Original Paper

What do hospital labs really need to streamline diagnostic testing: Apple vs. Microsoft environment?

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ABSTRACT

Molecular diagnostic (MDx) tests are now commonplace in virtually every hospital and pathology laboratory, however many questions have arisen, such as "What do diagnostic laboratories require from the MDx revolution in order to better improve patient care?" and "Is a fully integrated 'black-box' device the answer to simple rapid diagnostic testing or do mainstream laboratories require more in terms of available testing menu and streamlined workflow?" With more and more 'black-box' devices available on the market, laboratories need to first decide if they need to make such an investment, and if so, in which to make the most appropriate investment, whilst also considering the cost of consumables. Currently the associated costs of an integrated solution can be prohibitive for small to medium sized laboratories, however this does not necessarily mean that they need to miss out on the many benefits that MDx testing can bring. Here we examine what role an open-platform suite of MDx assays can play in the MDx testing landscape. In order to be successful we assume that open-platform tests will utilise a universal sample preparation method for all sample types and be compatible with a broad range of existing Real-Time PCR hardware. This is in effect the 'Microsoft' model, which provides software compatible with existing hardware, compared to the 'Apple black-box' model of supplying both the hardware and software. Clearly there is a place for both approaches in the clinical diagnostic sector, but until the 'black-box' systems broaden their testing menu for all sample types and reduce the cost of consumables, their use may be limited to single analyte niche testing rather than being a central workhorse in the mainstream hospital and pathology laboratories. The goal for testing laboratories is to provide rapid and definitive identification of pathogens in order to aid optimal patient management. In the current setting this is only available by using a battery of tests from different manufacturers, or by relying on traditional methods that can take several days to generate a result. It is proposed that a true open-platform MDx testing system may bring the benefits of rapid and accurate testing to many small to medium laboratories without the need for a large upfront investment and associated high consumable costs.

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INTRODUCTION

THE MOLECULAR DIAGNOSTIC LANDSCAPE: CURRENT AND FUTURE TRENDS

The use of molecular diagnostics (MDx) has numerous advantages over conventional techniques used for infectious disease testing. Key advantages include speed, sensitivity, specificity and the ability to use such methods independently of sample viability. In addition, MDx tests can be performed on many different specimen types such as blood, CSF, sputum, swab samples and faecal material to determine the presence or absence of specific pathogenic microorganisms.

Molecular diagnostic testing is the fastest growing segment of the *in vitro* diagnostic (IVD) marketplace. The increase in consumption of these new technologies is being driven by multiple growth factors. These include the need for automation, ease of use and reliable sample processing methods. Currently immunoassays account for approximately 25% of the global IVD market place with MDx accounting for approximately 6%. However it is predicted that MDx is poised to take a substantially larger share of the marketplace. The molecular diagnostic testing segment was worth $6.4 billion in 2011 and in 2016 is expected to be worth nearly $14.6 billion, a compound annual growth rate (CAGR) of 17.8%.[1] Figure 1 shows the current percentage of the molecular diagnostics market, as can be seen infectious diseases holds the largest market segment accounting for 71% of the total MDx clinical diagnostic market. To date the infectious disease market was dominated by tests for the detection or quantitation of blood borne pathogens such as HIV and HCV with the remainder tests for STIs such as *Chlamydia*, *Gonorrhea* and HPV. This situation is likely to change with pathogenic microorganisms such as Multiple Resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* emerging as major hospital acquired infections. Furthermore, with the recent outbreaks of Influenza H1N1 09 and SARS molecular diagnostic approaches to respiratory tract infections will increase due to demand for rapid testing facilities at airports and border crossings in order to contain the possibility of new outbreaks of disease.

Figure 2 shows the CAGR expected from 2010-2015 by market segment and region. The molecular segment is the growth powerhouse of the IVD market and was able to achieve a 10% expansion in 2010 despite a difficult year for the global economy. The key areas of growth in the MDx segment are infectious diseases, oncology, genetic testing and blood banking, all of which are potentially influenced by the use of rapid and simple open platform diagnostic technology.

