distribution channels **903** that distribute reagents from reservoirs **603** across a plurality of fluidic circuits. Piece **905** includes reagent chambers **1107**. Piece **905** is covered with deformable layer **907**. Clamping elements **1103** apply pressure to deformable layer **907**. Deformation of the deformable layer against piece **907** blocks movement of liquid through passages. This prevents movement of reagents through fluidic circuits during shipping.
(8) FIG. **7** shows a cartridge **701** comprising a body **1205** having, on side **1311**, fluidic channel **1315** and valve seat **1317**. On another side, the cartridge has a reagent container having open compartments **1201** that can comprise a seal of a layer of material, for example through a heat seal, to fluidically isolate fluids contained in the compartments until use.
(9) FIG. **8** shows a cartridge **801** comprising a body having a first side having open compartments **811**, ports **813** and reaction chamber **815**. The body also has a second side comprising valve seats **817**. The layer **819** can be bonded to the first side of the body, sealing off the open compartments. The film **821** is capable of transmitting heat and will cover and seal reaction chamber **815**. The deformable layer **1303** provides areas that function as diaphragms. When pressed against the second side, for example by a clamping device, the deformable layer **1303** is pressed into the valve seats, closing the valves and preventing fluid movement through fluidic circuits until use.
(10) FIG. **9** shows an embodiment of a cartridge having a fluid distribution channel. Body **905** comprises a surface on one side that comprises a plurality of fluidic channels **901** oriented in a first direction. Body **905** also comprises a surface on a second side comprising a channel **903** having an orientation that is oblique to the first direction, for example, at right angles to the first direction. Channel **903** on a second side communicates with each of a plurality of fluidic channels on the first side through vias **904** that traverse body **905**. Channel **903** is closed by a cover layer **907**. Channel **903** optionally communicates with a source of fluid through a bore **920** in piece **905**. Fluid channels **901** are covered by a deformable layer **909**. Channels **901** also can comprise valve seats. Portions of the deformable layer can function as diaphragms to open or close the valves. These can be operated through pneumatic layer **911** comprising pneumatic channels that actuate the diaphragms. Alternatively, the cartridge can be engaged with an interface that provides an actuation force to the diaphragms.
(11) FIGS. **10**A and **10**B show a segment of cartridge **1000** having a control line configured to disable a selected diaphragm valve in the cartridge. FIG. **10**A shows an exploded view of the cartridge. FIG. **10** B shows an exploded view in clamshell format. The cartridge comprises a fluidics layer **1001**, pneumatic layer **1003** and a deformable layer **1005** sandwiched between them. Fluidics layer **1001** includes at least one fluidic channel **1007** that includes recessed valve seat **1009**. The fluidics layer also comprises a control line **1011** having a branch **1013** that communicates through a via **1015** with a surface

of the fluidics layer mated with the deformable layer. The pneumatic layer comprises a pneumatic channel **1017** comprising one or more branches **1019**. Each branch controls one diaphragm valve. The branch includes a valve relief **1021** positioned on the deformable layer opposite the valve seat in the fluidics layer into which the deformable layer can be deformed and which can transmit pressure to the diaphragm, actuating the diaphragm into the valve seat **1009**. The branch also comprises a valve seat **1023** positioned opposite via **1015**, which via connects to pneumatic control line **1011**. Assertion of positive or negative pressure against control line **1011** to the diaphragm actuates the diaphragm against or away from the valve seat **1023** in the pneumatic layer. When pressed against the valve seat, this prevents transmission of pressure through pneumatic actuation channel **1017**, rendering the diaphragm valve **1009** that controls fluid in fluidic line **1007** inoperative.
(12) FIG. **11** shows a shipping clamp **1103** on cartridge **905**.
(13) FIG. **12** shows a cartridge comprising a body **1205** and a reagent reservoir **1201**. The reagent reservoir has compartments, **1209**, that can contain a liquid and that can be sealed with a layer such as heat seal, chemical seal, adhesive or laser weld. The body can comprise puncturing elements (not shown) to puncture seals in a floor of compartment **1209** when the reagent reservoir is pressed against the body. The puncturing elements can be a solid material, e.g., that protrude from the body, and that may have a tapered end that is pointed or sharp and that is adapted to apply concentrated pressure to the floor and to puncture a hole in the floor. This creates a fluidic connection between the compartment and a fluidic circuit in body **1205**. This combination also includes flanges **1207** and breakable tabs **1203**. When reagent reservoir **1201** is pressed against body **1205**, flange **1207** engages tab **1203** and applies a force which breaks tab **1203**, thereby creating a vent in compartment **1209**. This allows fluid in compartment **1209** to drain through the aperture in the floor of the compartment and into the fluidic circuit.
(14) FIG. **13** shows a diaphragm valve with a thin sealing layer **1303** that can comprise a heat seal material.
(15) FIG. **14** shows a tool for introducing a dimple into a diaphragm.
(16) FIGS. **15**A and **158** show cartridge **1501** having a body **1503** attached to an deformable layer **1505** and having a cover **1507** on the deformable layer so that the deformable layer in the cartridge is not open-faced. This cartridge includes a diaphragm valve **1513** that is normally open and that regulates fluid flow along a fluidic channel **1515**. The cover **1507** covers the deformable layer and comprises an aperture **1509**. The deformable layer includes a boss **1511** fitted with the aperture. A mechanical actuator, such as a piston, can be used to close the valve by actuating the diaphragm by the provided boss. This cartridge further comprises a chamber **1517** for receiving a swab or other sample and a reaction chamber **1519** in fluidic communication with channel **1515**. The reaction chamber **1521** can be covered with a seal and/or can have a separate heat spreader layer **1521**.
(17) FIGS. **16**A and **168** show, respectively, a front and back view of a multi-sample cartridge.
(18) FIG. **17** shows a revolving multi-chamber turret. Cartridge **1701** comprises a base **1703**. The base has a central barrel **1705** comprising a pump chamber **1707** and movable syringe **1709**, a floor **1711** comprising a port station comprising a port **1713** and a channel **1715** fluidically connecting the barrel chamber to the port in the floor. The cartridge also has a turret **1717** configured to revolve around the central barrel **1705** and comprising a plurality of turret chambers (e.g., **1719**), each turret chamber comprising a turret chamber aperture **1721**, wherein the turret is configured to rotate around the syringe barrel, wherein positioning a turret chamber at the port station puts the turret chamber aperture in fluid communication with the barrel chamber through the floor aperture and wherein the floor covers a turret chamber aperture when turret chamber is positioned at least one position other than port station. At least one turret chamber further comprises a channel communicating between the port and an exit port **1723**.
(19) FIGS. **18**A and **188** shows cross-sectional views of a self-aligning, self-resetting pogo pin **1801** reset into its home position, and fluidically connected to the cartridge, respectively.
(20) FIG. **19** shows an exploded view of an interface slot.
(21) FIG. **20** shows a cartridge interface **1901**.
(22) FIG. **21** shows a schematic of a cartridge of this disclosure.
(23) FIG. **22** shows a bottom view of a cartridge circuit.
(24) FIG. **23** shows the valve states and flow for a cell lysis operation.
(25) FIG. **24** shows the valve states and flow for nucleic acid capture.
(26) FIG. **25** shows the valve states and flow for movement of liquid into a waste chamber.
(27) FIG. **26** shows the valve states and flow for creation of a reaction mixture.
(28) FIG. **27** shows the valve states for thermal cycling.
(29) FIG. **28** shows the valve states and flow for movement of the amplification product to output ports.
(30) FIG. **29** shows a cutaway view of a normally open valve actuated by a ram having a tip with flexible elements.
(31) FIG. **30** shows a three-dimensional view of a valve of this disclosure.
(32) FIG. **31** shows a valve of this disclosure in a closed configuration. A flexible end of the ram presses a deformable membrane against a valve seat. The ram is configured to press the deformable membrane so as to seal the valve inlet and the valve outlet by pressure against the perimeter of the inlet and outlet in the valve seat.
(33) FIG. **32** shows a valve having a valve chamber defined by a recess in a fluidic layer and a diaphragm comprised in a laminate layer.

