Feasibility for Genechron to develop its miRNA as diagnostics and prognostics

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Feasibility Study Report

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1. Introduction: MicroRNA and their utility as biomarkers

The first miRNA (lin4) was discovered in worms (*C.elegans*) in 1993; in 2001 the first miRNA was reported in mammals; this year miRBase, the world online platform for searching published miRNA sequences released version 22 of its software, with more than 38000 different miRNA reported from 271 species. Of these nearly 4000 miRNAs are from humans. While, the functions of most of these miRNAs still remain to be discovered, these molecules have been demonstrated to be involved in several crucial life processes and human diseases.

MiRNAs are small non-coding endogenous RNAs that regulate gene expression by directing their target Messenger RNAs for degradation or repression. Messenger RNA are the molecular precursors of proteins, thereby degradation or repression results in the absence of the associated protein. Their discovery added a completely new insight to the understanding of the complex gene regulatory networks that exist in mammals.

It has been speculated that miRNA may fine-tune the expression of as much as 30% of all mammalian protein-encoding genes. Their expression levels (both increases and decreases) are therefore critical and are considered to play a role much earlier in the cellular response; significantly before the protein or enzymes upon which the present biological diagnoses of liver diseases are targeted towards, and therefore provide an early warning. They have been shown to be involved in a wide range of biological processes such as cell cycle control, apoptosis and several developmental and physiological processes including stem cell differentiation, hematopoiesis, hypoxia, cardiac and skeletal muscle development, neurogenesis, insulin secretion, cholesterol metabolism, aging, immune responses and viral replication.

In addition to their important roles in healthy individuals, miRNAs have also been implicated in a number of diseases including a broad range of cancers, heart disease and neurological diseases. Consequently, miRNAs are intensely studied as drug targets, candidates for diagnostic and prognostic biomarkers and predictors of drug response.

2. Genechron's validated microRNA biomarkers and their comparison

MicroRNA 1, 133 and 206

The muscle miRNA that are within the patent portfolio of Genechron which have been validated are indicated in table 1; these represent a comprehensive panel of miRNA biomarkers linked to skeletal muscle that are able to be absolutely quantified using the proprietary methods that form the company's know-how.

miRNA	Skeletal muscle disease relevance	Cardiac/Cardiovascular disease relevance
1	Provides information on muscle differentiation (lower in damaged muscle, restored to normal after repair).	Provides information on myocardial Infarction and heart failure (decreases in expression indicative of potential infarct).
133	Indicates muscle differentiation (low in damaged muscle, restored after repair)	Decreased levels indicative of cardiac hypertrophy
206	Increases as a function of muscle regenerative responses totissue damage	Significant increases imply cellular apoptosis and myocardial infarction

This panel of markers has the potential to be used in

- Sarcopenia
- Mitochondrial dysfunction based myopathic diseases
- Cardiac and cardiovascular damage and degeneration that present as a comorbidity with the above skeletal muscle diseases

There is a total absence of relevant and approved diagnostic and monitoring products for skeletal muscle diseases globally; yet needs are high and growing. Using the lowest prevalence estimates, analysis of Sarcopenia alone indicates that the number of affected individuals in Europe in 2016 was 10,870,000 which is expected to rise to 18,735,000 in 2045 (a 72.4% increase). Using the higher prevalence estimates, this number is 19,740,000 in 2016, rising to 32,339,000 in 2045 (a 63.8% increase).

The average hospital related cost for caring for patient with Sarcopenia and Myopathies is €1000/visit. Using the lowest possible assumption that a patient visits a hospital twice a year (however in reality it can be up to 4 times), this results in a total European healthcare system financial burden of between €21 billion and €39 billion for 2016, growing to between €37 billion and €65 billion in 2045. All of this is dependent on a correct diagnosis revealing more accurate demographics, while the values above do not account for costs of therapeutics, those related to addressing co-morbidities an lost days of productivity, therefore healthcare costs will be much higher.