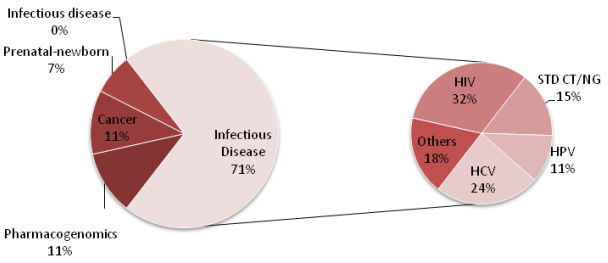

Figure 1: The current molecular diagnostics market share (source: US Molecular Diagnostic Market, Frost and Sullivan 2006)

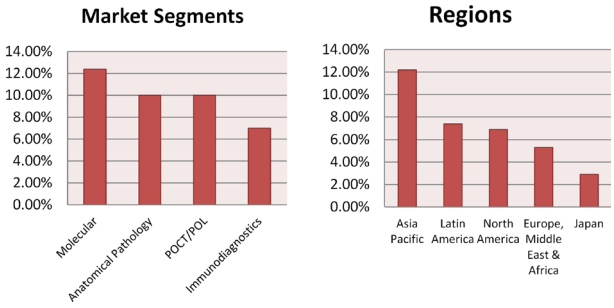

Figure 2: IVD market growth by segment and region expected from 2010-2015[2]

In 2010, estimates for the growth of the IVD market as a whole ranged from 4–5.5%. However, analysts agree that emerging markets such as Asia Pacific are reaching double-digit growth, a trend that's expected to continue (see figure 2). Overall high economic growth in emerging markets has lead to a thriving middle class and consequently greater demand for improved healthcare services. Governments in these regions are therefore investing substantially in the healthcare sector.

The emerging markets are not merely consumers of healthcare, but are gaining ground in their capacity to develop and manufacture the latest in medical technology. It has been speculated that these markets may surpass the developed countries in the production of innovative healthcare products over the next decade.

The U.S. still holds its position as global leader in medical technology and continues to show the greatest capacity for the development of new technologies and devices. However, it is predicted that the U.S. will lose ground to other countries during the next decade. By contrast, China, India, and Brazil are likely to see gains during the coming decade. China, which has demonstrated the largest improvement in its medical technology innovation capacity during the past 5 years, is expected to continue to grow rapidly and may outpace other countries and achieve a level comparable to the developed nations of Europe by 2020.[2]

The diagnostic pathology industry: An overview

The rising costs of hospital health care, illustrated in figure 3, are driving the need for rapid testing for infectious diseases to allow more informed patient triage in order to reduce transmission, prevent the use of unnecessary therapies and reduce hospital stays. Molecular diagnostic tests promise to answer the call for more community based testing and self-diagnosis, especially in the field of Respiratory Tract Infections (RTI), Sexually Transmitted Infections (STI) and Gastroenterology (GI). All of these conditions can be caused by any number of infectious agents and thus an accurate diagnosis requires a large number of traditional tests to be performed, or alternatively require the use of a MDx system with a broad testing menu.

Recent outbreaks of infectious diseases such as Influenza H1N1 09, avian influenza H5N1 and Severe Acute Respiratory Syndrome (SARS) and the rise of sexually transmitted infections (STIs) have highlighted the need for rapid testing in all areas of the community, particularly air travel, schools, and at national borders. Traditional laboratory based diagnostics cannot match the MDx approach in terms of speed, accuracy and utility, therefore molecular methods are gaining traction in almost all hospital pathology laboratories. Table 1 shows a comparison between closed systems versus a true open platform system for the use in hospital and pathology laboratories.