DETAILED DESCRIPTION OF THE INVENTION

I. Instruments for Engaging and Operating Fluidic Cartridges

(34) In one aspect provided herein is a cartridge comprising: (a) a body comprising a fluidic circuit comprising: (1) a sample chamber comprising an opening configured to receive a sample and a via through the body; (2) a reaction chamber;

(3) diaphragm valve elements including a valve inlet and a valve outlet, each configured as a via through the body, and a valve seat; (4) a plurality of ports through the body; and (5) one or more fluidic channels in a surface of the body, wherein the one or more fluidic channels put the sample chamber (e.g., through the via), the reaction chamber, the valve elements (e.g., through the valve inlet and valve outlet), and each of the plurality of ports in fluidic communication with each other; (b) a cover layer attached to the body and sealing the via, the fluidic channels and the reaction chamber; and (c) a deformable layer attached to the body, wherein the deformable layer (i) comprises a plurality of holes, each hole communicating with a port; and (ii) in combination with the valve inlet, the valve outlet and the valve seat, form a diaphragm valve configured to regulate fluid flow in the fluidic circuit.
(35) In another aspect provided herein is an instrument comprising: (a) at least one cartridge interface comprising: (1) an engagement assembly having a first position to receive a cartridge as described herein and a second position to engage a received cartridge with a manifold assembly and an optional thermal regulator; (2) a manifold assembly having a plurality of channels, each channel opening onto a front port and a back port, wherein, when the engagement assembly has received a cartridge and is in the second position, a plurality of front ports fluidically engage ports in the cartridge and pneumatically engage the diaphragm of the diaphragm valve, and wherein the deformable material serves as a gasket for fluidic engagement; (3) an optional thermal control assembly (e.g., thermal cycler) configured to place a heat spreader in thermal contact with a thermal cycling chamber of an engaged cartridge and to regulate temperature of the thermal cycling chamber, when the engagement assembly is the second position; (b) a pneumatic and fluidic assembly comprising: (1) a source of pneumatic pressure; (2) a plurality of fluid sources; (3) a plurality of transmission lines connecting a source of pneumatic pressure in each of the plurality of sources in fluid communication with a back port of the manifold assembly; (4) a pump configured to move fluids from the source through the transmission lines.
(36) FIG. **1** shows an interface configured for a cartridge. Referring to FIGS. **4** and **5**, for a single sample cartridge, the interface may also include three fluidic connections **405** and one pneumatic connection **407** to control the valve. These can be low-dead-volume connections which connect to the pneumatic and fluidic assembly through tubes. Alternatively, they can be rams such as pogo pins (e.g., **1801** of FIG. **18**).
(37) This configuration permits samples to be inserted into cartridges, and cartridges to be independently inserted into a slot, even if other slots are processing other samples. Thus, in one embodiment, the system can process samples independently.
(38) The cartridge described in FIGS. **1-5** minimizes the cost of manufacture by minimizing the functions that need to be handled by the disposable cartridge. These functions are moved onto a pneumatic and fluidic assembly, which can be a permanent or semi-permanent part of the system.
(39) In this embodiment, the cartridge can comprise an injection molded body, for example, a plastic, a deformable film; and a foil, such as a metal foil, each bonded to the body. The body can have integrated alignment features **209** and **225** so that it can be easily and accurately inserted into the interface. The plastic material can include any plastic known to those skilled in the art, such as polypropylene, polystyrene, polyethylene, polyethylene terephthalate, polyester, polyamide, poly (vinylchloride), polycarbonate, polyurethane, polyvinyldiene chloride, cyclic olefin copolymer (COC), or any combination thereof.
(40) The cartridge may be scribed with a barcode or QR code for optical identification or have an EEPROM or RFID or other similar identification device mounted on the cartridge that can assist in sample tracking and optionally contain information about the chemistry, process to be performed, lot number, expiration date, and other information.
(41) The body can have a folding tab **211** that can be snapped shut after the swab is inserted, either by the operator or the system. More than one style of body, each adapted to a swab, punch type, or sample type can be produced. After the tab is snapped shut, the body can serve to contain the sample, providing protection against contamination and facilitating re-testing or recovery of the sample as required.
(42) The body can also define the volumes for two process chambers. The swab, punch, or other sample type is placed in a compartment **207** that also serves as a lysis chamber. To accommodate the swab, punch, or other sample type, it can have a volume ranging from, e.g., 10 μL to 15 ml or 1 ml to 10 ml. Cells are lysed and DNA extracted from the swab, punch, or other sample type in this chamber. The second chamber **301**, called the reaction chamber, can serve to capture DNA or house a small amount of lysate for direct amplification. It can also be where cleanup and/or amplification occurs. To minimize the duration of thermocycling and the amount of energy required, this second chamber can have minimal volume, perhaps ranging from 2 μl to 25 μl, although other configurations are practical.
(43) Referring to FIGS. **2** and **3**, to an area of the cartridge body **201**, a deformable film **203** can be bonded on one side, and a cover sheet **205**, such as a plastic film or metal foil, can be bonded to the other.
(44) The deformable material used in cartridges disclosed herein can be a plastic material (plastic deformation) or an elastic material (elastic deformation). The plastic material can comprise, without limitation, a polymer or a metal. Suitable plastic materials include, without limitation, polypropylene and polyethylene. Suitable metals include aluminum. Suitable elastic materials include, for example, elastomeric materials such a polysiloxanes, e.g., PDMS. Other deformable materials are further described herein.
(45) In one embodiment, the deformable film serves as a gasket for three low-dead-volume connections. These provide an inlet, an outlet, and a purge line that can be used to flush out the cartridge and outlet line. The deformable film also serves as the flexible diaphragm for a valve. The valve seat **305** can be formed into the cartridge body. The inputs **306** and outputs **307** to the valve can be vias through the body, channels between the body and the deformable, or both.
(46) The valve can be actuated by positive or negative pressure or applied to the deformable material over the valve seat. In

