Lab on a Chip

An Outlook on Microfluidics: The Promise and The Challenge

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An Outlook on Microfluidics: The Promise and The Challenge

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1. Abstract

This perspective considers ways in which the field of microfluidics can increase its impact by improving existing technologies and enabling new functionalities. We highlight applications where microfluidics has made or can make important contributions, including diagnostics, food safety, and the production of materials. The success of microfluidics assumes several forms, including fundamental innovations in fluid mechanics that enable the precise manipulation of fluids at small scales and the development of portable microfluidic chips for commercial purposes. We identify outstanding technical challenges whose resolution could increase the accessibility of microfluidics to users with both scientific and non-technical backgrounds. They include the simplification of procedures for sample preparation, the identification of materials for the production of microfluidic devices in both laboratory and commercial settings, and the replacement of auxiliary equipment with automated components for the operation of microfluidic devices.

2. Introduction

Our understanding of microfluidics—how fluid flows behave and how they can be controlled at the micron scale—has developed rapidly since the establishment of the field [1]. Such progress has enabled successful applications of microfluidics in fields like biotechnology,

healthcare, and materials science. Individual components in samples can often be isolated and analyzed separately, and reactive fluid streams can be precisely mixed to synthesize materials with specific shapes or compositions. For instance, microfluidics is an essential tool in next-generation genomic sequencing platforms [2, 3, 4, 5]. It is an integral component of common diagnostic tests, such as pregnancy tests, urine dipsticks, and strips for monitoring blood glucose levels [6, 7, 8]. In single-cell analysis, it enables miniaturized assays to be performed in picolitre-sized droplets that are produced through high-throughput processes and that contain individual cells [9, 10, 11, 12]. The assays can probe the response of cells to exogenous factors, such as antigens, environmental stressors, or other biomolecules [9, 10, 12]. They can also be designed for single-cell sequencing by assigning tags, or barcodes, to the genomic information of individual cells prior to sequencing [13, 14, 15, 16]. Microfluidics can be used for the formulation of materials [17]: for example, it is employed in the synthesis of lipid nanoparticles for drug delivery [18, 19, 20, 21, 22] and the production of microparticles in cosmetic products [23, 24]. We summarize these applications in **Table 1**.

The future holds exciting opportunities both to pursue fundamental research on microfluidics, and to work on commercial applications of microfluidics. Advances in our understanding of flows at the micron scale have largely enabled current applications. Microfluidics is particularly well-matched to applications that require the precise control or manipulation of fluids, either at small length scales or in small quantities, as highlighted in **Table 2**. Microfluidics has already proven to be successful in the realms of point-of-care diagnostics and the production of materials. Nonetheless, we believe that these areas have yet to be fully explored. Additionally, applications such as food safety would benefit from or perhaps require new types of microfluidic devices to sample and identify the composition of products. An awareness of commercial

applications and technical challenges associated therewith can guide future research. Microfluidic devices can be developed as freestanding technologies, or as part of systems that include non-microfluidic components. Fabrication methods that are commonly used for research and development, including soft lithography and glass microcapillaries [25, 26, 27], have enabled rapid progress of a technical, academic sort; however, the transition to the production of devices with commercial materials remains difficult. Moreover, systems that use microfluidic devices often require skilled operators, external equipment, and tedious sample preparation procedures. Innovations in fluid handling, automation, and sample preparation will result in microfluidic devices that are increasingly simple to use, yet even more functional.

2. Promising Areas of Application

2.1. Diagnostics

Microfluidics has had success in biomedical diagnostics, although the microfluidic components may be concealed in complex systems of other types. As the field continues to grow, new capabilities will be achieved. Microfluidic technologies will be used for refined diagnosis of disease by characterization through sequencing and single-cell analysis [28]. Genetic information can perhaps reveal the response of patients to potential medications [28, 29, 30]. The susceptibility of bacteria to combinations of antibiotics can guide treatment [31]. Pathogens, such as bacteria and viruses [9], or biomarkers, including extracellular vesicles [32] and circulating tumor cells [33], can be identified with a high degree of specificity. The ability to identify rare bacteria directly from blood would circumvent time-intensive bacterial culture procedures and would enable earlier diagnosis of sepsis [34, 31]. Challenges that remain in all of these applications include design of devices, scale-up of device production, and cost of tests.