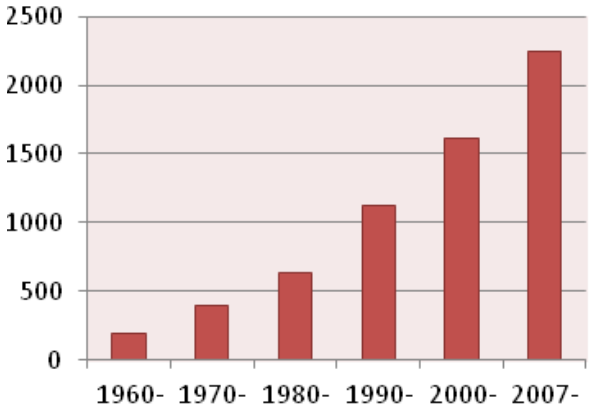

Figure 3: Rising healthcare costs 1960-2007 expressed in $B 2007[3]

Table 1: Closed vs. open platform systems upfront cost, consumables and test turn around times

	Closed Platform	Open Platform
Utilise existing infrastructure	No	Yes
Upfront instrument cost	$17,500 - >$100,000	N/A
Single analyte test	Yes	Yes
Full target menu	No	Yes
Run time	45mins - 2hours	Approx. 3hours
CLIA waved	Yes	No
Hands on time[1]	2 minute	10-20 minutes
Cost per test	$25-70[2]	$2-50[3]
Suitable for full screening purposes (e.g. GI, RTI and STI)	No	Yes
Maximum samples per run	1-16	96

[1] Hands on time per sample
[2] Single analyte test
[3] Multiple analyte test

Technology options for hospital and pathology laboratories closed vs. open platform

The Apple model: The closed technology option

Recently more and more companies are touting the use of closed 'black-box' systems that are able to extract nucleic acids from the primary patient sample and perform amplification and detection within an enclosed device. A number of systems have been developed including the GeneExpert™ (Cepheid, Sunnyvale California), Simplexa™ (FocusDx Cypress, California), IDBox™ (GenturaDx, Hayward California), Quidel instrument (San Diego, California), Biocartis instrument (Mechelen, Belgium), Panther™ (GenProbe San Diego, California) and Enigma ML (Enigma San Diego, California).

The advantages of these systems include ease of use and full integration from sample to result, allowing assays to be run using operators with little or no technical training (CLIA waved). However, such "black-box" systems also come with a number of disadvantages, the two most important being limited target menu (see tables 2, 3 and 4) and the high cost of consumables associated with the closed system platforms.

Target menu options closed vs. open platform systems

These limitations in target menu reduces the impact of the closed "black-box" system, especially when the result is negative, as the laboratory then has no choice but to

Table 2: GI target menu available for various molecular instruments

GI targets included in the system menu	
Cepheid	*C. difficile*, C. diff-epi*
FocusDx	C. difficile
Biocartis	N/A
Quidel	*C. difficile*
GenProbe	N/A
Open platform	*C. difficile*, C.diff-epi, *Cryptosporidium parvum*, *Giardia intestinalis*, *Dientamoeba fragalis*, *Entamoeba histolytica*, *Blastocystis hominis*, *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Listeria monocytogenes*, *Yersinia entercolitica*, STEC, Norovirus GI, Norovirus GII, Adenovirus, Rotavirus, Astrovirus, Sapovirus

*C. diff-epi = Epidemic *C. difficile*

Table 3: RTI target menu available for various molecular instruments

Upper respiratory tract targets included in the system menu	
Cepheid	Flu A, Flu B, *Mycobacterium tuberculosis.*
FocusDx	Flu A, Flu B, H1N1, RSV
Biocartis	N/A
Quidell	N/A
GenProbe	N/A
Open platform	Flu A, Flu B, Flu A H1, H3 and H5, RSV (A & B), Metapneumonia, Parainfluenza 1,2,3,4, Rhinovirus A/B, C, Bocavirus, Adenovirus, Coronavirus NL63, OC43, HKU1, 299E, SARS, *Mycobacterium tuberculosis*