No prognostic or diagnostic system exists that correlates with the disease progression, including the measurement of concomitant comorbidities such as cardiac and cardiovascular degeneration.

The problems that this absence of clinically validated biomarkers creates, stretches throughout the whole value chain of healthcare; from primary care in local medical centres and hospitals through to the creation of new therapeutics by small and large

companies. Ultimately our products will provide solutions that reduce costs and risks for all these stakeholders, impacting on a global scale.

The changing global demographic in which age-related diseases are now prevalent and represent a significant burden and drain on health care systems is well documented; these diseases, and specifically the myopathies, impact an enormous number of our populations; are slow, progressive resulting in significant patient morbidity and loss of quality of life and productivity, which in turn creates an exacerbated stress on the patient resulting in the development of further significant comorbidities.

The primary morbidity and the resulting comorbidities are then treated with a plethora of medicines that a patient has to take daily at significant cost either to themselves or the healthcare system, or both. At the primary care level, poly-pharmacy has become a real issue; a given patient having to take 7 to 10 different pills a day often results in side effects occurring which were not seen previously or in the efficacy of one therapeutic cancelling out the effect of another; independent of this the disease continues to progress with increasing costs.

The market potential of this approach extends from preclinical development of therapeutics, along the total value chain into patient care and management.

Preclinical to clinical transition of new therapeutics: Genechron's muscle MiRNA biomarkers are highly conserved across species, with ours proven in small and large preclinical animal models. Being able to use an easy to use and longitudinal based blood biomarker to provide additional information on therapeutic efficacy, which correlates to the human scenario will both reinforce the validity of the therapy being developed and inform the selection of patients and clinical trial design.

Targeting cardiovascular disease as a primary morbidity: The market is presently crowded and a significant number of clinical diagnostics and patient monitoring systems exist. However assays that can simultaneously and with high sensitivity assess skeletal muscle disease with cardiological co-morbidity is absent, therefore there is the opportunity to position Genechron's muscle miRNA approaches as a cardiological morbidity diagnostic/prognostic product.

Targeting diseases in which both skeletal muscle disease and cardiac muscle disease present as comorbidities: COPD (chronic obstructive pulmonary disease) has no effective cure and is fatal, cancer is a global problem, chronic kidney disease is linked with ageing and diabetes is almost unmanageable within present healthcare systems. For all of theses disease muscle atrophy is a serious complication, being associated with increased morbidity and mortality.

Future diseases in which miRNA become validated: many diseases and their miRNA profiles are still not scientifically validated e.g. neurological disorders and bone diseases such as osteoporosis; still indicating a vast number of miRNAs that need to be measured and correlated with each other and anthropometric, body composition, functional status and biochemical indicators. These offer future opportunities.

There are also additional areas of market application such as sports medicine and veterinary practice; these are large and valid markets and are presently being explored

The muscle miRNA panel has been reproducibly confirmed experimentally to be indicative and implicated in Sarcopenia but has been disputed in the rare muscle diseases; sarcopenia, its underlying pathology and associated comorbidities have

become significant socioeconomic problems, with alarmingly increasing prevalence; yet no reliable diagnostic exists, outside of physical measurements, by which point the disease is in a fairly advanced degenerative process.

Whereas prior approaches focused on the miRNA linked exclusively to the muscle cells themselves, which was also performed with regard to the miRNA 1, 133 and 206, it is now increasingly apparent that the disease necessitates a more comprehensive diagnosis.

Muscle damage in all forms, also results in significant fibrosis (tissue scarring) and inflammation (a common effect in all tissue damage) and that the total miRNA profile of the damage correlated with other standardised clinical measurements is more informative. Similar to the capacity to measure cardiac/cardiovascular comorbidity, we know that using Genechron's complete miRNA panel the company will be able to measure absolute levels of fibrosis and inflammation as a function of muscle disease, correlated to muscle function read out.

