Can We Manufacture Diagnostic Test Strips Using an Inkjet Printer?

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Abstract—Developing countries face an increasing double disease burden of chronic health conditions like cancer, cardiovascular disease, and diabetes alongside traditional communicable diseases like tuberculosis, HIV/AIDS, and malaria. Rural patients often cannot afford to visit established medical centers because of the cost or time associated with travel. Poor education and social stigma prevent patients from seeking medical attention or getting tested for curable illnesses. Access to affordable and accessible tools for screening and diagnosis of common illnesses can greatly reduce the strain on fledging health care systems. This article provides a proof-of-concept for manufacturing dipstick test strips that can be used for a variety of screening tests including diabetes and urinary tract infections. By repurposing a traditional, piezo inkjet printer with chemically active solutions that match the fluid properties of traditional printer ink, test strips can be printed in a just-in-time manner in low-resource settings.

Keywords—lean manufacturing, inkjet printing, urinalysis, test strips, dipsticks

I. INTRODUCTION

A. The Double Disease Burden and the Need for Accessible, Low-cost Screening Devices

Overcoming the lack of access to primary and pre-primary health care is one of the largest opportunities available to healthcare innovators focused in developing countries. There is a significant lack of trained medical professionals who can diagnose and treat the growing double burden in developing regions. In Kenya and Zambia, for instance there are only an average of two physicians per 10,000 citizens—a stark disparity and tenfold difference to the twenty-six physicians per 10,000 in the United States [1]. Access to healthcare is further limited when people need to travel long distances for basic medical care [2] [3]. Most clinics and major hospitals are located in or near urban areas, far from rural communities. In fact, while the Kenyan government had a target of all people being within one hour travel from a government health facility by 2010, only approximately 61% of people live within this target range [4]. People must therefore rely on public transportation systems, which can use up to two working days to travel back and forth and can cost up to an entire day’s wages, in order to reach primary care facilities—assuming they are able to see a doctor immediately and do not need to wait for long test results. Moreover, the health care situation is further compromised by the double burden of infectious diseases alongside the increasing prevalence of chronic illnesses [5] [6]. For example, in sub-Saharan Africa every woman has a 50% chance of attaining a urinary tract infection in her lifetime [7] [8]. Additionally, given major changes in lifestyles diabetes has become an epidemic in sub-Saharan Africa [9]. There is a large gap between the need for healthcare and the accessibility to and affordability of healthcare to community members. In low resource settings, access to healthcare is hard to come by. Just getting to a clinic or hospital can take a person a few hours, not to mention the amount of money they would have to spend getting there. Many individuals only live on a few dollars a day, so this cost of traveling is insurmountable, not even including the cost of the healthcare itself. While mass manufactured, current health care devices routinely address these issues in the developed world, they are unsuitable for low-resource contexts. The need can be filled through the introduction of lean manufactured, low-cost screening and diagnostic devices for low-resource communities.

B. The ASSURED Framework

In order to guide the design of new medical devices for low resource settings, the World Health Organization has developed the ASSURED framework: Affordable, Sensitive, Specific, User-friendly, Rapid and robust, Equipment-free, and Deliverable. Devices must be affordable to the end user; otherwise, they simply will not be used because of excessive monetary or time cost. Sensitivity and specificity are statistical parameters that identify the rate of true positive and true negative results; a device that is not accurate will naturally not see much use. Additionally, user-friendly designs will be intuitive to understand and simple to use for people with any range of education. A robust and ruggedized design eliminates the need for frequent, costly, and specialized repair. Rapid testing is critical to device success. In many situations, if results take longer than thirty minutes to generate, end-users may not be willing to wait around for the results or use the device. A device that eliminates use of ‘equipment’ or excessive electronics is much more likely to be successful, again by reducing the risk of breakdown and being accessible to wide range of education levels. Finally, devices must actually be delivered to the hands of end users, a challenge
that often prevents good innovations from ever reaching market [10].

