mediates for many industrial reactions. They explored several nitrogen-containing ligands, a variety of pyrolysis temperatures, and different supports. Their best catalyst was prepared by pyrolysis of iron(II) acetate and phenanthroline at 800°C on carbon supports. A remarkable feature is that the nitro group is selectively hydrogenated in the presence of aldehydes, ketones, and C=C bonds. Although the mechanism of their catalyst is not known, it must involve several steps, as two N-O bonds must be cleaved in addition to the formation of the N-H bonds of the product. Characterization of the catalyst particles revealed Fe_2O_3 nanoparticles, which suggests that some form of "nano-rust" is the catalyst, but the nitrogen-doped layers around the particles of Fe_2O_3 indicate that nitrogen arising from the phenanthroline is incorporated into the support.

These three papers do not merely report proof-of-principle results; they describe catalysts based on inexpensive metals that exhibit impressive activities and selectivities that are comparable to, or even exceed, those of well-established catalysts based on precious metals. None of the new catalysts were designed by keeping the ligands and oxidation states the same as those on a precious metal catalyst while simply changing the metal; rather, their design relies on understanding and exploiting their characteristic reactivity. The striking diversity of approaches, all ultimately fruitful, illustrates that there is no exclusive single "recipe" for success in developing catalysts based on cheap metals—an observation that is encouraging to chemists seeking to design and develop catalysts based on abundant, inexpensive metals.

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ENGINEERING

Devices for Low-Resource Health Care

Devices designed for low-resource settings can improve access to life-saving health care around the world.

Rebecca Richards-Kortum and Maria Oden

Most of the world receives health care in low-resource settings (see the figure), yet medical technologies are designed to be used mainly in high-resource settings, where designers take for granted basic infrastructure that supports their safe use and effective distribution. The corridors of many hospitals in low-resource settings are lined with donated medical equipment, but up to three-quarters of these devices do not work, often due to lack of spare parts or consumables (*1*). As a result, most of the world's population lacks access to life-saving technologies developed decades ago, including infant incubators, oxygen concentrators, and simple laboratory diagnostics. In this Perspective, we review the challenges of developing and translating medical technologies and highlight promising new technologies to improve health in low-resource settings.

Low-resource settings present challenging design constraints, including inadequate electricity and clean water, limited funding, weak supply chains, lack of trained users, and lack of technology management policies (*1*, *2*). Alarms and fail-safe features that make devices safe in high-resource settings can be damaged in harsh environmental conditions, causing devices to fail or be unsafe in low-resource settings. Efforts to design new technologies for low-resource settings have generally been more successful than attempts to adapt existing technologies by removing costly or complex features (*1*, *3*). Designs that eliminate or minimize cost of consumables may be most sustainable. Because consumables are often reused in low-resource settings, designers should ensure that they can be cleaned safely.

Evaluating technology performance presents further challenges in low-resource clinics. It is difficult to design ethical trials of potentially life-saving appropriate technologies when the benefits of counterpart technologies in high-resource settings are well documented. Moreover, collecting accurate data in understaffed clinics is challenging.

Successful product design requires multidisciplinary partnerships. There are many benefits to engaging local innovators, yet opportunities for quality engineering education in low-resource settings are limited, especially in Africa (*4*). Many efforts have identified unmet clinical needs in low-resource settings, but it can be difficult to identify early-stage industrial partners to develop a parallel business case. Engaging partners working to strengthen regional health systems can assist in wider-scale implementation.

A growing number of academic programs, nongovernmental organizations, and companies are addressing these challenges (*2*). Here, we highlight successful efforts and remaining barriers for several technologies.

Birth asphyxia contributes to more than a quarter of neonatal deaths in low-resource settings (*5*). To address this problem, Laerdal, a medical company that specializes in life-saving equipment, developed affordable, reusable neonatal resuscitation tools, including an easily cleanable bulb suction device to clear the infant's airway and a manual resuscitator with a self-inflating bag. To train providers to recognize and treat birth asphyxia, Laerdal developed NeoNatalie, an electricity-free, low-cost neonatal simulator that mimics chest rise with mechanical ventilation (*6*).