MicroRNA122

MiRNA122 is highly abundant and specific to all vertebrates; its nucleic acid sequence is completely conserved between species, highlighting its evolutionary significance and translational application along the healthcare value chain. Within the liver its expression accounts for greater than 70% of the total miRNAs present with a high level of tissue specific expression; miRNA122 expression in the liver is at least 1000 time greater than in any other tissues.

MiRNA122 is particularly relevant because of this tissue specificity; considering the large number human miRNAs it is remarkable to have one expressed with the observed high kind of propensity in liver. There has, therefore been a lot of attention paid to miRNA122 changes in liver diseases, particularly in the circulation, in the plasma and serum compartment. Various studies have demonstrated that in drug-induced liver injury there is increase in the serum levels of miRNA122, which occurs significantly before the expression of the enzyme and serum proteins that are used to diagnose liver damage.

Serum miRNA122 variations have been identified as the biomarker for many types of liver damage from many sources; Some studies have also revealed that serum miRNA122 can be used to differentiate between different types of liver damage that has occurred, which we summarise below.

- In human hepatocellular carcinoma (HCC or liver cancer) data show that miR-122 has a low expression, compared to healthy controls and that this correlates with poor prognosis.
- In both human and murine models of liver damage from alcohol and from Hepatitis B, miRNA122 levels were elevated under damaged conditions, with levels correlating to disease scoring and severity.
- In response to acute hepatotoxicity in humans, miRNA122 levels correlated with serum liver protein levels, and further noted that when comparing HBV-associated liver damage to HCC-associated liver damage, the miRNA122 profiles were distinct. MiRNA122 levels correlated with disease severity - although not viral titer - in chronically HCV infected patients,
- miRNA122 levels correlated with disease severity in patients with non-alcoholic fatty liver disease.

- In human liver transplants, miRNA122 was identified as a biomarker for liver damage, its expression was also significantly increased prior to and during acute transplant rejection.
- Serum levels of miRNA122 were elevated in patients experiencing acute acetaminophen poisoning, and these levels were higher than with other forms of acute liver damage.
- In a preclinical mouse model system, the circulating form of miRNA122, could be used to not only detect liver damage, but also to differentiate between causes: drug-induced injury led to miRNA122 being found in the protein fraction of the mouse serum, while alcohol and inflammation-induced liver damage led to circulation of miRNA122 in exosomes.

The relevance and broadness of the applicability of miRNA122 in liver damage, we present below, indicating in which market segments and geographies the final medical device we are developing can be applied. Given the large scope of application and the number of diseases, versus the complexity of methods used for liver disease assessment it is important to indicate the relevance of our objectives.

'Monitoring of changes in miRNA profiles might provide earlier warning of changes in liver function preceding appearance of hepatocellular carcinoma, resulting in more effective treatment and improved survival Such improvements are urgently needed'

3. Present market acceptance of miRNA

As experimental markers, microRNA are widely used and reported in the literature; additionally non-coding RNA discovery, of which microRNA are one component, results in numerous molecules being identified and reported on a monthly basis.

The clinical and more importantly commercial use of these markers in higher regulated aspects of healthcare has proved significantly more problematic, as fundamentally the aim is to generate a commercial product that will be reimbursed by some entity, or private person.

This means that the quality and reproducibility of the measurement and its correlation in a statistically relevant number of precisely defined patients has to be repeatedly performed to enable commercialisation: this has created the following barriers.

Source of tissue and collection method: At the clinical level the collection and storage of human tissue samples are not standardised and to a large extent depend on the infrastructure and staff availability for correct collection and storage. RNA nucleic acids are very sensitive and any change in condition between samples handled can induce degradation and therefore variation. Additionally assessing microRNA expression from solid tissue vs circulating RNA from serum or plasma from the same patient can reveal great variation (as witnessed in breast cancer), which the clinicians do not like as it prevents effective patient management.

Number of molecules vs and correlated with existing and known clinical parameters: there are no major diseases that can be identified with one, two or even three microRNA markers. For typically complex diseases there are more than 8 different microRNA that need to be looked at for each patient; the reason is that all complex diseases affect multiple components of the same tissue. For example, heart disease has heart muscle, vasculature, neurological, homeostatic , inflammatory and immune components all of which will produce various non coding RNA; and more importantly one component in the tissue may affect the other as a result of normal biological process rather than disease specificity.