C. Current Healthcare Devices

Current market screening devices have often been developed only through the mindset of a developed context user. While these devices are very effective for screening and medical diagnosis, there are certain aspects of their manufacturing process and distribution that make them unsuitable for use in low-resource settings. Transporting vaccines is a simple task in the United States due to wide availability of refrigerated vehicles and an expansive infrastructure; the same cannot be said for Kenya. Other aspects of manufacturing in developed contexts contribute to high prices and specialized distribution schemes that cannot be replicated in different contexts. Having a high stock of raw materials or partially completed products may increase mass manufacturing efficiency, but raises upfront costs. Having long, moving, and intricate manufacturing lines can drastically increase the chance of failure of a particular step and bring an entire manufacturing process to a halt. Another characteristic of traditional manufacturing is that most products spend significant time waiting, either on assembly lines, shipping containers, or shelves in end-user environments. Overproduction, or producing in expectation of higher demand, can increase this waiting time or lead to expired, and totally wasted, products. Other products may be designed overly complex for the actual needs of the end user; the result of this over-processing is wasted resources in the form of a partially used product. Finally, errors at any stage of the process may lead to product defects that result in a totally unusable, and therefore wasted, product.

One example of traditional manufacturing methods applied to a medical device are commercially available urinalysis test strips. These test strips are manufactured in bulk orders of several thousand at single factories, and must be shipped from manufacturer to end user. These strips are typically manufactured on highly specialized printing machines that will load an absorbent material with reagent, cut the material, and attach it to a dipstick in assembly line fashion. The strips must spend significant time being shipped to end users and then sit on shelves waiting for use. Additionally, urinalysis strips often have ten or eleven parameters to test for a wide variety of diseases, when end users may only be interested in the results of certain tests. Finally, bulk manufacture and bulk ordering mean that healthcare providers are ordering hundreds of strips at a time, when they may need significantly less.

D. Lean Manufacturing

Lean manufacturing provides a more concrete structure towards interpreting the ASSURED framework in a design situation. Lean manufacturing focuses on eliminating waste while delivering high-quality products on time, at low-cost, and with high efficiency [10]. These types of waste curtailed include: transport, inventory, motion, waiting, overproduction, over-processing, and defects [11] (figure 1). The tenets of lean manufacturing can be used to guide development of low-cost screening tools for low-resource settings, particularly tools which counter the double disease burden of infectious diseases and chronic illnesses. For example, a local, small scale manufacturing system incorporated into the end user environment for disease-specific urinalysis test strips can reduce transport, motion, waiting, overproduction, and over processing waste. Lean manufacturing of these strips could consist of a drawing, stamping, or printing chemical reagents onto highly absorbent paper in health clinics for immediate use by health staff to screen for only certain diseases, such as UTIs or diabetes.

II. MANUFACTURING APPROACHES

A. Current Approaches

Urinalysis test strips are a widely used in developed and developing contexts for basic diagnosis and screening as a first pass before microscope urinalysis, or where microscope urinalysis is unavailable. Test strips will often come with ten or eleven parameters to detect a variety of biomarkers, such as leukocytes, nitrites, urobilinogen, protein, pH, blood, specific gravity, ketone, bilirubin, and glucose (figure 2). Most users will be able to read color changes in each of these tests to determine relative concentrations of each biomarker, as test strip packages come with colorimetric legends. Health practitioners use these abnormal concentrations to aid in making diagnoses for patients complaining of other symptoms.

Current approaches for manufacturing test strips are highly industrialized and focus on limited-customization and high throughput. Most urinary test strips are manufactured by large companies with machines that require significant space and
energy. For resource-constrained settings, such as Sub-Saharan Africa, this lengthy and complex supply chain increases the cost of the product significantly. Another negative characteristic of this current approach is that most mass-manufactured urinary test strips have ten or eleven unique parameters on each test strip. The large number of tests is useful for accuracy and screening for a wide variety of disease, but present a disadvantage in low resource and low education settings. Thus, a lean manufacturing solution should be jointly prioritized with simplicity. A test strip with fewer testing parameters but similar diagnostic accuracy for a particular disease, such as only UTIs, meets these design constraints.