There are many successful applications of microfluidics in rapid, point-of-care diagnostics, including pregnancy tests, tests for sexually transmitted diseases, and test strips for monitoring blood glucose [6, 7, 8, 35]. These tests are portable, affordable, easy-to-use, and can be deployed at scale; therefore, they would be suitable for tracking the spread of infectious diseases such as COVID-19 [36], tuberculosis [37], and sexually transmitted infections like HIV, syphilis, and chlamydia trachomatis [35]. We believe that future research efforts should focus on expanding the range of diseases that can be diagnosed, reducing the cost of tests, and increasing their specificity. For example, microfluidic devices made from paper are simple to produce by patterning hydrophobic and hydrophilic regions on paper to guide the flow of aqueous fluids [38], and can be incinerated for safe disposal. Test zones can be impregnated with reagents that yield visible color changes based on the concentration of physiologically relevant compounds in blood or urine [38]. In low- and middle-income countries (LMICs), there is a pressing need for tests of this kind given that a large proportion of the diseases that affect life expectancy cannot be diagnosed by tests offered in most primary healthcare clinics [39, 40]. The costs of regulatory approval, however, are prohibitive and limit the profitability of simple microfluidic diagnostic tests. Accordingly, the widespread deployment of such tests, especially in LMICs, presents a real challenge.

2.2. Therapeutics

Microfluidics can serve as a tool in the development of therapeutics [12]. For example, candidate antibodies for therapeutics can be screened [41]. In principle, the human gut microbiome can be profiled to formulate treatments for inflammatory bowel disease [42]. The toxicity and effectiveness of drugs can be assessed with organs-on-chips [43]. Lipid

nanoparticles can be formulated using microfluidic devices [18, 19, 20, 21, 22]. Thus, microfluidics provides countless opportunities for therapeutic discovery and validation.

2.3. Food and Consumer Product Safety

Can microfluidics be used in grocery stores? Microfluidics can be utilized as a tool in the quality control of food, agricultural, and consumer products [44]. In the food domain, for instance, it is essential to prevent food from being: (i) contaminated with pathogenic bacteria such as *E. coli*, (ii) improperly stored, (iii) deliberately adulterated as in the case of contamination of baby formula with melamine, or (iv) mislabelled [45, 46, 47, 48]. Prototypes of microfluidic devices have been developed to detect foodborne pathogenic bacteria; these range from microneedle arrays to smart packaging [49, 50, 51, 52, 48]. Economical and simple microfluidic tests for screening or genomic sequencing at the point of sale or consumption would improve food safety by, for instance, enabling the identification of mislabelled seafood products [46, 45] or genetically-modified organisms [49]. The variability of food also presents an important challenge in the application of microfluidic technologies because sample preparation varies significantly. Indeed, understanding how food should be sampled to obtain a complete and representative description of its composition is an exciting research opportunity.

2.4. Production of Materials

Microfluidic devices can be used to produce materials and chemicals because the flow rate and composition of reactive fluid streams can be precisely controlled. This control of flow is especially advantageous because materials can be generated continuously. Multiple emulsions can be used to make droplets or core-shell particles containing special contents, such as active pharmaceutical agents or cosmetic compounds [26, 27], and *in situ* polymerization can enable the synthesis of particles with specific shapes or compositions [53, 54]. Particles have a

multitude of applications, ranging from personal care [23] to drug delivery [18, 19, 20, 21, 22]. These applications will surely expand given the value added to products by encapsulation and the ability to make materials with reproducible sizes and desired compositions.

In microfluidic platforms, heat exchange, mass transfer, and mixing can be controlled precisely for chemical synthesis. Reactions occur on small scales and at low volumes [55]. Chemical reactants can reach target temperatures in shorter times than in macroscale reactors, and sub-millisecond mixing times can be achieved [55, 56]. Safety can be improved due to a reduction in both manual processing steps and the volume of reacting chemicals, and portability can be achieved [57, 58]. Continuous flow platforms can be used to make or consume active pharmaceutical ingredients [58] or to produce toxic or explosive chemicals—like isocyanates, cyanides, peroxides, and azides—on-demand [57]. The application of microfluidics for synthesis will expand given the ease of customizing products for desired applications. Factors to consider in developing microfluidic reactors include the resistance of devices to chemical degradation and the time needed to establish desired reaction conditions as it relates to the reaction kinetics [57, 55].