These measurements then have to be correlated with age, gender, weight, and a plethora of numerous other biometrics in a large enough patient population to become valid. The issue is further complicated in that for many diseases, co-morbidities also significantly impact the disease and need to be factored in.

For example, in muscle disease there is the necessity for larger scale clinical studies that validate the microRNA and tie it into additional metrics: for example for skeletal muscle diseases the microRNA measurements will need to be statistically integrated with clinical measurements from a large number of patients corresponding to weight, body mass index, waist circumference, fat free mass, %fat, muscle in Kg, extracellular water, intracellular water, SMI (relative skeletal muscle index) and total cholesterol, muscle function and with clinical outcome analyses (objective assessments: Short Physical Performance Battery (SPPB), 6MWT, and 3TUG test, Myomether with a handgrip, spirometry FVC; subjective assessments (fatigue measurement by the “Fatigue Assessment Scale” and the “Checklist Individual Strength-20”), to be able to define the relevance. All of these measurements would also need to be performed over a long enough time scale to prove that the microRNA levels correspond to disease severity and/or response to therapy.

This does not means that the opportunity is not there, more that significant resource needs to be engaged to generate a clinically related product that can be reimbursed,

less so for use in early stage clinical development, and like all products the simpler and broader the application can be the more lucrative it can become.

Market interest has not abated, as proven by the established German Nucleic acid company, Qiagen purchasing the incumbent microRNA company, Exiqon and investing resources to try and generate a dedicated clinical microRNA market.

4. Recommended microRNA(s) to focus on

Based on the points above, it is the recommendation that Genechron focus on the development and application of serum microRNA122 (miRNA122) as it has been confirmed as an early and very specific marker, for liver damage.

Liver damage is a huge problem, no cheap, effective or broadly applicable assay presently exists that can be used in any stage of healthcare, while the species conservation implies that a product based on this has applicability in earlier stages of therapeutic development and also into unexplored markets such as animal health.

More importantly, liver tissue damage results in this one microRNA's level being significantly impacted, meaning that there is not the necessity to add in other microRNA to generate a product that overlaps with existing screening and diagnostic approaches. It fundamentally has the possibility to generate a yes-no answer of whether to recommend the patient for more advanced diagnostics.

It also has significant future innovation potential; as development in a Point of Care device, to measurements from totally non invasive samples such as Saliva to potentially creating systems that measure it without the need for high technology.

5. Geography of market

The geography for liver disease is global, as is indicated below in the Liver Disease section. Every form of liver disease and damage is growing dramatically all over the planet and there is still no effective therapeutic, except to effectively and accurately diagnose as early as possible and prescribe preventative or disease progression slowing interventions; any product developed will therefore have application in all levels of healthcare, providing the method is simple, reliable and affordable.

Summary of healthcare settings:

Primary care	The primary care level is the "gatekeeper", the first point of medical consultation. As a patient you are usually seen by a primary care physician, also called a general practitioner or family physician. Primary care is provided at a doctor's office, health center or Urgent Care center. The Emergency Room is also often a source of primary care for the un- or under-insured. Demand for primary care continues to grow as patients become older and sicker. At the same time, there's an increasing shortage of general practitioners. To meet the demand, physicians are starting to utilize nurse practitioners and physician assistants
Secondary care **(aka 'specialised care' or 'specialist centres')**	Medical specialists and other health professionals, who typically don't have initial contact with patients, provide secondary care. For example, a primary care physician might refer a patient to a cardiologist, rheumatologist, or a urologist or other specialty physician. Some secondary care physicians do not require a patient to have a referral from a primary care practitioner. Another category of secondary care is hospital care, or acute care. The term covers care as an admitted patient in a hospital, a visit to a hospital ER, attendance in childbirth, medical imaging (radiology) services and care within an intensive care unit. Physical therapists, respiratory therapists, speech therapists, occupational therapists and other allied health professionals often work in secondary care.
Tertiary care	This is a specialised consultative health care for inpatients. The patients are admitted into these centres on a referral from primary or secondary health professionals. Tertiary health care is provided in a facility that have personnel and facilities for advanced medical investigation and treatment. Services provided include cancer management, neurosurgery, cardiac surgery and a host of complex medical and surgical interventions. Advanced diagnostic support services and specialised intensive care which cannot be provided by primary and secondary health centres are available at the tertiary health centres.
Quaternary care	The term **quaternary care** is sometimes used as an extension of tertiary care in reference to advanced levels of medicine