another embodiment the valve can be actuated by a ram exerting mechanical force on cover sheet **205**.
(47) The deformable material may also fill a hole in the body, creating a flexible valve on the far side of the body. The deformable material can be pressed from the near side to deform through the body, and seal against a surface on the far side of the body.
(48) In addition to being mechanically simple, structuring the cartridge around one molded body with functional elements on the surface increases the robustness. Leaks are critical problems, so the fluidic and pneumatic connections need to line up to enable sealing. Tolerance variations accumulate across assemblies, typically with each part contributing some variation. As a result, simpler assemblies can be more robust even with the same part tolerances. Furthermore, the single sample cartridge and other simplified cartridges in this instant disclosure involve only a few connections, further reducing the risk of leakage. Additionally, the effect of thermal expansion increases with size, so having few connections that are also close together reduces the risks still more.
(49) This embodiment integrates parts, reducing materials and assembly costs. In one embodiment, it is designed with pneumatic ports, fluidic ports, and valve controls (either mechanical or pneumatic) onto one side. This simplifies connections and permits more space for other functions such as a temperature regulator (e.g., a thermocycler) to contact the cartridge, an optical system to interrogate the cartridge, or other measurement devices.
(50) Cartridges constructed in this or other embodiments can also be built to accommodate multiple samples. These multi-sample cartridges can permit the operator to run multiple samples without having to insert multiple cartridges. (See, e.g., FIGS. **6** and **16**)
(51) Alternatively, single-sample cartridges can be assembled onto multi-cartridge holders. Operators running many samples at a time are able to take the rack containing used cartridges out of the system and insert the new rack containing unused cartridges. Operators running only a few samples are able to populate only as many spaces as they wish. The remaining spaces can be filled with dummy cartridges or left empty depending on the configuration.
(52) The single-sample cartridges become particularly advantageous when paired with a latched cartridge interface **101** that can permit them to be inserted and removed singly. This can provide more flexible sample flow.
(53) This interface can have a number of cartridge positions **103** or ‘slots’ that can open and close independently. They can apply a compressive force on the cartridges. They can be held closed by solenoids, or another means controlled by the software, or could be manually latched.
(54) An operator with a new sample to run can insert the sample into a cartridge, and snap the cartridge top closed. He or she can then ask the system to open a slot. If a slot is not in use, the system opens it, permitting the sample to be inserted. If a processed cartridge is in the slot, the operator removes it. The operator could read the barcode, QR code, RFID or other identifying material on the cartridge before it is inserted or the system could read as it is inserted or afterwards. The operator can then push the interface closed, and enter additional information if necessary. The system can then start processing the sample immediately or start it automatically when next possible.
(55) In an alternative embodiment, an operator with a new sample can manually open a slot or direct the system to open a slot. If a slot is not in use, the system opens it. If a processed cartridge is in the slot, the operator removes it. The operator inserts a cartridge. The operator could read the barcode, QR code, RFID or other identifying material on the cartridge before it is inserted or the system could read as it is inserted. The operator could then read the barcode, QR code, RFID or other identifying material on the sample if there is one and place the sample into the cartridge in the slot; alternatively the operator could enter sample tracking information manually into the system. After the sample has been added, the top of the cartridge can be closed by the operator or by the instrument. The operator can then push the interface closed manually or the instrument can close the interface. The system can then start processing the sample immediately or start it automatically when next possible.
(56) This instant embodiment can be automated with a loading system that automatically inserts and removes cartridges as needed into slots. The automation can include mechanisms to load samples from a variety of sample types such as a collection of tubes containing swabs, microtiter plates containing liquid samples that can include preprocessing from single sources or mixtures, tubes containing liquid samples that can include preprocessing from single sources or mixtures, blood containers such as Vacutainers, or other containers for additional sample types.
(57) The interface for each cartridge can float, permitting it to seal around the various fluidic and pneumatic connections on one side, while pressing the cartridge against the thermo regulator (e.g., thermocycler) **109** on the other. As shown, the floating interface rotates, pressing the cartridge against a fixed temperature regulator. Alternatively, multiple smaller thermocyclers could be used. These can rotate or translate, possibly pressing the cartridges against a common pneumatic and fluidic assembly.
(58) After processing, the slot may remain closed to avoid contamination. The interface can press the cartridge against a temperature regulator, e.g., a Peltier device. This contact can be against the foil or film **205** enclosing the reaction chamber. Depending on the chemistry used, on the opposite side of the reaction chamber, the interface can house an LED, filter, and photodiode for reaction quantification or another detector.
(59) In such an embodiment, when the reaction is a short tandem repeat (STR) reaction, in many jurisdictions for casework samples, the amount of human DNA must be quantified. The typical forensic process is to quantify an extracted sample using real time polymerase chain reaction (PCR) in a separate instrument before the sample is STR amplified. In this instant disclosure, a human specific probe is added to the STR mixture which has fluorescence outside the range used by the STR kit. The reaction chamber **301** is interrogated by a suitable wavelength of light for the human specific probe while the STR is being PCR amplified. The human specific probe can be a quencher such as a Black Hole Quencher® or a TaqMan®