3. Technical Challenges

3.1. Materials for the Scale-up of Microfluidic Device Fabrication

Currently, most academic laboratories produce microfluidic devices from polydimethylsiloxane using soft lithography [25, 59]. Polydimethylsiloxane (PDMS) has many appealing features: it is optically transparent, which allows samples to be imaged through a device; its surface can be treated and sealed; it is compliant, which enables its easy removal from molds and its conformal contact with or adhesion to other surfaces; it is permeable to many gases

and some liquid vapors, which can be advantageous when establishing an oxygen-rich environment for cell growth, but not ideal when it is important to limit the evaporation of water from aqueous solutions [60, 61]. Despite these qualities, its processing is time-intensive [61]. It is difficult to seal [62]. It swells in the presence of many non-polar organic solvents, which limits the hydrophobic chemicals that can be used in conjunction with it [63]. It selectively extracts hydrophobic molecules from aqueous streams in contact with it [61, 63, 64], and its surface treatment is difficult to maintain [61]. Given these shortcomings, the identification of affordable materials and processes that are amenable to easy and inexpensive use in both research and industrial settings presents a significant challenge in the scale-up of the production of microfluidic devices. This challenge and others are summarized in **Table 3**.

Materials are needed that are affordable and simple to process in small numbers for laboratory experiments, and yet can be produced economically at large scale for commercial use. They should exhibit broad solvent compatibility and form durable seals to avoid leakages. They should be amenable to the creation of ports for tubing and to surface functionalization because interfacial properties strongly influence flow behavior when more than one type of fluid is used. To realize this approach with a single material, that material would have to be amenable to multiple processing methods that could be executed both at the benchtop and in industrial-scale plants, such as rapid prototyping and injection molding [65]. Alternatively, a two-step process could be considered, wherein one material would be appropriate for research and another for commercial production, and protocols could be established to transition between the two materials. Either approach would simplify the transfer of devices created in academic or research laboratories to industrial-scale production intended for mass markets.

Microfluidic devices can be cast from thermoplastics [66], including polystyrene [61], polycarbonate [67], and cyclic olefin copolymer [68], silicon, or glass [66, 17]. Technologies such as hot embossing [69], laser cutting [70], wax printing for paper-based devices [71, 38], and 3D printing [72] have been tested with variable results. Future work should center on identifying materials in combination with processing techniques that meet dimension, solvent, and bonding requirements for desired applications.

3.2. Operation of Microfluidic Devices and Sample Processing

Many microfluidic devices rely on external equipment. This equipment—fluid pumps, compressed gas lines, microscopes, computers, or electrical supply outlets—can be integral to the operation of devices. By replacing equipment with smaller components, perhaps even their equivalent in microfluidic form, that can be integrated into machines with simple user interfaces, microfluidic devices could be made more accessible, affordable, and scalable. These analogs should be compatible with industry-standard manufacturing procedures, such as injection moulding or embossing [73], and should not contribute appreciably to the cost of devices. Moreover, the machine automation of tasks may be preferable to manual intervention, especially if labor is costly, its availability limited, and its involvement in the operation of devices encumbering [73]. This automation would reduce the requirement for trained operators and make devices more accessible.

Prior to loading samples into devices, they often must be prepped using auxiliary equipment, such as vacuum lines, centrifuges, filters, or mass balances. In some cases, procedures are well-defined, and the required sample volume is predetermined. In other cases, samples may need to be macerated, diluted, filtered, centrifuged [49], and/or incubated, and the appropriate quantity and method of sample collection remains ill-defined. In either case, current sample preparation

procedures take time, involve expensive infrastructure and/or necessitate manual intervention. In practice, these requirements restrict the applications of microfluidic technologies; factors like the availability and cost of skilled technicians or specialty equipment become critical. For instance, the preparation of sputum, a highly viscous specimen used to diagnose respiratory disease, for analysis requires trained technicians and external equipment, including vortex mixers, centrifuges, and strainers; thus, the development of power-free microfluidic chips for sputum liquefaction could prove invaluable in LMICs [74]. The accessibility of microfluidics would also be improved by simplifying sample preparation through, for example, the design of microfluidic chips that accomplish basic operations associated with sample preparation. Moreover, researchers should determine operations in sample preparation that are generic, or applicable to multiple applications.

3.3. Programmability of Microfluidic Chips

Microfluidic chips are distinct from microelectronic processors: the former cannot be programmed, and their design is often specific to an application. Researchers have tried to change this paradigm and produce programmable microfluidic chips; however, progress has been slow and widespread commercial adoption has been hampered by issues with reliability, generalizability, and costs [75, 76]. Instead, the immediate practical challenge is the integration of discrete microfluidic chips, each of which performs a specific function, into a single system. Each component works reliably on its own, but has unique flow requirements, geometric features, and actuation modes [77], which makes it difficult to connect to other components which have different and sometimes incompatible specifications. Improvements should be made in the design of component chips to make them compatible with larger scale systems.