	which are highly specialized and not widely accessed. https://en.wikipedia.org/wiki/Clinical_researchExperimental medicine and some types of uncommon diagnostic and surgical procedures are considered quaternary care. These services are usually only offered in a limited number of regional or national health care centers
Home, nursing and community care	Many types of health care interventions are delivered outside of health facilities. They include many interventions of public health interest, such as food safety surveillance, distribution of condoms. They also include the services of professionals in residential and community settings in support of self care, home care, long term care, assisted living, treatment for substance use disorders among other types of health and social care services. Community rehabilitation services can assist with mobility and independence after loss of limbs or loss of function. Many countries, are dealing with aging populations, so one of the priorities of the health care system is to help seniors live full, independent lives in the comfort of their own homes. There is an entire section of health care geared to providing seniors with help in day-to-day activities at home such as transportation to and from doctor's appointments along with many other activities that are essential for their health and well-being.

6. Served industry markets

Improper functioning of the liver causes many severe diseases; viral induced liver failure, Non-alcoholic Fatty Liver Disease, Alcohol induced liver disease, drug induced liver injuries due to poly-pharmacy, Primary Biliary Cirrhosis and Cancer, towards which virtually all liver diseases essentially progress.

If diagnosed early enough, most of the diseases can be stopped and liver damage regressed; however the existing diagnostic systems rely on expensive and cumbersome medical infrastructures located in hospitals, which only diagnose liver disease when it has progressed to an advanced stage.

There are presently, greater than 1 billion at-risk patients globally who require an effective and rapid surveillance and monitoring for liver diseases, and this number is rapidly growing. This volume of patients cannot pass through hospitals to use the existing equipment, and indeed it has been reported in developed countries that over 75% of patients with liver damage are never referred until it is too late. Since 1970, the mortality rate therefore has increased by 400%. This is in stark contrast to other conditions such as heart diseases and many cancers where mortality decreased due to advances in diagnosis and treatment. Liver diseases such as Non alcoholic fatty liver disease (NAFLD), which is estimated to affect more than 350 million people worldwide by 2030; it is estimated that NAFLD will increase massively in the Middle East, India, China and South East Asia but also in regions such as North America and Europe.

The liver is one of the most important organs of the human body and performs major functions, such as removal of harmful substances from blood, maintains adequate level of chemicals in the body and stores nutrients for all cellular and biological activities. Improper functioning of liver causes many severe diseases, such as hepatitis A, B, C, Non-Alcoholic Fatty Liver Disease (NAFLD), Primary Biliary Cirrhosis and cancer.

There are presently, greater than 1 billion at-risk patients globally who require an effective and rapid surveillance and monitoring for liver diseases, and this number is rapidly growing. In 2014, Williams and his colleagues published in *The Lancet* an analysis of how liver disease is managed in healthcare within the UK, the conclusions of which are relevant in other developing countries and more profoundly worldwide, they stated:

> *'Liver disease. stands out as the one glaring exception to the vast improvements made during the past 30 years in health and life expectancy for chronic disorders such as stroke, heart disease and many cancers. Mortality rates have increased 400% since 1970 and in people younger than 65 years have risen by almost five-times. Liver disease constitutes the third most common cause of premature death'*

This conclusion was related only to the developed world's major disease demographic problems (obesity and ageing), and did not address the significantly large number of other liver diseases. Integrating these events, which give rise to liver damage in geographical areas that do not have a similarly high tech healthcare infrastructure, but require support nonetheless, increases the need to resolve the underlying cause.