probe or other chemistries well know to one skilled in the art. As the PCR cycles increase, the fluorescence from the human specific probe is monitored to quantify the amount of human DNA in the reaction. In a preferred embodiment, the number of amplification cycles can be adjusted based upon the amount of human DNA measured; this can be on a cartridge-by-cartridge monitoring if independent thermal cyclers are in use. One advantage is that the human specific probe will allow the concurrent STR amplification to achieve an optimal amplification and produce an amount of STR product that is optimal for the kit regardless of amount of starting DNA in the sample. A second advantage is the real monitoring concurrent with the STR amplification allows integration of a sample-to-answer system without having an additional separate quantification process. A third advantage is for low copy number samples where there is barely enough sample to produce a good STR profile the integration of the quantification with the STR amplification prevents the aliquot typically used for quantification from causing the remaining sample to not have enough DNA for a successful STR amplification.
(60) In addition to actuating the valve diaphragms (e.g., **311**, **1301**) mechanically, they can be actuated pneumatically. In one embodiment, the interface **1901** (FIG. **19**) provides, for each valve, an interface diaphragm **1903** that conveys a pressure to the cartridge diaphragm **1301**, pushing it against the valve seat **1317** to close the valve. The interface diaphragm is bonded to the interface block **1905** and encloses a threaded hole **1907** with a fitting **1908** to connect to the flexible tube carrying the pneumatic signal. Each hole can correspond to a valve, which it can close or permit to open, controlled by the pneumatic signal. The interface diaphragm may be silicone rubber bonded with RTV, with rings **1909** to limit delamination from fatigue. However, other deformable materials can be used.
(61) The interface block **1905** is a component in the interface latch subassembly **1901**. The block has alignment features **1911** and **1913** that mate to the cartridge alignment features **2003** and **2005** accurately locating the cartridge in the interface. The block mounts flexibly to a hinge arm **1915** that pivots to engage the cartridge to the interface, or permit the operator to insert or remove cartridges. A frame **1917** loosely guides the cartridge during insertion, ensuring that it can mate with the alignment features.
(62) The single body cartridge allows on-chip storage/integration of reagent reservoir, including, for example, for example, capillary electrophoresis separation gel. This embodiment also permits STR manipulation without having reagents contact PDMS, which can interfere with certain biochemical reactions. This embodiment permits an integrated reaction chamber: The reaction chamber volume is defined by the outside of the fluidic layer and enclosed (e.g., by heat seal plastic, heat seal foil, graphite, etc.). It can connect to the circuit either by vias through the fluidics layer, or by enclosed channels along the surface.
(63) In systems that use STR components that are sensitive to PDMS or other diaphragm materials, the second side can house the STR components in reservoirs **603** (FIG. **6**) and use reaction chambers **605** separate from the PDMS layer **909**. To improve room-temperature stability, the STR components can be stored separately. Vias through the fluidics layer may push or pull the STR components into the reaction chamber, without having the bulk of the STR mixture contact the PDMS or other membranes.
(64) In addition to STR components, other reagents can also be stored on the second side of the fluidics layer. For laminated cartridges, which need to maintain a high degree of flatness near the pneumatic and fluidic circuits, these storage chambers could be above or below the laminate, or off to the side. The storage volumes would need vents near the top, and outlets near the bottom or narrowed sections capable of drawing the fluids upwards like a straw.
(65) To minimize the risk of contamination from one sample to another, reagents that are used before amplification could have separate chambers above the laminated area. Reagents used after amplification, when contamination is less of a risk, can be shared among all sample circuits. This approach permits all reagents needed to run the system to be stored on a single cartridge.
(66) Those reagents which require low pressures for movement or containment can be handled with diaphragm valves. Those reagents which require higher pressures, such as the separation gel, can be drawn out at low pressure into another chamber, and then pushed into the capillaries at high pressure.
II. Cartridges Having a Fluid Distribution Channel
(67) A double-sided fluidic layer offers a number of capabilities for multi-sample cartridges, such as an embodiment as shown in FIG. **6**. For example, as shown in FIG. **9**, if the circuits for individual samples are on one side of the fluidic layer, e.g., through channel **901**, the other side of the fluidic layer could provide right-to-left channels, e.g., **903**, to distribute reagents. Reagent distribution can otherwise require an additional fluidics part or external manifold.
III. Pneumatic Channels to Selectively Block Diaphragm Valves
(68) The right-to-left channels can also route pneumatic control signals to enable or disable specific circuits, as shown in FIG. **10**A-B. This selective enabling or disabling of circuits can permit some samples to be run immediately, and other circuits to be reserved to run samples later.
IV. Cartridges Having a Deformable Layer Sealed to a Plastic Body
(69) Cartridges of this disclosure can have a body comprising a solid material. The solid material can be rigid, plastic (capable of irreversible deformation) or elastic (capable or reversible deformation). The body can be stiff or compliant. In some embodiments, the solid material is a polymer, e.g., a thermoplastic, such as polypropylene. The body can comprise an external surface comprising elements of fluidic circuits, such as channels, compartments, vias and valve seats. The body can be made by injection molding of the thermoplastic. These features can be covered with a layer of material attached to the surface of the cartridge body. The layer can function to seal otherwise open features such as channels and compartments. The material can be a deformable material that can deform to contact a valve seat, thereby closing the valve. In certain embodiments, the solid material is inelastic (not capable of elastic deformation). For example, the solid material

is not an elastomer, such as PDMS.
(70) The material can be attached to the surface of the body using a selective bonding process in which the material bonds to selected portions of the surface during the bonding process and does not bond to un-selected portions of the circuit after the bonding process is complete. For example, the material may bond to surfaces other than fluidic elements during the bonding process, and not bond to fluidic elements, such as channels and valve seats, after the bonding process. Methods for selective bonding include, for example, thermal bonding (e.g., heat sealing, welding, laser welding), chemical bonding (e.g., chemical bonding of oxide to PDMS) and selectively placed adhesives.
(71) In one embodiment a layer of the deformable material is attached to a surface of a cartridge body through thermal bonding. This can include thermally bonding the material directly to the surface, or thermally bonding the material through an intermediate layer of material. In the latter case the material can be a laminate in which a deformable material is coated with a layer of material that contacts the surface and that melts at lower temperature. In either case bonding typically comprises contacting the deformable material to the body to form a combination and using a die to apply heat and pressure to the combination. Application of heat and pressure melts substrates in locations at which the material and body are in contact and fuse them, e.g., through coalescence. This process is more generally referred to as welding.
(72) A material that bonds to a body through application of heat and pressure is referred to herein as “heat seal”. Heat seals are well known in the art and are commercially available. For example, 4titude (Walton, Surrey, UK) commercializes a variety of heat seals. These heat seals are described on the website 4ti.co.uk/sealing/heat-seals/. These include, for example, Clear Seal, Clear Weld Seal and Foil Seal. Heat seals also are produced by Axygen, a Corning brand (Corning, Tewksbury, MA, USA). These include Axygen® PlateMax heat sealing film and sealing film rolls. See the website: catalog2.corning.com/LifeSciences/en-US/Shoppi ng/Prod uct.aspx?categoryname=Genomics+and+Proteomics(Lifesciences)%7cPCR+Products(Lifesciences)%7cSealing+Films+and+Tapes+for+Microplates(Lifesciences)%7cHeat+Sealing+Films+and+Tapes+for+Microplate
(Lifesciences).
(73) The deformable material can be a homogenous or non homogenous material. In certain embodiments, the heat seal material is made from the same material as the body of the cartridge. It can comprise a thermoplastic (e.g., polypropylene, polyethylene, polystyrene, cycloolefin co-polymer (COC), mylar, polyacetate) or a metal (e.g., aluminum). See, e.g., WO 2012/136333. The heat seal can be produced by contacting a heat seal layer with the body and applying heat and pressure. Non-homogenous films include laminates having a first side for contact with the heater and a second side for contact with the body. The first side has higher melting temperature (“high melt”) than the second side (‘low melt”). This permits use of a heat source to bring the lower side to its melting temperature before the first side allowing bonding to the body without bonding to the heater.
(74) In the single sample cartridge, one side of the body into which compartments are formed is covered in a film or foil that can be adhered or thermally attached to the body. This encloses a second functional layer while only requiring one molded part. This permits functional details—valves, channels, etc. on different sides of the body. In the case of the single sample cartridge, this permits the valves, pneumatic connections, and fluidic connections to be on one side of the cartridge, while the reaction chamber is on a different side of the cartridge. As a result, the temperature regulator controlling the reaction chamber temperature can do so through a thin film, rather than the deformable gasket, which can result in quicker and more controlled thermocycling.
(75) Referring to FIG. **13**, in this embodiment, the valve diaphragms **1301** are formed by a film, such as a plastic film. These films are sealed to the cartridge body **1311**, enclosing the fluidic circuit **1315**. The sealing can be through a heat-seal, a pressure-seal, laser welding, chemical bonding, adhesive or other method well known to one skilled in the art. These valves can be actuated by a control circuit on the system **1305**. However, the control circuit can be a permanent part of the system interface **1309** and need not be part of the disposable cartridge **1311**. This control circuit can be mounted to a mechanical support plate, with through vias to conduct the pneumatic signals. Gaskets **1313** between the support plate **1307**, control circuit **1305**, and the cartridge will prevent leaks. In one embodiment the gaskets **1313** can be part of the interface **1309**. In an alternative embodiment the gaskets **1313** can be part of the disposable cartridge **1311**.
(76) Depending on the film used, there can be a slight overhang around the perimeter of the valve, channel, or volume. This overhang can be due to adhesive or plastic flow during bonding. To prevent these from affecting the quality of the valve seal, the valve inlet, outlet, or both can be through vias in the valve seat **1317**. The valve seat, away from the perimeter, can be less affected by the overhang.
(77) Because of the limited flexibility of the film, it may be necessary to create a dimple over the valves. This can be achieved by coining the film downwards against the valve, with the limitation that the heat applied must not be enough to bond the film to the valve seat. A preferred approach would be to vacuform the dimples. The ordinary process of heat sealing involves applying a combination of heat and pressure to create a bond. If the heated tool (**1401**) was made from a porous material and had cavities cut above the valves, suction could be applied that can draw the film over the valve into the cavity, creating a dimple. This can occur at the same time as the film was being bonded to the body in other areas.
(78) This embodiment can allow multiple fabrication and material options. For example, PDMS, which is commonly used in microfluidics, could be replaced with such a material, such as the heat seal films. This embodiment also reduces requirement for flatness in pieces, permitting other cartridge materials, such as polypropylene.
(79) The use of the fluidics layer for reagent storage and the use of sections of the enclosing film for shipping as in the embodiment of **601**, and the use of sections of the enclosing film to implement valves as in the embodiment of **701**, permits the cartridge functions to be served by one molded piece and one or more bonded films. Another embodiment, as shown in