4. Conclusion

As technical challenges are resolved and applications are identified, microfluidic technologies will serve new functions. The identification of materials for the commercial production of devices and the simplification of procedures for the preparation of samples would enable chips to be developed more efficiently. Advances in fluid handling would lead to the elimination of auxiliary equipment and to improved integration of separate microfluidics chips. The accessibility of microfluidics would be improved by the development of affordable and commercially viable:

- Materials with broad solvent compatibility that can be translated from use in research and development to commercial production;
- Methods for moving fluids that do not require external pumps;
- Microfluidic chips that accomplish specific sample preparations, such as pre-concentration, purification, and crude separation.

We believe that simpler and more adaptable microfluidic technologies would be well-suited for applications in diagnostics, food safety, and the production of materials and chemicals. Ultimately, we envision a future in which microfluidic devices can be used in doctors' offices to run diagnostic tests, in the lab to discover therapeutics, in the grocery store or at home to verify the composition and safety of food, and in manufacturing facilities to fabricate industrial materials. It is our hope that microfluidics will become a technology upon which we can all rely.

Conflicts of Interest

There are no conflicts of interest to declare.

Table 1. Successful implementations of microfluidics

	Areas	***Current examples***
probe small samples	*Single-cell profiling*	*Single-cell analysis* [9]*; next-generation, high-throughput genomic sequencing* [13, 14, 2, 4, 5, 3]
	Bioassays	*Pregnancy tests; test strips for monitoring blood glucose; urine test strips* [6, 7, 8]
make materials or products	*Materials production*	*Production of cosmetics* [23]*, lipid nanoparticles for drug delivery* [18, 19, 20, 21, 22]
	Printing	*Flow through nozzles or mechanics of droplet formation in droplet-based (3D) printing applications* [78]

Table 2. Promising areas of application of microfluidics

Applications	***Examples***	***Selected commercial ventures***
Diagnostics	▪ *Time-sensitive diagnostic testing (e.g., sepsis* [34, 79]*, infectious diseases especially during pandemics* [36, 37, 35]*)* ▪ *Antibiotic susceptibility testing* [31, 80, 81] ▪ *Essential diagnostic tests for low- and middle-income countries* [82, 39, 6] ▪ *Liquid biopsies for detection of rare biological species* [32] ▪ *Genomic screening for testing efficacy of prescribed medicines* [28, 29, 30]	*Abbott (i-STAT)*[1] *OPKO (Claros1)*[2] *Cepheid (GeneXpert)*[3] *Pattern Biosciences*[4] *Lucira Health*[5] *Cytovale*[6] *GRAIL*[7]
Therapeutics	▪ *Organ-on-a-chip for screening of therapeutics and their toxicities* [43] ▪ *Antibody discovery* [41] ▪ *Profiling the human gut microbiome for discovery of markers of inflammatory bowel disease* [42] *and other autoimmune diseases* ▪ *Lipid nanoparticles* [18, 19, 20, 21, 22]	*Emulate Bio*[8] *HiFiBiO Therapeutics*[9] *AbCellera Biologics*[10] *Acuitas Therapeutics*[11]
Food and consumer product safety	▪ *Detection of mislabelled/misrepresented foods* [46] ▪ *Identification of foodborne bacteria* [49, 83]	*Agilent (2100 Bioanalyzer)*[12]
Production and formulation of materials	▪ *Synthesis of core-shell particles* [26, 27] ▪ *Production of 'designer' particles with controlled shapes and compositions* [53, 54] ▪ *Production of active pharmaceutical ingredients* [58] ▪ *Continuous flow synthesis of toxic chemicals* [57] ▪ *Authenticity of perfumes*	*Precision Nanosystems*[13] *Capsum*[14]

[1] https://www.pointofcare.abbott/us/en/offerings/istat
[2] https://www.opko.com/what-we-do/our-technology
[3] https://www.cepheid.com/en_US/systems
[4] https://pattern.bio
[5] http://lucirahealth.com
[6] https://cytovale.com
[7] https://grail.com
[8] https://www.emulatebio.com
[9] https://hifibio.com
[10] https://www.abcellera.com
[11] https://acuitastx.com
[12] https://www.agilent.com/en/product/automated-electrophoresis/bioanalyzer-systems/bioanalyzer-instrument/2100-bioanalyzer-instrument-228250
[13] https://www.precisionnanosystems.com
[14] http://capsum.net/en/