Within developed countries, the reason proposed by Williams *et al* was very worrying, as indicated in the figure below. They determined that the major reason that liver diseases are so fatal is because patients suffering from are not referred

properly or quickly enough for sequential clinical care to be implemented that could have any effect.

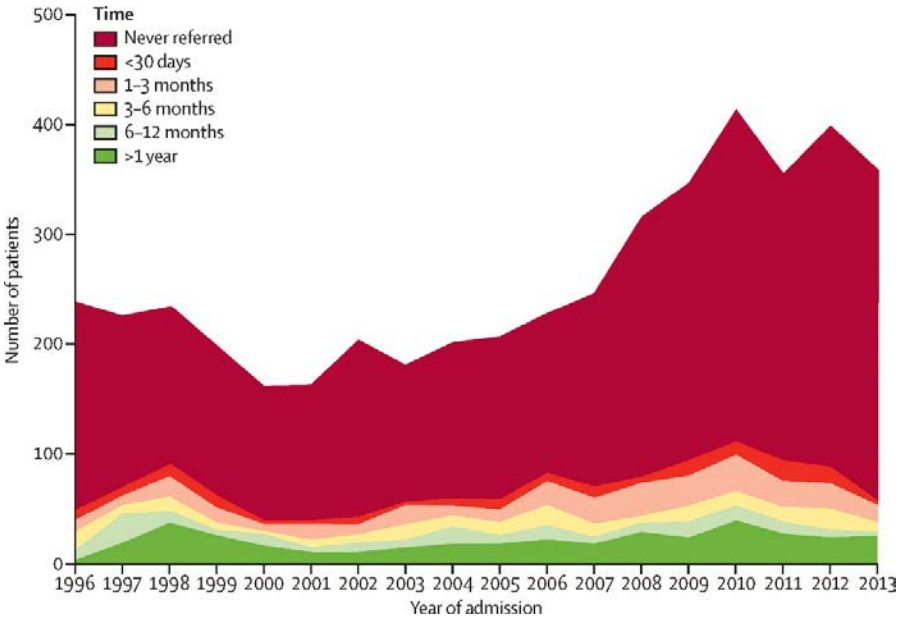


Figure 1: Liver disease referrals in the UK from 1996 to 2013. Image taken from Roger Williams 2014 publication in the Lancet.

The reason why there are not sufficient referrals is because **there is not an effective, easy to use, low-cost and reliable early warning diagnostic system which can used at the primary care site**. Such a device would detect liver damage early enough and reliably enough to enable an informed interventive health care decisions to be made, to benefit the patient's life. This need has prompted innovation in the liver diagnostic sector, as reported on March 17th 2015 in the Health Economic Times article - New Market for liver disease spawns race for better testing '*As drugmakers develop new medicines to battle a liver disease epidemic, they have created an urgent need for better diagnostics'*.

7. Liver diseases

The healthcare marketplace has determined the users needs: an affordable, sensitive, easy to integrate into existing infrastructures patient management system for liver disease. The market is large and unfortunately growing, due to the increasing global obesity issues.