B. Felt Stamp Manufacturing

There are a variety of novel options that can be a viable manufacturing method in resource-constrained settings. An alcohol-based stamp is a rapid, inexpensive, and low-technology option for producing dipsticks. A small clinic or office can easily manufacture the dipsticks in the location where they are needed, which immediately cuts down transport waste. Because the work is done by hand, it has the secondary impact of creating an employment value channel. Additionally, because the strips are made sheet by sheet, there is little waste generated and sheets can be immediately used by health workers, reducing inventory waste and over production waste.

However, there are often complications from oversimplification of a process, especially a process initially optimized for use in a healthcare system. Ink stamp reservoirs represent unused inventory that can potentially be contaminated through inattentive stamping or open-to-atmosphere containers. Any contamination would increase the likelihood of defect waste as well. While the human work can be valuable with regard to one value, it also introduces a high degree of variability between each batch of stamps produced and significant motion waste that can be replaced by a more specialized machine. When competing with professionally produced strips, off-centered design or skewed stamping can diminish customer faith in the product and ultimately damage the venture. Even with a perfectly skilled worker, there is no control for the concentration of reagent solution in each stamp and defects are again more likely. While some strips may receive enough solution to accurately conduct tests, other may be too thinly coated to read properly or too thickly coated that they damage the underlying paper substrate.

C. Inkjet Printing Manufacturing

Inkjet printing provides an economically and socially sustainable opportunity to manufacture dipsticks at low-cost, in precise amounts, and at local stations – lean manufacturing techniques which can drastically improve the ability of healthcare systems in resource-constrained settings. Traditional inkjet printing involves depositing droplets of ink onto paper or other materials and modern, commercially available printers are capable of rapid, high-resolution printing at low-cost. The ink is propelled through the print head through either thermal or piezoelectric processes. Generally, piezo printers tolerate a wider variety of ink properties due to their method of action. Piezo printers expand a small piezoelectric component when a voltage is applied, thus generating a pressure in a contained ink chamber to force the ink through the print head nozzle. By simply replacing the normal printer ink with solutions containing active chemical reagents for diagnostic and screening tests, an “image” of reagents can be printed onto dipstick material, which can then be cut and sold as individual tests. A variety of solutions can be prepared in refillable ink cartridges and slotted in and out to generate any number of experiments or even groups of experiments, such as a three-point test for UTIs looking for the presence of nitrates, leukocytes, and elevated pH or a two-point test for diabetes looking for glucose and ketones. Critically, this method of manufacture allows for manufacture of precise amounts of dipsticks containing only relevant tests to symptoms, cutting down on wasted chemicals for unneeded tests. However, repurposing an inkjet printer is not as simple as just filling a cartridge and printing a new document; a number of potential waste issues can damage the printer, prevent normal use, and raise the overall cost of printing.

1) Ink Reservoir Tracking

Dipstick manufacture and cleaning could potentially involve very high throughput use, beyond the normal levels of a commercial inkjet printer. The option to print high volumes of strips must be considered in the event of high user demand. Alternatively, in very rural areas, printer use could vary between high throughput and low throughput use. Some printers do not measure ink levels directly, but rather use an indirect system such as counting the number of pages since the last refill and estimating ink level. Users must be familiar with common ink level warnings and understand how to reset readings that may be inaccurate. Inaccuracies may arise from “printing” a cleaning solution or changing cartridges for a new test before a cartridge is totally empty. Users must also be able to reliably inspect the ink levels directly, rather than rely on faulty printer software, in order to minimize reagent solution waste. In all these cases, there is significant need to overcome inventory and over-processing waste.