FIG. **8**, uses this construction.

V. Clamp-Sealed Cartridges

(80) FIG. **11** shows a section of the cartridge **601**. By using raised lines or areas, e.g., ridges, **1101** to control the bonding of the film, vents can be built into the fluidic layer **905**. These raised areas can provide a localized contact when bonding, controlling which areas are bonded and which areas are not, resulting in defined channels.

(81) To close off the outlets **1109** and vents **1105** to these reagent chambers **1107**, bar clamps **1103** can be built into the shipping container for the cartridge. These bar clamps can have some rigidity, but can be covered by a deformable or other material that can conform to the cartridge surface. It may have a basic shape or be formed to mate with the cartridge surface.

(82) Bar clamp **1103** is able to hold the seal film cover (**907**, not shown in FIG. **11**) against the body or fluidic layer **905**, closing off the defined channels. After shipment but before use, the cartridge is removed from its packaging, which either removes the shipping clamps as the packaging is opened, or the clamps are removed separately from the cartridge after the cartridge is removed from the packaging.

(83) If the flexible bar clamp is U-shaped as shown, it can close each channel in two places to prevent leakage. The operator will then be able to confirm that no leakage has taken place by examining the area between the two seals. Any leakage past both seals will generally leave a residual amount between the two seals.

(84) Before use, the two vias leading to each of the reagent reservoirs are held closed by a shipping clamp. This shipping clamp can apply a uniform force to a flexible pad, causing the pad to deform and hold the valves closed. Alternatively, it can include a number of small rubber contacts that can individually hold each valve closed. This shipping clamp can then be removed before the cartridge is inserted into the system.

VI. Diaphragm Valve with a Bossed Diaphragm

(85) Diaphragm valves also can be actuated mechanically using a ram, e.g., a pin. These can be actuated by a solenoid. If actuated by solenoid, it may be beneficial to add a boss (such as element **1511**) to the outside of the deformable. This permits a ram to push against the boss, creating a centered force sealing the valve, even if the solenoid is not centered over the valve.

VII. Turret Cartridge

(86) Cartridges actuated mainly by a syringe pump or by a manually operated syringe are included in this instant disclosure. The cartridges can be controlled by motors controlled by the computer on the system.

(87) One embodiment of a cartridge utilizes a syringe pump for actuation, with selectable, specialized areas arranged in a ring. These areas can each store reagents, house the swab or punch, contact a temperature regulator, connect to the capillary for separation, etc.

(88) Referring to FIG. **17**, the cartridge can implement a rotary selector valve, either by rotating the cartridge body **1717** or an internal valve. By rotating, various inputs or outputs can be selected. This rotation can be driven by, for example, a stepper motor. The syringe **1709** can in turn be driven by for example, a linear stepper motor. This permits a broad range of general functions to be controlled by two stepper motors. The interface can also make use of one or more temperature regulators. Thermocycling can be implemented by cycling the temperature of a temperature regulator, or by rotating to contact one of multiple controlled heat sources to reduce the power usage and may increase thermocycling speed. It can also have an LED, filter, and photodiode for reaction quantification.

(89) One, two or three positions on the hub can be temperature controlled. One position on the hub can be open on top, for sample insertion. One or more positions can have external, retractable magnets.

(90) Turret cambers can include: (A) Vent: air to injection chamber; (B) Vent: to denature heater; (C) lysis chamber/swab vial; (D) lysis buffer/Waste; (E) mix chamber/beads; (F) water; (G) ethanol; (H) STR lyosphere (amplification reagents); (I) capture solution and size standard (or lyosphere); (J) eluting agent; (K) electrophoresis separation gel; (L) reaction chamber.

(91) Gel injection may be to a booster pump instead of directly to the capillary. This would avoid the need for high-pressure seals, in the sample cartridge (This would permit gel injection in parallel with other functions.) If the capillary can be mounted directly, denature heading may be complete by one of the heated positions, without an external denature heater. An external waste gate, at the cathode end of the capillary may still be necessary.

(92) This embodiment can permit an interface consisting of one rotary and one stepper motor, eliminating pneumatic pumps, manifolds, anode module/gel filling mechanism, etc.