Table 4: STI menu available for various molecular instruments

Sexually transmitted infection targets included in the system menu	
Cepheid	N/A
FocusDx	N/A
Biocartis	N/A
Quidell	N/A
GenProbe	N/A
Open platform	HPV, *Chlamydia trachomatis, Neisseria gonorrhoea, Mycoplasma genitalium, Trichomonas vaginalis*

revert to a battery of conventional tests in order to make an accurate patient diagnosis. Thus the inclusion of fully integrated systems in a laboratory setting does not necessarily help in streamlining workflows in situations where definitive pathogen identification are required.

Costs involved in MDx uptake by laboratories: Instruments and consumables

Another issue affecting the uptake of closed system MDx assays is the large investment required for proprietary hardware (in excess of $100,000 in some cases) and the high cost of consumables, which can be as high as $70 for a single test for a single analyte. This is particularly relevant as most hospital and pathology laboratories work around tight budgets and are bound by government reimbursements that do not always reflect the true cost of MDx testing. In some cases, running a single test on some closed system instruments costs much more than any available reinbursement. Alternatively a "user-pays" system that passes on the full cost of the test can push the price of each test to beyond the reach of most patients. A more cost effective system, with a broad screening menu of pathogen detection is required to provide economical optimal patient care by delivering the accurate and rapid diagnostics required for best practice patient management.

Clearly there are times when paying above reimbursement rates for a single analyte has merit. One hospital manager always runs an expensive Enterovirus assay on selected patients, as if the assay is positive the patient can be sent home with a paracetamol instead of taking up valuable space on the ward and creating further cost to the hospital. This is however the exception and not the norm as we are aware of another hospital manager who tested a black-box instrument for the detection of the common GI pathogen *C. difficile* and although the results obtained were superior and far more rapid that conventional EIA and cytotoxic culture, the machine was not placed within the laboratory for the following reasons:

1. Only a single GI analyte could be tested on the machine and no additional information could be obtained with that sample (as multiplexing was not possible on that system). Thus the lab still had to return to the sample and perform additional conventional tests increasing the overall workload not simplifying it and adding further cost to the department.
2. The cost of the consumables was above the budget of the department.

3. Other rapid molecular assays were available to the laboratory that could be run on existing equipment and provided more information on patient management.

The Microsoft model: Open platform plug and play with existing manufacturers

To address the high costs of proprietary hardware, MDx assays can be designed to be compatible with routine equipment that laboratories have already purchased, such as automated DNA/RNA extraction equipment and real time cyclers. Furthermore, as may laboratories are currently using this kind of instrumentation the end users have become increasingly well versed in the use and interpretation of results obtained using such equipment. In adopting an open-platform based MDx testing, laboratories can avoid another capital investment. Even though the hardware is becoming more common, there is currently little standardisation and end-users are free to choose an instrument from their manufacturer of choice. Table 5 shows a list of the most common molecular diagnostic hardware available from proven suppliers.

With the choices of hardware available any given laboratory may have use a different combination of instruments to other laboratories. In order to capitalise on existing hospital and pathology infrastructure it would be desirable to design multi-analyte diagnostics that are capable of running on all existing platforms. This is in stark contrast to expecting the institution to make a further capital outlay for a piece of equipment that can only assay for either one or a very small number of pathogens.

Centralisation of workflow to reduce departmental costs and improve patient care

Another issue limiting the uptake of MDx assays in conventional pathology laboratories is the lack of a centralised testing facility, as traditional testing was best peformed in separate independent departments by specialist technicians. A good example of the shortcomings of running independent departments is when a physician is looking for a rapid diagnosis of the microbial cause of a presenting GI case, yet is faced with a hospital that runs separate bacteriology, virology, parasitology and molecular divisions, each with its own nuances. However, in this same setting, an open platform system with a complete target menu would allow the molecular division to run all the preliminary testing, resulting in a more streamlined workflow and ultimately better patient management. Any presumptive positive samples could then be sent to the specialist division for further characterisation, such as antibiotic susceptibility testing.