Table 3. Technical challenges in microfluidics

Challenge	***Related issues***	***Possible solutions***
Materials for the scale-up of microfluidic device fabrication	*Selection of materials with broad solvent compatibility for large-scale production of devices; functionalization of the surface of devices; increased bonding strength to improve sealing*	*Polystyrene* [61], *polycarbonate* [67], *cyclic olefin copolymer* [68], *silicon and glass* [66]
Operation of microfluidic devices and sample processing	*Reliance on external equipment and trained users for operation of microfluidic chips; difficulty of sample preparation*	*Capillary wicking* [38]*; passive fluid pumping* [84]*; universal sample preparation with centrifugal microfluidic chips* [85]
Programmability of chips	*Lack of universal or programmable microfluidic chips; difficulty of integrating separate microfluidic chips that each perform different functions*	*LEGO-like microfluidic devices* [86]*; programmable valve arrays in microfluidic cells* [87, 88, 89]*; digital microfluidic chips* [90, 91]

References

[1] H. A. Stone, A. D. Stroock and A. Adjari, *Annu. Rev. Fluid Mech.*, 2004, **36**, 381-411.

[2] M.-J. R. Shen, R. C. Kain, K. M. Kuhn, A. H. Talasaz, A. Jamshidi, G. Sakaldasis, E. Vermaas, S. Bohm, T. Khurana, H. A. Eltoukhy and J. Gong, 16 May 2013, International Patent WO 2013/070627 A2.

[3] B. Hindson, S. Saxonov and M. Schnall-Levin, 21 August 2018, United States of America Patent 10,053,723 B2.

[4] B. Hindson, S. Saxonov, P. Hardenbol, C. Hindson, D. Masquelier, M. Jarosz and M. Schnall-Levin, 9 May 2017, United States of America Patent 9,644,204 B2.

[5] M. S. Bowen, K. L. Gunderson, S. Lin, M. C. R. Baciagalupo, K. Vijayan, Y.-S. Wu, B. M. Venkatesan, J. Tsay, J. M. Beierle, L. Berti and S. R. Park, 15 July 2014, United States of America Patent 8,778,849 B2.

[6] P. Yager, T. Edwards, E. Fu, K. Helton, K. Nelson, M. R. Tam and B. H. Weigl, *Nature,* 2006, **442**, 412-418.

[7] M. M. Gong and D. Sinton, *Chem. Rev.,* 2017, **117**, 8447-8480.

[8] A. K. Yetisen, M. S. Akram and C. R. Lowe, *Lab Chip,* 2013, **13**, 2210-2251.

[9] M. T. Guo, A. Rotem, J. A. Heyman and D. A. Weitz, *Lab Chip,* 2012, **12**, 2146-2155.

[10] T. S. Kaminski, O. Scheler and P. Garstecki, *Lab Chip,* 2016, **16**, 2168-2187.

[11] I. Barbulovic-Nad, H. Yang, P. S. Park and A. R. Wheeler, *Lab Chip,* 2008, **8**, 519-526.

[12] P. S. Dittrich and A. Manz, *Nat. Rev. Drug Discov.,* 2006, **5**, 210-218.

[13] R. Zilionis, J. Nainys, A. Veres, V. Savova, D. Zemmour, A. M. Klein and L. Mazutis, *Nat. Protoc.,* 2017, **12**, 44-73.

[14] F. Lan, B. Demaree, N. Ahmed and A. R. Abate, *Nat. Biotechnol.,* 2017, **35**, 640-646.

[15] E. Z. Macosko, A. Basu, R. Satija, J. Nemesh, K. Shekhar, M. Goldman, I. Tirosh, A. R. Bialas, N. Kamitaki, E. M. Martersteck, J. J. Trombetta, D. A. Weitz, J. R. Sanes, A. K. Shalek and A. Regev, *Cell,* 2015, **161**, 1202-1214.

[16] A. M. Klein, L. Mazutis, I. Akartuna, N. Tallapragada, A. Veres, V. Li, L. Peshkin, D. A. Weitz and M. W. Kirschner, *Cell,* 2015, **161**, 1187-1201.

[17] X. Hou, Y. S. Zhang, G. Trujillo-de Santiago, M. M. Alvarex, J. Ribas, S. J. Jonas, P. S. Weiss, A. M. Andrews, J. Aizenberg and A. Kademhosseini, *Nat. Rev. Mater.,* 2017, **2**, 17016.

[18] R. Cross, *Chem. Eng. News,* 2021, **99**, 16-19.

[19] A. Jahn, W. N. Vreeland, M. Gaitan and L. E. Locascio, *JACS,* 2004, **126**, 2674-2675.