A simple, low-cost option to avoid these wastes is to provide a troubleshooting guide for common printer errors, the most frequent among which are page count and ink level tracking. Additionally, a maintenance guide can indicate procedures such as frequency and depth of cleaning needed. These guides can be saved electronically, to prevent additional transport or inventory waste, and contain pictographic instructions for widespread use in many contexts. To actually solve the problem of resetting ink level readings, many third party ink cartridges are incorporated into the design. These cartridges come with a small electronic chip that can be manually reset to overcome ink level or page count errors.

2) Ink Tube and Print Head Cleaning

Many of the tests used in dipstick analysis are highly sensitive to the solution environment and cross contamination can prevent accurate readings. For example, certain tests for UTIs must be carried out in acidic environments for the proper chemical reactions to occur. At the same time, if residual acid remains in an ink line printing a pH test, the results will be invalid. In another example, inkjet printers do not immediately
print the top layer of ink from a cartridge. Rather, the ink travels through a long ink line and ultimately sits in a small chamber in the print head. This ink must be used or flushed out, and the ink line sterilized, between switching tests. Users must be trained to flush the lines with sterile water and ethanol to sanitize them, and then know to load the reagent solutions through the ink lines.

To clean the internal components of the printer, several cartridges containing clean water or a disinfectant and washing fluid, such as ethanol or acetone, are loaded into the printer and cleaning fluid is flushed through the system in order to clean the ink lines. While this represents a small amount of inventory waste, it prevents significant inventory and defect waste that would occur from cross contamination. Often, this clean is accomplished by “printing” a number of sheets to ensure that both cleaning and reagent solutions fully travel the entire ink line pathway. Alternatively, many printers have a power flushing software mechanism which is designed to flush the print head and load new fluid when a new ink cartridge is inserted; the same software function can be used to load a cleaning solution and then a new chemical reagent solution. Keeping the print head clean and free of reagent build up will also reduce motion and defect waste as the machine will be less likely to breakdown.

3) Proprietary Ink Cartridges

Most printer manufacturers earn significant amounts of their revenue through printer ink, and therefore take extra measures to ensure only certain ink cartridges can be used with their printers. Using custom cartridges requires extra resources and limits users’ choices among manufacturers. Refillable cartridges do exist for several large-name manufacturers, but can be difficult to clean. Continuous ink supply systems present an interesting solution. CISS printers have large, easily accessible and refillable reservoirs and are design for high throughput use; however, they are susceptible to sterility issues as the seal is not as airtight. Either method is viable, however, as refillable ink cartridges can be recycled or cleaned by a specialty service.

The ease of refilling and emptying solutions makes the CISS printers very attractive. That style use, however, is not typical of end-user implementation as it leads to inventory waste of old solutions or mixing of different solution batches. Large reagent solution volumes, typically in CISS reservoirs, also lead to waiting waste which could impact the chemical reaction or lead to degradation of the machine. On the other hand, third party, refillable cartridges are easily loaded at a manufacturing center and sealed for shipping and transport. Sealing these cartridges will prevent inventory and defect waste. While shipping does involve some transportation, an ink cartridge is capable of printing several hundred pages so the transport waste will be minimal. Empty cartridges can be recycled or sold back to the manufacturing center, which can easily wash them out with a rinsing solution such as ethanol or acetone, reload them, and sell them again. Moreover, as mentioned above, third party cartridges provide an easily solution to overcoming common ink level errors.

4) Chemical Solution Damage to Printer Components

Reagent solutions present a completely different chemical environment than printer ink to the internal components of a printer, so materials and solutions must be carefully controlled to prevent damage. As mentioned in an above example, certain reactions for the UTI test can only take place in acidic environments. However, strong acids can erode plastic so the pH must be carefully controlled by diluting the acid to a non-damaging, but reaction-active range. Other solutions are only dissolvable in alcohols and must also be carefully controlled to prevent solute dissolution and build-up within the ink lines or print head. Finally, the frequent use and cleaning of the printer mean absorbent ink waste pads and other components that are designed to prevent damage must be cleaned, replaced, or altered regularly to ensure proper printer function. In all of these scenarios, there is potential for inventory and over processing waste.