Table 5: Sample processing and real-time PCR hardware found in hospital and pathology laboratories

Sample processing equipment	Real-time PCR hardware
Qiagen (M48, Qiasymphony, Qiacube, EZ1)	Roche Lightcycler™ I and 480
Roche MagnaPure systems	ABI Fast7500
Themo KingFisher Flex	Cepheid SmartCycler I and II
Biomerieux EasyMag	Qiagen RotorGene
	Biorad CFX96
	Stratagene Mx3000

To further streamline processes and remove boundaries between departments, testing laboratories should be able to collect a single sample from a patient, process the sample using an open platform protocol that allows for the simultaneous lysis for DNA containing pathogens (e.g *Cryptosporidium* and *Salmonella*) and RNA containing viruses (e.g Norovirus and Rotavirus). This would allow the laboratory to screen for all relevant pathogens from the same sample at the same time without the need for multiple independent tests, complex extraction procedures and independent amplification conditions. Indeed numerous managers have commented that a if such a broad menu open platform MDx option was available for GI testing they would utilise this option over the conventional methods thus streamlining and centralising patient testing.

Universal sample preparation is required for a true open platform solution

Traditionally each sample type had to be processed with separate extraction kits that have been optimised for the target organism of interest. A wide range of kits are commercially available from numerous suppliers for a number of different sample types. For example individual kits can be purchased for the purification of nucleic acids for gram negative bacteria, gram positive bacteria, viral samples, blood, sputum, faeces, plant tissues, human tissues and numerous other sample types.

In consideration of all factors limiting the use of MDx assays, our goal was to produce a simple reliable universal lysis/extraction method that would work under identical conditions for human cells, bacteria, RNA and DNA containing viruses that allow end-users to assay for bacteria, viruses, protozoan and human analytes from the same sample. This was achieved by developing a simple 15 minute method that does not require the addition of enzymes to assist in cell lysis and yet protects the labile RNA species in the sample from degradation during the processing step. This method is compatible with

downstream assays targeting double stranded DNA, double stranded RNA and single stranded RNA in the same tube from the same sample whilst reducing hands on time and costs.

Multiplexing capabilities can extend the test menus

Traditionally, molecular assays have been designed whereby a probe is labelled with a single colour and detected in a single PCR channel thus one analyte is detected per reaction. Most modern real time PCR instruments are capable of detecting at least 4 different coloured probes with a number of machines now able to detect up to 6 individual dyes. Using a multiplex approach whereby up to 6 probes can be labelled with different colours allows the detection of multiple targets in the same tube and further streamlines the molecular detection of infectious disease.

One way to improve the multiplexing capability of current real time instruments further is to use dual labelled probes (see figure 4) which can improve the multiplex capabilities of a four-channel machine to 10 analytes per reaction.[4] One drawback of this approach is that multiple infections can quickly become impossible to differentiate and cause the results to become uninterpretable. Multiple infections are particularly common in human papilloma virus infection and are also becoming more widely recognised in GI and RTI thus the use of such approaches although increasing multiplexing capabilities have to be viewed with caution.

Multiplexing has traditionally been difficult due to the different nucleic acid sequence composition of individual pathogens. In effect the temperature at which a PCR reaction can be carried out can become problematic as the primers and probes present in the reaction will bind to the targets at different temperatures and so some targets may be amplified more preferentially than others due to the kinetics of the reaction (see figure 5). We have developed a novel chemistry that reduces this temperature bias. This has the advantage that multiplexed reactions become far easier to design and all targets can be amplified at the same temperatures. This results in assays that do not favour the amplification of one target over another thus improving both assay sensitivity and specificity.