[20] R. Karnik, F. Gu, P. Basto, C. Cannizzaro, L. Dean, W. Kyei-Manu, R. Langer and O. C. Farokhzad, *Nano Lett.,* 2008, **8**, 2906-2912.

[21] N. M. Belliveau, J. Huft, P. J. C. Lin, S. Chen, A. K. K. Leung, T. J. Leaver, A. W. Wild, J. B. Lee, R. J. Taylor, Y. K. Tam, C. L. Hansen and P. R. Cullis, *Mol. Ther. Nucleic Acids,* 2012, **1**, e37.

[22] S. J. Shepherd, C. C. Warzecha, S. Yadavali, R. El-Mayta, M.-G. Alameh, L. Wang, D. Weissman, J. M. Wilson, D. Issadore and M. J. Mitchell, *Nano Lett.,* 2021, **21**, 5671-5680.

[23] M.-H. Lee, S.-G. Oh, S.-K. Moon and S.-Y. Bae, *J. Colloid Interface Sci.,* 2001, **240**, 83-89.

[24] R. K. Shah, H. C. Shum, A. C. Rowat, D. Lee, J. J. Agresti, A. S. Utada, L.-Y. Chu, J.-W. Kim, A. Fernandez-Nieves, C. J. Martinez and D. A. Weitz, *Mater. Today,* 2008, **11**, 18-27.
[25] Y. Xia and G. M. Whitesides, *Annu. Rev. Mater. Sci.,* 1998, **28**, 153-184.
[26] L.-Y. Chu, A. S. Utada, R. K. Shah, J.-W. Kim and D. A. Weitz, *Angew. Chem. Int. Ed.,* 2007, **46**, 8970-8974.
[27] A. S. Utada, E. Lorenceau, D. R. Link, P. D. Kaplan, H. A. Stone and D. A. Weitz, *Science,* 2005, **308**, 537-541.
[28] N. J. Schork, *Nature,* 2015, **520**, 609-611.
[29] F. R. Vogenberg, C. I. Barash and M. Pursel, *Pharm. Ther.,* 2010, **350**, 560-576.
[30] B. D. Juran, L. J. Egan and K. N. Lazaridis, *Clin. Gastroenterol. and Hepatol.,* 2006, **4**, 822-830.
[31] Ö. Baltekin, A. Boucharin, E. Tano, D. I. Andersson and J. Elf, *PNAS,* 2017, **114**, 9170-9175.
[32] J. C. Contreras-Naranjo, H.-J. Wu and V. M. Ugaz, *Lab Chip,* 2017, **17**, 3558-3577.
[33] M. N. Karabacak, S. P. Spuhler, F. Fachin, E. J. Lim, V. Pai, E. Ozkumur, J. M. Martel, N. Kojic, K. Smith, P.-i. Chen, J. Yang, H. Hwang, B. Morgan, J. Trautwein, T. A. Barber and Scott, *Nat. Protoc.,* 2014, **9**, 694-710.
[34] D. Wu and J. Voldman, *IEEE Engineering in Medicine and Biology Society Conference*, 2019, 1571-1574.
[35] M. Murtagh, "The Point-of-Care Diagnostic Landscape for Sexually Transmitted Infections (STIs)," 2019, World Health Organization.
[36] N. J. Brendish, S. Poole, V. V. Naidu, C. T. Mansbridge, N. J. Norton, H. Wheeler, L. Presland, S. Kidd, N. J. Cortes, F. Borca, H. Phan, G. Babbage, B. Visseaux, S. Ewings and Clark, *Lancet Respir. Med.,* 2020, **8**, 1192-1200.
[37] S. D. Lawn, A. D. Kerkhoff, M. Vogt and R. Wood, *Lancet Infect. Dis.,* 2012, **12**, 201-209.
[38] A. W. Martinez, S. T. Phillips, G. M. Whitesides and E. Carrilho, *Anal. Chem.,* 2010, **82**, 3-10.
[39] World Economic Forum, "Diagnostics for Better Health: Considerations for Global Implementation," 2021, World Economic Forum, Geneva.
[40] C. Boehme and M. Pai, "Diagnostic Gaps in Global Health," Think Global Health: A Council on Foreign Relations Initiative, 21 February 2020. [Online]. Available: https://www.thinkglobalhealth.org/article/diagnostic-gaps-global-health. [Accessed 16 June 2021].
[41] K. Eyer, R. C. L. Doineau, C. E. Castrillon, L. Briseño-Roa, V. Menrath, G. Mottet, P. England, A. Godina, E. Brient-Litzler, C. Nizak, A. Jensen, A. D. Griffiths, J. Bibette and P. Bruhns, *Nat. Biotechnol.,* 2017, **25**, 977-982.
[42] J. Halfvarson, C. J. Brislawn, R. Lamendella, Y. Vásquez-Baeza, W. A. Walters, L. M. Bramer, M. D'Amato, F. Bonfiglio, D. McDonald, A. Gonzalez, E. E. McClure, M. F. Dunklebarger and R. Knight, *Nat. Microbiol.,* 2017, **2**, 17004.
[43] L. A. Low, C. Mummery, B. R. Berridge, C. P. Austin and D. A. Tagle, *Nat. Rev. Drug Disc.,* 2021, **20**, 345-361.
[44] S. Neethirajan, I. Kobayashi, M. Nakajima, D. Wu, S. Nandagopal and F. Lin, *Lab Chip,* 2011, **11**, 1575-1586.