VIII. Lead-In Guiding Fluid Delivery Pogo Pin

(93) FIGS. **18**A and **18**B show a low-dead-volume floating connector **1808** in cross-section. When the interface is open as shown in FIG. **18**A, the pogo is forced down against the home lead-in **1801** by a spring **1802**. This will reset the pin to a consistent home position relative to the pogo block **1803**. When the interface closes onto a cartridge that is off-center, the pogo contacts the engagement lead-in **1804** and is pushed up, freeing the engagement play **1805**. The engagement lead-in then guides the cartridge within this play. Once aligned, the conic surfaces of the pogo pin **1806** and cartridge **1807** connect. The slight taper magnifies the force of the spring, creating a seal. This seal requires some flexibility in the cartridge. Since the surrounding wall thickness is driven by the engagement lead-in, this limits the lead-in size. The engagement lead-in **1804** and the engagement play **1805** will both need to be large enough to accommodate all manufacturing and other tolerance variations. If the pogo pins did not self-reset to a consistent home position, the engagement lead-in can changed to accommodate variations from the engagement play as well.

IX. Vent Tabs

(94) In an embodiment shown in FIG. **12**, the cartridge includes two injection molded plastic parts, a cartridge body and a reagent reservoir. When in use, the reagent reservoir can be pressed against the body. This can snap open the vents, and engage connections between the body and the reservoir.
(95) For cartridge concepts that have bodies **1205** and moveable reagent reservoirs **1201**, such as the cartridge of the embodiment of **701**, there is another approach to providing vents. This approach does not require additional parts. This is to build in designed-to-fail tabs (e.g., **1203**) into the reagent reservoir. Before use, these tabs will remain closed, but will have a slight interference with the cartridge body **1205**. When the reagent reservoir is engaged by pressing, these tabs will try to pull away from the main volume. It will tear or crack, opening a small vent in the reservoir.
(96) This embodiment can provide a vent for on-cartridge reagent reservoirs without requiring additional degree of freedom in the interface or additional part in the cartridge.
X. Fluidic Device with Diaphragm Valve
(97) The cartridge can utilize off-cartridge pumps to move liquids. To avoid the need for high mechanical precision, these valves and channels can be larger than traditional microfluidic valves and channels.
(98) The cartridge of this disclosure can include diaphragm valves. Diaphragm valve can be formed having a valve chamber in the fluidics layer of the cartridge and a deformable membrane attached to a surface of the fluidics layer and providing a diaphragm for opening and closing valve. In one embodiment, the valves are normally open. That is, at ambient pressure the valve is open and closing the valve involves applying positive pressure to the diaphragm opposite the valve seat. Applying negative pressure to the diaphragm opposite the valve seat can further open the valve. The diaphragm can be actuated by pneumatic or mechanical pressure. In an embodiment of this disclosure the diaphragm is mechanically actuated by positive pressure applied by a ram or rod having an end configured for insertion into the valve chamber. In certain embodiments the rod has a compliant end that promotes contact between the diaphragm and a valve seat, thereby sealing the valve closed. Withdrawal of the rod relieves pressure on the diaphragm, thereby opening the valve.
(99) In one embodiment of a normally open valve, a surface of the fluidics layer comprises a recess that both defines a valve chamber and functions as a valve seat. At ambient pressure the deformable membrane does not sit against the valve seat and the valve is in an open configuration. Positive pressure on the deformable membrane from the side opposite the fluidics layer pushes the deformable membrane against the valve seat, closing the valve. The valve seat can take a curved shape that is convex with respect to the surface of the fluidic layer, against which the deformable membrane can conform. For example, the valve shape can be a section of a sphere or an inverted dimple or a dome. Such a configuration decreases the dead volume of the valve, e.g., by not including a valve chamber that contains liquid while the valve is closed. This valve also comprises a surface against which the deformable membrane can conform easily to close the valve. In another embodiment, the concave surface can comprise within it a sub-section having a convex surface, e.g., an inverted dimple comprising an extraverted dimple within it forming, for example, a saddle shape. The convex area rises up to meet the deformable membrane under pressure, creating a better seal for the valve.
(100) Valve seats can be recessed with respect to the rest of the surface by about 25 microns to about 1000 microns, e.g., about 700 microns. Valves can communicate with fluidic channels that are either microfluidic or macrofluidic (e.g., having an aspect less than 500 microns or having an aspect greater than 500 microns or at least 1000 microns). In certain embodiments of a normally open valve, the concavity is recessed less than the channels to which it is connected. In certain embodiments the channels can enter partially into the concavity, for example forming a vault. In certain embodiments, the channels and concavity are formed by micromachining, injection molding or embossing.
XI. Valve Actuated by Ram with Compliant End
(101) One embodiment involves closing a fluidic valve with a ram. The valve can be comprised in substrate that contains the valve and one or more input and output fluidic channels. There can be more than one input and output. These channels can enter the surface of the dome valve at any location on the surface as long as there is a sealing surface between channels. In certain embodiments, channels can enter the valve chamber through vias that connect with the channels. The dome valve is then covered with a membrane either elastic or non-elastic film. The film is affixed to the perimeter of the dome to create an air and liquid tight seal. The ram is then pressed against the film diaphragm with sufficient force to deform the diaphragm and press the film onto the dome surface. The pressure from the ram creates a fluidic seal between the orifices of the ports entering the dome valve.
(102) In one embodiment the valve is configured as a router. The router can have, for example, four inlets/outlets. In this configuration the forked ram, when engaged, can block access to the router by some, but not all, of the inlets/outlets. For example, the forked ram could allow fluid flow through the router in a north-south direction or not it in an East-West direction.
(103) The ram is structured such that there are one or more flexure posts defining an identical dome surface to match the valve dome surface with the offset of the thickness of the diaphragm. The flexure posts with the seal seat tips will be able to self align to the target seal areas of the dome, namely the perimeter of the orifice for the input and output channels of the valve. The flexure posts also concentrate the stress generated by the force applied to the overall post onto the active seal area.
(104) Referring to FIGS. **29** and **30**, a fluid chip body comprises a recess forming a valve seat (“dome valve”). The recess defines a space that functions as a valve chamber. The fluidic chip body also includes fluidic channels (which can be microfluidic channels) in fluid communication with the valve through inlets and outlets. A surface of a fluidic chip body into which the recesses impose is overlaid with a deformable membrane (“elastic film”). A ram actuates the valve by applying pressure to deformable membrane. The ram can include a fork or slotted end that provides compliance to the

flexure posts tines of the fork. An end of the ram has a form that complies with the shape of the valve seat. Referring to FIG. **31**, when pressed against the deformable membrane, the ram deforms the deformable membrane against the valve seat. By contacting the valve seat around the valve inlet and valve outlet, the diaphragm closes the valve, preventing fluid flow through the valve. Relieving pressure on the diaphragm by withdrawing the ram allows the deformable membrane to assume its neutral position, opening the valve to fluid flow. The ram can be actuated, for example, by a solenoid.