Bioengineering Department, Rice University, 6100 Main Street, Houston, TX 77005, USA. E-mail: rkortum@rice.edu

Challenging health care settings. Photos of a neonatal unit at an Ethiopian district hospital (**A**) and in a laboratory at a health center in the Democratic Republic of the Congo (**B**) illustrate the difficult conditions often found in low-resource settings. To be successful, new device designs must address the challenges of limited physical infrastructure, low economic resources, lack of consumables, and lack of tools and maintenance personnel. The early phases of technology development should emphasize clinical, scientific, and private-sector partnerships to enable sustainable implementation.

With global input, the American Academy of Pediatrics developed a training curriculum for these technologies called Helping Babies Breathe (HBB) (*6*). Implementation of HBB in Tanzania reduced early neonatal mortality by 47% (*5*).

HBB is being implemented in more than 50 countries and is a part of the World Health Organization (WHO) Essential Newborn Care Course (*6*). Studies of HBB show that even with a simple technology, there is a need for ongoing training and mentoring to change clinical management and patient outcomes (*5*, *6*). HBB's success illustrates the importance of partnerships that couple design, education, and efforts to improve health systems; early engagement of partners ensures that design constraints are set to facilitate future integration of a technology into the health system.

Premature birth is the leading cause of newborn death. Over half of premature babies struggle to breathe; in the developed world, this is easily treated using continuous positive airway pressure, in which pressurized air and oxygen are gently delivered through nasal prongs. At $6000, continuous positive airway pressure machines designed for high-resource settings are too costly for most developing-world hospitals. Recently, we reported a $400 continuous positive airway pressure system that delivers the same therapeutic flow and pressure as systems used in high-resource settings (*7*). The device was designed with analog electronics to ensure that it would be robust. In 1 year of clinical evaluation of five devices at a central hospital in Malawi, no device failed, whereas 40% of study oxygen concentrators regularly used in the ward failed when circuit boards were damaged by line voltage spikes (*8*). Often, technologies such as the oxygen concentrators designed for high-resource settings fail when used in low-resource settings because of the large mismatch between the context for design and that for actual use (*1*).

Global efforts to expand access to HIV care have led to a need for improved laboratory diagnostics for HIV-infected patients. In particular, protocols to initiate and monitor therapy with antiretroviral drugs require $CD4^+$ T cell counts. The gold standard for CD4 testing is flow cytometry, but these devices are expensive and complex (*3*). Developers first attempted to meet this need by modifying existing flow cytometers to reduce cost. For example, the BD FACSCount is a low-cost flow cytometer, but it requires skilled operators and frequent calibration (*3*). Alternative technologies have been designed explicitly to meet the needs of low-resource settings. For example, the Alere PIMA device uses a fixed-volume, static cytometer and can run on battery or solar power (*3*, *9*). It cannot be maintained or repaired on site, but the company maintains local inventory stocks to swap out nonfunctional devices (*3*). Despite the limitations of both approaches, introduction of point-of-care CD4 testing with these devices has improved patient care in low-resource settings, increasing the proportion of patients who initiate the necessary treatment and decreasing time to receive necessary therapy (*10*).

In 2012, a WHO expert panel proposed that point-of-care CD4 technologies should be affordable (<$5), sensitive (99%), specific (98%), user-friendly (requiring minimal operator training), rapid and robust (<1 hour, no special temperature requirements for shipping or storage, no operator calibration, minimal routine maintenance), equipment-free (battery operated and no moving parts), and deliverable (commercially available and approved) (*3*). No CD4 devices yet meet these criteria (*3*, *9*, *11*), and some devices fail frequently in the field (*11*). CD4 devices explicitly designed for low-resource settings more closely approach the target specifications for use at the point of care than simplified versions of designs originally developed for high-resource settings (*3*).

Efforts to improve laboratory diagnostics for *Mycobacterium tuberculosis* (MTB) led to the recent introduction of GeneXpert. Designed to provide sample-to-answer nucleic acid testing for MTB and drug resistance using polymerase chain reaction amplification, the assay has shown improved sensitivity compared to microscopy (*12*). However, laboratory temperatures exceeded the operational range for GeneXpert more than 10% of the time in four of six sites in one multicountry study (*12*). Moreover, the subsidized price for each Xpert test cartridge in low-resource settings ranges from $10 to $17, much higher than the $3 South African National Health Laboratory Service charge for standard fluorescence microscopy, which includes overhead, supplies, and personnel costs (*13*). While the Xpert test offers important benefits, the hardware and consumables are expensive; it is often more challenging for health systems to sustain the cost of consumables than to purchase one-time hardware costs.