[45] E. Garcia-Vazquez, J. Perez, J. L. Martinez, A. F. Pardiñas, B. Lopez, N. Karaiskou, M. F. Casa, G. Machado-Sciaffino and A. Triantafyllidis, *J. Agric. Food Chem.,* 2011, **59**, 475-480.
[46] V. Ferrito, A. Raffa, L. Rossitto, C. Federico, S. Saccone and A. M. Pappalardo, *Foods,* 2019, **8**, 537.
[47] K. Warner, W. Roberts, P. Mustain, B. Lowell and M. Swain, "Casting a Wider Net: More Action Needed to Stop Seafood Fraud in the United States," 2019, Oceana.
[48] J. R. Choi, K. W. Yong, J. Y. Choi and A. C. Cowie, *Sensors,* 2019, **19**, 1-31.
[49] Y. T. Atalay, S. Vermeir, D. Witters, N. Vergauwe, B. Verbruggen, P. Verboven, B. M. Nicolaï and J. Lammertyn, *Trends Food Sci. Technol.,* 2011, **22**, 386-404.
[50] D. Kim, Y. Cao, D. Mariappan, M. S. Bono Jr., A. J. Hart and B. Marelli, *Adv. Func. Mater.,* 2021, **31**, 2005370.
[51] H. Yousefi, H.-M. Su, S. M. Imani, K. Alkhaldi, C. D. M. Filipe and T. F. Didar, *ACS Sens.,* 2019, **4**, 808-821.
[52] B. Kuswandi, Jayus, A. Restyana, A. Abdullah, L. Y. Heng and M. Ahmad, *Food Control,* 2012, **25**, 184-189.
[53] S. Xu, Z. Nie, M. Seo, P. Lewis, E. Kumacheva, H. A. Stone, P. Garstecki, D. B. Weibel, I. Gitlin and G. M. Whitesides, *Angew. Chem. Int. Ed.,* 2005, **44**, 724-728.
[54] D. Dendukuri, D. C. Pregibon, J. Collins, T. A. Hatton and P. S. Doyle, *Nat. Mater.,* 2006, **5**, 365-369.
[55] Y. Liu and X. Jiang, *Lab Chip,* 2017, **17**, 3960-3978.
[56] H. Kim, K.-I. Min, K. Inoue, D. J. Im, D.-P. Kim and J.-i. Yoshida, *Science,* 2016, **352**, 691-694.
[57] K. F. Jensen, *Chem. Eng. Sci.,* 2001, **56**, 293-303.
[58] A. Adamo, R. L. Beingessner, M. Behnam, J. Chen, T. F. Jamison, K. F. Jensen, J.-C. M. Monbaliu, A. S. Myerson, E. M. Revalor, D. R. Snead, T. Stelzer, N. Weeranoppanant, S. Y. Wong and P. Zhang, *Science,* 2016, **352**, 61-67.
[59] G. M. Whitesides and J. C. Love, *Sci. Am.,* September 2001, 38-47.
[60] G. M. Whitesides, *Nature,* 2006, **442**, 368-373.
[61] E. Berthier, E. W. K. Young and D. Beebe, *Lab Chip,* 2012, **12**, 1224-1237.
[62] M. A. Eddings, M. A. Johnson and B. K. Gale, *J. Micromech. Microeng.,* 2008, **18**, 067001.
[63] J. N. Lee, C. Park and G. M. Whitesides, *Anal. Chem.,* 2003, **75**, 6544-6554.
[64] E. K. Sackmann, A. L. Fulton and D. J. Beebe, *Nature,* 2014, **507**, 181-189.
[65] C.-W. Tsao, *Micromachines,* 2016, **7**, 225.
[66] K. Ren, J. Zhou and H. Wu, *Acc. Chem. Res.,* 2013, **46**, 2396-2406.
[67] D. Ogończyk, J. Węgrzyn, P. Jankowski, B. Dabrowski and P. Garstecki, *Lab Chip,* 2010, **10**, 1324-1327.
[68] S. A. Aghvami, A. Opathalage, Z. K. Zhang, M. Ludwig, M. Heymann, M. Norton, N. Wilkins and S. Fraden, *Sens. Actuators B Chem.,* 2017, **247**, 940-949.
[69] L. Peng, Y. Deng, P. Yi and X. Lai, *J. Micromech. Microeng.,* 2014, **24**, 013001.
[70] D. I. Walsh III, D. S. Kong, S. K. Murthy and P. A. Carr, *Trends Biotechnol.,* 2017, **35**, 383-392.
[71] E. Carrilho, A. W. Martinez and G. M. Whitesides, *Anal. Chem.,* 2009, **81**, 7091-7095.