Conveniently, carefully controlling the pH and diluting as necessary will actually reduce waste as certain quantities chemicals can be used to fill multiple cartridges. These dilutions reduce the inventory and waiting waste of materials that would otherwise have to be bought frequently. Moreover, after a single shipment, one order of chemicals can last several orders of strips, reducing the overall transport waste of frequent shipping. Refillable ink cartridges and CISS printers both offer airtight, rubber seals that prevent evaporation of volatile solvents. Over the several months of prototype development, evaporation has not been observed and so there is no cause for motion, over processing, or defect waste. Finally, software and hardware fixes for printer errors, such as waste ink pad lifespan error, can also be included in the troubleshooting guide in order to limit over processing waste impact on the manufacturing process.

5) Mimicking Traditional Ink Properties

Though the use of piezoelectric print heads widens the variety of inks that can be cleanly printed, there are still certain physical properties that must be matched to ensure the highest quality printing and no cross-contamination on the dipstick itself. The two most important controllable physical parameters are solution viscosity and density, as fluid flow through the ink lines and print head must be as similar to traditional ink as possible to maintain good resolution and printing. Accounting for the solutions needed to dissolve reagents, ensuring proper chemical environments for reactions, and not damaging the internal printer components limits the choices for viable solvents. However, by using fully miscible solvents such as water, acetic acid, ethanol, and isopropanol, viscosities and densities can be aggregated towards a mean, weighted according to the relative volume of each fluid that falls within the tolerable range for piezo printers.

Fortunately, as mentioned above, piezoelectric print heads can tolerate a fairly wide range of ink viscosities and so have a large tolerance to limit over processing waste generation. The range is wide enough that a mixture of solvents such as water,
acetic acid, and/or ethanol can fall within the tolerable limits. A rough approximation of ink viscosities and reagent solution viscosities is conducted using a drop test to ensure that the solutions were similar to one another. Prototype printing showed no discernible issues with a clean, clear printing of solutions were similar to one another. Prototype printing viscosities is conducted using a drop test to ensure that the ink viscosities and reagent solution viscosities are within the tolerable limits. 

III. SENSITIVITY AND SPECIFICITY OF MANUFACTURED TEST STRIP

Two tests were performed to test the sensitivity/true positive rate and specificity/true negative rate of stamped pH test strips. The test strips were made using bromophenol red as a pH indicator on Teslin substrate, a highly absorbent and damage-resistant paper. Bromophenol red is expected to change from yellow-red to purple between pH 5.2 and 6.8. Using a 0.1% w/w bromopherol red solution in equal volumes of water and acetic acid, Teslin substrate paper was stamped to create test squares. For the sensitivity test, the pH included the following values: 6.5, 6.8, 7.0, 7.5, and 8.0; each pH value was tested fifty times (n=50). For pH 6.5, there was no observed color change in any of the test strips. For pH 6.8-8.0, there was a gradient of observed color changes in all the test strips with the color becoming a darker purple as the pH increased; this color change would fade after several minutes indicating the test should be read rapidly (figure 3). Using ImageJ, average color histograms were obtained for pH values 6.5, 7.0, and 8.0 for an 8-bit RGB color scheme. These data are summarized in table 1. There was a significant difference between pH 6.5 and either pH 7.0 and 8.0 (p < 0.0001) using a one-way ANOVA test and Tukey HSD post-hoc test. Statistical tests are summarized in table 2.

For the specificity test, the pH included the following values 4.5, 5.0, 5.5 and 6.0; each pH value was tested fifty times (n=50). There was an observed color change from yellow-red to green for each test strip in every pH value. The color change started as yellow for pH 4.5 and changed to green as the pH values increased. However, there was a clear difference between the green result in the specificity test and the purple result in the sensitivity result. These data suggest that bromophenol red can easily be stamped in solution on Teslin substrate paper and be used as a reliable pH indicator.