Existing intellectual property (IP) may be required to enter the MDx space

Another significant factor to the overall pricing structure of commercial molecular diagnostic reagents is the additional cost of licencing intellectual property (IP) from third parties so that the manufacturer has freedom

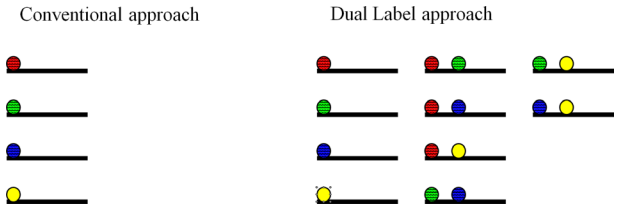

Figure 4: Increased multiplexing achievable using dual labelled probes versus single label probes

	Conventional sequence	Tm	Modified sequence	Tm
Primer1	GTACACACCGCCCGTCGCTCCTACC	77°C	GTATATATTGTTTGTTGTTTTTATT	52°C
Primer2	GAAGGAGAAGTCGTAACAAG	56°C	GAAGGAGAAGTTGTAATAAG	50°C
Probe1	TGAATAAAGAGGTGAAATTCTAGG	59°C	TGAATAAAGAGGTGAAATTTTAGG	59°C
Probe2	GAAGGGCCGCGAGCCCCCGCGC	87°C	GAAGGGTTGTGAGTTTTTGTGT	62°C

Figure 5: Improvement achievable using modified nucleic acid sequences to enhance the efficiency of real-time PCR multiplexing by converting C bases to T, thus resulting in a more similar melting temperature (Tm).

to operate within the jurisdiction that the test is being sold. Licensing fees and up-front payments can add millions of dollars to the development and production costs of a new diagnostic assay. These additional costs are absorbed in the final cost of the assay to the consumer. Thus novel companies having strong IP portfolios and who are not reliant on third party IP are able to offer cheaper assays to the end-user, as they may not have to pay additional fees to ensure freedom to operate. As previously stated this is particularly relevant to resource poor countries with emerging health markets such as India, China, and Taiwan, where the growing middle class markets are increasing the consumption of diagnostic technology. Thus open platform diagnostic assays that are compatible with the widest range of routine hospital hardware and are unencumbered from existing IP have the ability to penetrate the largest share of the current molecular diagnostic market including the developing countries.

Novel proprietary solutions have been developed that allows freedom to operate in the competitive MDx space without relying on third party licences. Such assays from Human Genetic Signatures Pty Ltd allow freedom to operate in most jurisdictions without infringing existing real-time patents reducing the end cost to the consumer. In addition, the 3base™ technology is not encumbered by any current DNA or RNA sequence-based IP. Furthermore, as noted above, the technology has now been refined to allow sample lysis to occur under universal conditions for any pathogen, allowing bacterial, viral and protozoan nucleic acids to be assayed at the same time in the same tube.

Advantages to the open-platform approach

The use of the open-platform approach has a number of advantages over closed systems for hospital and pathology laboratories that are equipped with the basic hardware to perform real time PCR.

- No capital outlay is required for the institution before they can run the assays on equipment that the technicians are already familiar with.
- A complete target menu is available, thereby streamlining the workflow of the laboratory and eliminating the need for multiple independent assays to be performed on the same sample.
- The assays are amenable for use in an emergency department setting as results are available in less than 3 hours, from sample to result. The physician can request a complete screen of possible bacterial, viral or parasitic infectious agents and can thus provide rapid and appropriate patient management,
- Our approach is unencumbered by existing IP resulting in tests that are more economical for the end user and importantly without the loss of sensitivity or specificity.
- The tests are ideal for use in resource poor settings that have centralised testing facilities that are predicted to become major markets in the next 5-10 years.
- The tests are available to the widest possible number of laboratories from the smallest pathology labs to the largest teaching hospitals.
- Sample extraction is universal for all pathogens whether they are DNA or RNA containing and can also be used on difficult to lyse organisms such as parasite cysts but has the advantage that labile RNA is protected during the critical sample-processing step.
- Samples can be processed using an automated system or can be processed manually depending on the resources of the institution.