[72] S. Waheed, J. M. Cabot, N. P. Macdonal, T. Lewis, R. M. Gujit, B. Paull and M. C. Breadmore, *Lab Chip,* 2016, **16**, 1993-2013.
[73] L. R. Volpatti and A. K. Yetisen, *Trends Biotechnol.,* 2014, **32**, 347-350.
[74] P.-H. Huang, L. Ren, N. Nama, S. Li, P. Li, X. Yao, R. A. Cuento, C.-H. Wei, Y. Chen, Y. Xie, A. A. Nawaz, Y. G. Alevy, M. J. Holtzman, J. P. McCoy, S. J. Levine and T. Huang, *Lab Chip,* 2015, **15**, 3125-3131.
[75] D. T. Chiu, A. J. deMello, D. Di Carlo, P. S. Doyle, C. Hansen, R. M. Maceiczyk and R. C. R. Wootton, *Chem,* 2017, **2**, 201-223.
[76] A. C. Fernandes, K. V. Gernaey and U. Krühne, *Biotechnol. Adv.,* 2018, **36**, 1341-1366.
[77] B. Mosadegh, T. Bersano-Begey, J. Y. Park, M. A. Burns and S. Takayama, *Lab Chip,* 2011, **11**, 2813-2818.
[78] R. L. Truby and J. A. Lewis, *Nature,* 2016, **540**, 371-378.
[79] L. Guillou, R. Sheybani, A. E. Jensen, D. Di Carlo, T. S. Caffery, C. B. Thomas, A. M. Shah, H. T. K. Tse and H. R. O'Neal Jr., *Plos One,* 2021, **16**, e0246980.
[80] N. Qin, P. Zhao, E. A. Ho, G. Xin and C. L. Ren, *ACS Sens.,* 2021, **6**, 3-21.
[81] N. G. Schoepp, T. S. Schlappi, M. S. Curtis, S. S. Butkovich, S. Miller, R. M. Humphries and R. F. Ismagilov, *Sci. Transl. Med.,* 2017, **9**, 1-12.
[82] C. D. Chin, V. Linder and S. K. Sia, *Lab Chip,* 2012, **12**, 2118-2134.
[83] Y. Dong, K. S. Phillips and Q. Cheng, *Lab Chip,* 2006, **6**, 675-681.
[84] G. M. Walker and D. J. Beebe, *Lab Chip,* 2002, **2**, 131-134.
[85] O. Strohmeier, M. Keller, F. Schwemmer, S. Zehnle, D. Mark, F. von Stetten, R. Zengerle and N. Paust, *Chem. Soc. Rev.,* 2015, **44**, 6187-6229.
[86] C. E. Owens and J. A. Hart, *Lab Chip,* 2018, **6**, 890-901.
[87] J. Kim, D. Taylor, N. Agrawal, H. Wang, H. Kim, A. Han, K. Rege and A. Jayaraman, *Lab Chip,* 2012, **12**, 1813-1822.
[88] L. M. Fidalgo and S. J. Maerkl, *Lab Chip,* 2011, **11**, 1612-1619.
[89] T. Thorsen, S. J. Maerkl and S. R. Quake, *Science,* 2002, **298**, 580-584.
[90] K. Choi, A. H. C. Ng, R. Fobel and A. R. Wheeler, *Annu. Rev. Anal. Chem.,* 2012, **5**, 413-440.
[91] R. Fobel, A. E. Kirby, A. H. C. Ng, R. R. Farnood and A. R. Wheeler, *Adv. Mater.,* **2014**, *26*, 2838-2843.