One test was performed to test the sensitivity of inkjet-printed test strips. The test strips were printed on an EPSON L210 commercial inkjet printer with neutral red as a pH indicator again on Teslin substrate paper. Neutral red is expected to change from red to yellow between pH 6.8 and 8.0. Using 0.1% w/w neutral red solution in equal volumes of water and ethanol, twenty test strips were printed (n=20) and placed in a pH 10 solution. A clear color change was observed in all test strips (figure 4). These data suggest that a pH indicator solution can be reliably printed using a commercial inkjet printer.

IV. OPERATION AND USE IN-CONTEXT

While a focus on developing an operational inkjet printer is a paramount and necessary first step, the use of such a printer in-context will serve an equally important role down the line. In a hypothetical case study, inkjet-printed test strips are a viable, effective, and self-sustaining method for reducing cost and improving healthcare quality in low-resource settings. Given the nature of these settings, some manufacture must occur outside of the setting. As mentioned before, replacement ink cartridges or chemical solutions may be manufactured offsite. However, in-lab testing has averaged costs per strip that rival the cost of commercially available strips (table 3). It is not unreasonable to hypothesize that a large-scale manufacturer may be able to supply chemicals, one of the highest priced components, at a lower cost than the small-scale manufacturing for testing purposes. The estimated cost for inkjet-printed includes start-up costs for paper, inkjet printer, and cartridges. The costs were estimated for printing approximately 12,000 test strips. However, the importance of this design is chemical solutions can safely sit in ink cartridges so that not all 12,000 strips need to be produced in one batch. Moreover, after the first batch is sold, the cost per strip will drop as some purchases, such as the printer, are only one-time investments.
Table 3. Cost Estimated of Test Strips

<table>
<thead>
<tr>
<th>Test Strip Type</th>
<th>Cost per Strip to End User</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inkjet-Printed</td>
<td>0.20 USD</td>
</tr>
<tr>
<td>Uric 10CF (current market)</td>
<td>0.17 USD</td>
</tr>
</tbody>
</table>

V. CONCLUSIONS AND FUTURE WORK

Moving forward, the accuracy of the UTI test must be tested on-site in resource-constrained regions, such as sub-Saharan Africa where there is a critical need for UTI detection in pregnant women and the general population. On-site testing will verify the literature review and in-lab testing that the printing process does not alter or damage the reliability and accuracy of the chemical tests being used. Moreover, the local ecosystem must be better characterized to understand ideal locations to serve as micro-manufacturing and printing stations. Access to reliable power and a clean environment are critical to keeping the tests available for sale and use and accurate without contamination. While unrelated to the printing technology itself, the need for low-cost rapid dipstick analysis must also be validated, so investigations into common diseases and the cultural and social stigma and treatment around them must also be carried out. While such investigations are not directly related to the printing technology, they serve as important focuses in the greater ecosystem and can help direct future test development as well as locations for printing and use of dipsticks.

While the success of the development of a urinary tract infection dipstick is noteworthy, inkjet printing dipsticks represents a viable platform technology that can have far reaching impacts. In just the healthcare realm, this platform can be used to produce any number of urinalysis tests such as for diabetes, pregnancy, preeclampsia, liver diseases, kidney diseases, and others. This technology can be used in local health clinics and hospitals as a reliable manufacture method and alternative to costly tests with unnecessary parameters, or in mobile community health worker paradigms where simplicity and screening are paramount as patients are only seeking basic health advice. However, the technology is not limited to just point-of-care contact in health care. It can represent a greater tool for public health and infrastructure evaluation. For example, simply by changing the solution being printed, a process as simple as switching an ink cartridge, tests for methanol detection in drinks or common toxins in water can be printed in the environment they are needed and used immediately. The convenience paired with modifiability of the technology is unrivaled and represents a viable platform for test development moving forward.

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