XII. Reaction Chamber

(105) In one embodiment a fluidic device of this disclosure comprises a reaction chamber that comprises a solid substrate, e.g., solid phase extraction material, for retaining analyte from the sample. The solid substrate can comprise a material that binds the analyte, such as a nucleic acid such as DNA. The amount of solid substrate in a chamber and the selected to retain the predefined amount of analyte. For example, the material can be a Whatman FTA paper or a carboxylated material. Alternatively, the solid substrate can be an absorbent or sponge-like material that absorbs a predetermined volume of fluid. The material can be in the form of a monolith. The material can be, for example, PVDF (polyvinyldiene fluoride) membranes, filter paper, glass particles, silica, or other solid phase extraction material. In operation, lysate is pumped through the chamber and a predetermined amount of analyte is retained on a solid substrate. Then, retained material is contacted with reagents, e.g., reagents for PCR. The resulting material can be incubated to form a reaction product. For example, the chamber can be put into thermal contact with a thermal-control device, such as a Peltier, and the reaction mixture can be thermal cycled. In another embodiment, the chamber can include a pocket or container designed to retain the defined volume of liquid.

XIII. Contaminant Deactivation

(106) In one embodiment the fluidic layer includes a waste chamber. A waste chamber can contain material that degrades nucleic acids, polypeptides, or other analytes. For example a material can comprise a chlorinated material, such as calcium hypochlorite. Alternatively, the waste chamber can include in absorbent material that absorbs waste containing liquid

(107) In another embodiment the nucleic acid degrading material is contained in a water-soluble capsules in yet another embodiment the nucleic acid degrading material is combined with an absorbent material such as cellulose or polypropylene fibers.

(108) In another embodiment, the waste chamber contains enzymes that degrade the nucleic acids (e.g., nucleases), polypeptides (e.g., proteases), or other analytes such as phosphorylated sites (e.g., phosphatases).

XIV. Cartridge and Method

(109) FIGS. **21** and **22** shows a fluidic cartridge configured for extracting nucleic acid from a sample, performing amplification on the sample, and outputting the amplification product. The cartridge includes a port configured to accept a sample container adapted to receive a sample, such as a swab; a port configured to accept a syringe pump containing or connected to reagents, such a lysis solution; a port configured to accept receptacles separately carrying PCR master mix and PCR primers; a reaction chamber, e.g., for thermal cycling; a waste chamber; a vent; an output port; fluidic channels (which can be microfluidic or microfluidic channels) in communication with these elements; valves for regulating flow of fluids in the fluidics circuit all of the cartridge. The valves can be, for example, diaphragm valves.

(110) FIG. **23** shows the operation of a cartridge. Closed valves are indicated in darker shade, open valves are indicated in lighter shade. Arrows indicate the flow of liquids which are moved by the syringe. Lysis solution from the syringe is moved through a fluidic channel into the container containing a sample. The sample can be heated or sonicated to facilitate cell lysis. In FIG. **24** lysate is pulled back into the syringe and nucleic acid is captured on a solid phase in the reaction chamber. In FIG. **25** lysis solution is transported into the waste chamber. In FIG. **26** PCR master mix and primers, which can be contained in separate containers, are moved into the reaction chamber, for example pushing the liquid from one side as the syringe provides vacuum from another side. In FIG. **27**, the reaction chamber is subjected to thermal cycling to amplify target sequences, for example, STR sequences, while all the valves are closed. In FIG. **28** the amplification product is moved to an output port where it can be transferred for further analysis.

XV. Integrated System

(111) The cartridges of this disclosure are useful in integrated and automated sample-to-answer systems that, starting from a sample comprising biological material, generate an analysis of the sample. In certain embodiments, the biological material is DNA and the genetic profile involves determining one or a plurality of alleles at one or a plurality of loci (e.g., genetic loci) of a subject, for example, a STR (short tandem repeat) profile, for example as used in the CODIS system. The system can perform several operations, including (a) extraction and isolation of nucleic acid; (b) amplification of nucleotide sequences at selected loci (e.g., genetic loci); and (c) detection and analysis of amplification product. These operations can be carried out in a system that comprises several integrated modules, including an analyte preparation module; a detection and analysis module and a control module.

(112) Systems provided herein may be fully integrated. Sample processing can be accomplished in a single system without having to remove a sample and transfer it to another system. Systems provided herein can be fully automated, enabling a user to process a sample without substantial input from the user.

(113) A sample preparation module includes a cartridge module assembly configured to engage and operate one or more than one sample cartridge. A sample cartridge is configured to receive one or more samples and to perform nucleic acid extraction and isolation, and DNA amplification when the cartridge is engaged with a cartridge module assembly in the system. It can also include controls and standards for assisting in analysis. In other embodiments, a sample cartridge is configured to receive one or more samples and to perform cell lysis, and enzymatic assays when the cartridge is engaged with a cartridge module assembly in the system.