Approaches that minimize the cost of consumables may be the most sustainable; as an alternative to reduce the cost of consumables for laboratory tests, diagnostic tests made of paper show considerable promise. Clinical evaluation of a paper-based device to measure liver function demonstrated accurate results with an estimated per-test cost of $0.10, well below the $4 per-test cost of existing commercial assays (*14*). Whole blood is applied to the device, and plasma

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passes through a filter that retains red and white blood cells to layers of paper containing colorimetric reagents. Fluid flow within the paper is directed by patterned hydrophobic barriers that are easily created using a wax-based printer and heat source. Results can be documented, analyzed, and transmitted with a cell phone camera, and devices can be safely disposed of by incineration. Paper-based tests to amplify and detect nucleic acids have been reported recently (*15*).

Health care innovation should be available to all the world's citizens, but technical and economic barriers remain. Low-resource settings present challenging constraints that require design for context, safety, reusability, and reparability. The current landscape of appropriate technologies reflects a reaction to economic incentives, largely shaped by philanthropic efforts rather than market forces. Often these funding mechanisms favor technical innovation over simplicity, and resulting technologies are too costly and difficult to maintain at scale. Alternative approaches that explicitly design technologies to function in settings that lack resources for consumables, effective distribution systems, supply chains, and technology management programs and that incorporate early private sector partnerships are needed. In parallel, efforts to develop and support innovators in low-resource settings must be strengthened. Partnerships that focus on developing and disseminating integrated packages of technologies that address focused areas (such as technologies for the neonatal unit) can navigate technical and implementation barriers more efficiently than single technologies.

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MICROBIOLOGY

Genomes from Metagenomics

Metagenomic approaches are rapidly expanding our knowledge of microbial metabolic potential.

Itai Sharon and Jillian F. Banfield

Evaluation of the functional capacities of microorganisms long relied on laboratory cultivation of individual species. About a decade ago, recovery of draft genomes for a few uncultivated bacteria and archaea from natural communities opened the way for physiological prediction of their environmental roles. Further development of the metagenomics methods used in those early studies now allows the rapid delivery of accurately reconstructed microbial genomes from diverse environmental samples. The resulting knowledge has the potential to revolutionize our understanding of the topology of the tree of life and the metabolic capacities distributed across it. Advances in bioinformatics promise a new era in which comprehensive genetic characterization is sufficiently rapid to find application in diagnostics for medicine, agriculture, forensic science, and biotechnology.

Metagenomics is a cultivation-independent method for studying microbes sampled directly from the natural environment. DNA is extracted and sequenced from one or a series of samples, and the resulting data is analyzed using computational tools. The approach addresses two important needs: It enables analysis of the 99% of microbes in nature that have not yet been cultivated, and it facilitates the study of organisms in the context of their community.

Because the DNA originates from multiple populations, the recovery of genomes from metagenomic data is a complex task. Until recently, genomes were reconstructed only from relatively simple environments with a few abundant genotypes (*1*). The advent of high-throughput DNA sequencing has enabled genomic sampling of much less abundant organisms and characterization of communities with relatively even species abundance levels, but the complexity of data analysis has increased greatly. Newly developed computational tools allow data assembly (*2*) and accurate assignment of genome fragments to specific organisms (*3*, *4*), a process termed binning.

In 2012, Wrighton *et al*. reconstructed 49 genomes with varying completeness levels for bacteria from at least five phyla for which there was almost no prior genomic information (*5*). The authors used a binning method that combines time-series abundance information with sequence compositional characteristics. More recently, Albertsen *et al*. (*6*) used information from multiple samples—an approach similar to that used for analysis of human infant gut microbial consortia (*4*)—to reconstruct 31 genomes with an average estimated genome completeness of 80% from DNA sequence information for an activated sludge bioreactor community. They were able to assemble the complete genome of an organism from the TM7 candidate bacterial phylum (lacking cultivated representatives) into a single contiguous sequence. Complete genomes for organisms that constitute ~1% of the community have also been reconstructed from environments such as the ocean (*3*) and, very recently, from adult human gut (*7*) and sediment (*8*, *9*). These examples demonstrate that metagenome-based genome recovery can now be applied to very complex systems.

Uncertainty about accuracy currently limits wide acceptance of metagenomics-derived

Department of Earth and Planetary Science, University of California, Berkeley, CA 94720, USA. E-mail: jbanfield@berkeley.edu