CONCLUSIONS

There is no doubt that closed platform sample to result "black-box" type equipment has the potential to revolutionise the molecular diagnostic industry by providing easy to use assays that can quickly identify specific pathogens of interest. However, there seems to be an ever-increasing number of instrument manufacturers that are entering this particular niche. With so many instruments becoming available will the market soon be saturated with these devices? Which one should a hospital choose? If the wrong decision is made it could be a costly white elephant. This situation is analogous to the microarray market some years ago where numerous instruments became available from a wide range of vendors. These instruments cost in most cases in excess of $250,000 in capital outlay. In the end two instrument makers (Affymetrix and Illumina) became the dominant market forces leaving labs that purchased rival equipment out of pocket and with instruments that were no longer supported and could not be used due to the consumables being discontinued. A similar scenario is likely with makers of "black-box" type instruments in that the majority while appealing at the time will loose out in the end to one or two dominant players. However, whoever wins the majority market share will still be vulnerable to new technologies as is the case with next generation sequencing and the microarray market.

In addition, to date the menu of these devices has been severely hampered to that of "in-favour" and highly profit driven analytes with the exclusion of targets that are tested daily in the hospital and pathology labs. Thus a negative result means that the laboratory has to return to the sample and perform a further battery of more conventional test to isolate the pathogen causing the disease. Furthermore, the cost of these tests can become prohibitive when a single cartridge can be up to $70. On the up side with more and more companies entering this space costs will be driven down. But how far down can these costs ultimately come? With the high cost of producing and manufacturing equipment, cartridges and reagents coupled to the IP barriers that have to be negotiated prior to selling the test in specific territories, prices are unlikely to significantly decrease. However, each assay requires a separate cartridge to be run on the system and if the manufacturers wanted to include a complete menu, in excess of 10 cartridges may be required to run a complete GI pathogen detection program for example. This would drive the cost so high it could very quickly become so costly as to be prohibitive, limiting the use of "black-box" devices as a primary screening tool.

An alternative more cost effective approach that could be used as a primary screening tool for the diagnosis of GI, RTI and STI could be to provide open platform

solutions that have the widest target menu. This means that any laboratory that is equipped with a real-time PCR instrument, from any manufacturer, can immediately begin testing without further capital outlay. This approach also reduces the chances of a hospital acquiring an instrument that may become obsolete in a few years as conventional real-time PCR is unlikely to be superseded in the near future due to the low cost and proven track record of this technology. Whilst next generation sequencing has made tentative forays into molecular diagnostic space, it is unlikely to be used as a routine screening tool for hospital diagnosis of infectious disease in the near future due to the prohibitive costs, turnaround time and complexity required in data interpretation.

Using the open platform approach even the smallest of laboratories can have access to a system that will test for a wide range of specific pathogens even if they had traditionally been hampered by lack of specialists in that area. By providing a complete menu for each sample type the workload of the laboratory can be effortlessly streamlined so that one sample can be tested for all the targets that would previously have to be tested by different departments. Importantly, since common PCR consumables are inexpensive large screening panels can be run easily and cost effectively which could not be achieved using the cartridge-based system required for close "black-box" instruments.

Patient triage can be improved at admission and in the emergency department so that optimal patient care is provided at the earliest opportunity by testing samples using the widest possible platform menu with the effect of reducing hospital stay and reducing the economic burden of infectious disease to the individual hospital.

Reduced costs of reagents would also enable such tests to be widely adopted in the health care system and help the placement of these tests in resource poor settings which already have centralised testing facilities. Having universal extraction and PCR conditions also simplify the use of such assays for the operator as different targets do not have to be treated differently again streamlining the process of sample to result-without the 'black-box"?

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