(114) The sample preparation module can include a receptacle for receiving one or more cartridges, an engagement assembly to engage the cartridge; a fluidic manifold configured to engage ports in a cartridge and to deliver pressure and/or fluids to the cartridge through the ports; a delivery assembly configured to deliver reagents, such as amplification pre-mix, from a compartment in the sample cartridge to an amplification compartment; a pneumatic manifold configured to engage ports in a cartridge and to deliver positive or negative pressure to the cartridge through the ports for moving fluids and operating valves, pumps and routers in the cartridge; a pump configured to deliver pressure to the fluidic and pneumatic manifold. Consumable reagents can be carried in a module, e.g., a buffer module, that is, removably engageable with the cartridge module.
(115) PCR can be carried out using a thermal cycler assembly. This assembly can include thermal controller, such as a Peltier device, infrared radiation source, resistive heating element, circulating water or other fluids, circulating air, movement of constant temperature blocks, or other material, which can be configured to heat and cool for thermal cycling and can be comprised in the cartridge module which can be configured to move the thermal controller into thermal contact with the thermal cycling chambers, for example, through a heat spreader (or thermoconductor that can spread/distribute heat and cooling) disposed over each of the reaction chambers. In some embodiments, the cartridge comprises a temperature regulator assembly having one or more (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10, 16, 24, 32, 40, 48 or more) thermocycling chambers and the sample cartridge can be in fluid communication with a fluidic channel.
(116) An analysis and detection module is configured to receive analyte from the sample preparation module and perform capillary electrophoresis on the analyte to detect analytes separated by electrophoresis and to analyze the detected analytes. It can include a capillary electrophoresis assembly, a detection assembly, and an analysis assembly.
(117) The capillary electrophoresis assembly can include an injection assembly, that can include a denature heater assembly, a positioning assembly for positioning an analyte for capillary injection; a cathode assembly; a capillary assembly; an anode assembly; a capillary filling assembly for filling a capillary with separation medium and a power source for applying a voltage between the anode and the cathode.
(118) A detection assembly can comprise a laser configured to illuminate the capillaries and a detector. The laser can be configured to excite fluorescent dyes in the analyte. In alternative embodiments, the laser can be replaced by an alternate light source such as an LED. The detector can include a CCD array, photomultiplier, diode array, or other detector, for detecting light produced by excited dyes and for producing an output signal.
(119) An analysis assembly can include a computer comprising memory and a processor for executing code (e.g., code on a tangible medium) for analyzing the output signal and producing a computer file containing an analysis of the signal. Such an analysis can include, for example, identification of alleles from various STR loci. The computer file can be in a format that is compatible with public databases. For example, the file can be in CODIS format which is compatible with the National DNA Index System (NDIS) operated by the FBI.
(120) The system can be operated by a control module. The control module can include a user interface configured to receive instructions from and deliver information to a user. It can include software programmed to execute routines for performing the operations mentioned, above, and transmit and receive information, such as computer files, from remote locations, for example, over the internet.
XVI. Method of Use
(121) The cartridges of this disclosure can be used in an integrated system for preparing a sample, for example, DNA isolation and amplification. For example, in one embodiment, a sample contained on for example a swab or a card punch, can be introduced into sample chamber **207**. The chamber can be snapped shut by the lid **211**. The cartridge can be engaged with cartridge interface **103**. Cell lysis buffer contained in an on-system reservoir can be feed through line **405** through interface assembly **401** into the fluidic channel in the cartridge and into the sample chamber **207**. After lysis, lysate can be moved through a fluidic channel on the chip, for example, which pumps the fluid into a reaction chamber **301**. In one embodiment, the DNA reaction chamber can include magnetically attractable particles that bind DNA and that can be immobilized in the reaction chamber by applying a magnetic force generated in the interface. This can eliminate the need for an intermediate DNA isolation chamber. Waste fluid can be moved through the cartridge and out through a vent. Reagents for performing PCR or other reactions can introduced into the reaction chamber through one of the fluid lines **405** connected to the interface. A thermal control mechanism in the system can apply heat to perform thermal cycling in a thermal cycling chamber **301** of the cartridge. In some embodiments the heat is applied to a heat transmission element, for example, a foil or metalized film, that improves thermal contact and transmission.
(122) The cartridges of this disclosure can be used in an integrated system for analyzing a sample, for example, DNA isolation and amplification with real time or end point detection. For real time measurement, the samples can be interrogated by an optical detection system while amplifying in reaction chamber **301**. The readout can be the change in fluorescence or by melting point. The probes can be human specific for human identification, forensics, or molecular diagnostic applications, or specific for pathogens for molecular diagnostic applications, or for bioagents for biodefense applications or nonspecific intercalators for determining amount of DNA present. Amplification methods include, for example, thermal or isothermal amplification reactions, for example, PCR, rolling circle amplification, whole genome amplification, nucleic acid sequence-based amplification, and single strand displacement amplification, single primer isothermal linear amplification (SPIA), loop-mediated isothermal amplification, ligation-mediated rolling circle amplification and the like
(123) The cartridges of this disclosure can be used in an integrated system for analyzing a sample. The assay can detect a polypeptide (e.g., immunoassay) or a nucleic acid (e.g., PCR). The assay can be multiplex or single analyte. They can

involve any assay to measure presence, amount, activity, or other characteristics of the sample. These include assays that involve detection by fluorescence, luminescence, chemiluminescence, Raman, absorbance, reflectance, transmittance, birefringence, refractive index, colorimetric and combinations thereof. In this instant disclosure, the enzyme master mix and the substrate might be individually added to the reaction and the progress or endpoint of the assay monitored optically.
(124) For STR applications, after thermal cycling, other reagents such as molecular weight markers (size standards) can be combined with the PCR product. Movement through the cartridge can be controlled when diaphragm valve **303** is actuated by pneumatic or mechanical actuators wherein forces transmitted through line **407**. Products of the PCR can be moved off chip for analysis through an output line.
(125) While preferred claims of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such claims are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the claims of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

Claims

1. A system, comprising: a cartridge and a cartridge interface configured to receive the cartridge, the cartridge comprising: a cartridge body having a valve seat recessed into a surface of the cartridge body; and a deformable laminate thermally bonded to the surface of the cartridge body and covering the valve seat, the deformable laminate and valve seat forming a diaphragm valve, wherein the deformable laminate comprises: a first side facing away from the cartridge body and comprising a first material, a second side comprising a second material and thermally bonded to the surface of the cartridge body, the first material having a higher melting temperature than the second material so as to permit the second material to thermally bond with the surface of the cartridge body upon application of heat before the first material reaches the melting temperature of the first material, and one or more ports; and the cartridge interface comprising: a manifold configured to supply positive pneumatic pressure or negative pneumatic pressure to at least a portion of the deformable laminate covering the valve seat so as to open or close the diaphragm valve, wherein the cartridge interface is configured to supply fluidic flow through the one or more ports of the deformable laminate.
2. A method of operating the system of claim 1, the method comprising: engaging the cartridge with the cartridge interface; and supplying positive pneumatic pressure or negative pneumatic pressure to at least a portion of the deformable laminate covering the valve seat.
3. A cartridge comprising: a cartridge body having a valve seat recessed into a surface of the cartridge body; and a deformable laminate thermally bonded to the surface of the cartridge body and covering the valve seat, wherein the deformable laminate comprises a first side facing away from the cartridge body and comprising a first material, and a second side comprising a second material and thermally bonded to the surface of the cartridge body, the first material having a higher melting temperature than the second material so as to permit the second material to thermally bond with the surface of the cartridge body before the first material reaches the melting temperature of the first material, wherein: the deformable laminate and valve seat form a diaphragm valve configured to open or close in response to pneumatic pressure applied to the deformable laminate, and the deformable laminate comprises one or more ports configured to allow passage of fluid.
4. The cartridge of claim 3, wherein the deformable laminate comprises a film of the first material coated with the second material.
5. The cartridge of claim 3, wherein the deformable laminate does not comprise an elastomeric material.
6. The cartridge of claim 3, wherein the deformable laminate is structurally configured for plastic deformation.
7. The cartridge of claim 3, wherein at least one portion of the deformable laminate comprises a permanent deformation.
8. The cartridge of claim 3, wherein the valve seat has a curved shape that is concave with respect to the surface.
9. The cartridge of claim 3, further comprising a valve inlet and a valve outlet on opposing sides of the valve seat and a fluid channel in fluidic communication with the valve inlet and the valve outlet.
10. The cartridge of claim 9, further comprising a reaction chamber in fluidic communication with the fluid channel.
11. A method comprising: engaging the cartridge of claim 3 with a cartridge interface configured to supply positive pneumatic pressure or negative pneumatic pressure to at least a portion of the deformable laminate covering the valve seat.
12. The method of claim 11, further comprising supplying the positive pneumatic pressure or the negative pneumatic pressure to at least a portion of the deformable laminate covering the valve seat, thereby actuating the deformable laminate into or out of contact with the valve seat.