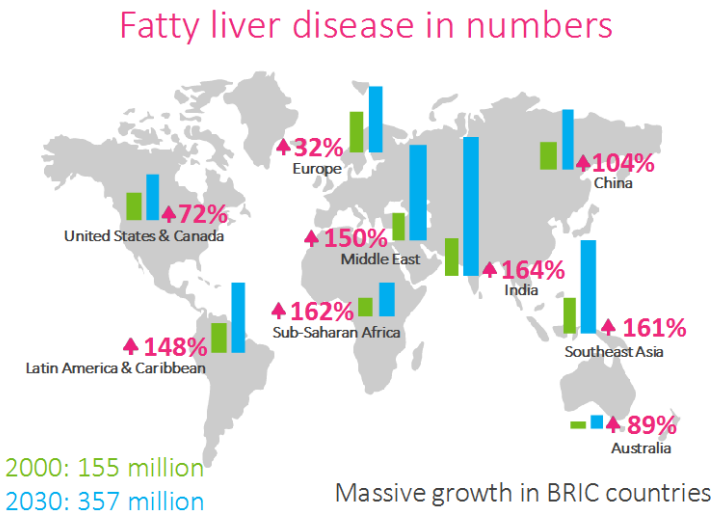
Non Alcoholic Fatty Liver Disease (NAFLD)
NAFLD is the most common cause of all liver disorders; it is the most frequent cause of end stage liver disease necessitating liver transplant, and is present in **up to 75% of individuals with obesity and type 2 Diabetes**; it is therefore a global problem as indicated by the demographics in below.

NAFLD is an umbrella term for a spectrum of liver damage including fatty liver, non-alcoholic steato-hepatitis and cirrhosis, without alcohol being the causative agent. NAFLD is best considered as the hepatic manifestation of the metabolic syndrome. Obesity and insulin resistance are major risk factors for NAFLD. A large European study found NAFLD in 94% of obese patients, 67% of overweight patients and 25% of normal weight patients. Between 40-70% of patients with NAFLD have Type 2 Diabetes. NAFLD is reversible if the underlying cause (obesity) is tackled. Over 75% of people with NAFLD have simple steatosis, which is a benign condition, and unlikely to progress to fibrosis or cirrhosis. 15% of those with NAFLD have evidence of liver inflammation (non-alcoholic steatohepatitis NASH) and may have fibrosis. Liver function tests are not reliable in this instance and may be abnormal. For those who develop NASH 5% will go onto HCC

Specific values of NAFLD frequency in Europe as a whole are absent, however national studies have revealed similar startling figures as for the USA: A Romanian study estimated NAFLD prevalence to be 20%, Two major European studies reported NAFLD prevalence rates of 42.6–69.5% in large samples of type 2 diabetic patients.

In the USA, figures reported in September of this year, revealed that the Healthcare (clinical and economical) costs of NAFLD were $103 billion; we can anticipate that values will be similar for Europe, and in light of the increasing global prevalence and demographics will overwhelm healthcare within a generation.

Levels of miRNA122 in serum and liver were significantly correlated in patients with NAFLD, suggesting that miRNA122 released from hepatic cells enters the bloodstream. Serum levels of miRNA122 were lower in individuals with mild fatty liver disease, compared to those with severe fatty liver disease, but higher in patients with mild fibrosis compared to those with severe fibrosis. This result is in agreement with those of previous studies, reporting decreased levels of hepatic miRNA122 at advanced stages of fibrosis in patients with liver disease. The reason for the discrepancy in miRNA122 levels in NAFLD stage may represent the loss of hepatocytes in worsening liver injury. Because hepatocytes are the primary source of miRNA122 and since worsening of liver fibrosis results in the replacement of hepatocytes with extracellular matrix, hepatic miRNA122 levels may be expected to decrease with severe fibrosis. These results indicate that levels of miRNA122 have significant prognostic value for patients with NAFLD.



Global development of NAFLD from 2000 to 2030

Drug induced liver injuries (DILI).

DILI is the fourth leading cause of liver damage in Western countries and is a growing problem in the BRIC geographies; it is the most frequent cause of market withdrawal of a drug and rejection of applications for a marketing license. The U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) proposed guidelines for DILI in 2009 and 2010, respectively. At present frequencies are at 14 per 100 000 inhabitants and is increasing and more drug combinations plus OTC drugs and dietary supplements are inadvertently combined. The rising number of marketed drugs, aging population and poly-pharmacy make it imperative to understand the clinical presentation of DILI. Of the estimated 10,000 documented human drugs, more than 1000 have been associated with DILI, although causality has not always been established clearly. Numerous tests for DILI have been explored, but less than ten are adopted or qualified as valid. The tests for DILI are individual or a panel of proteins, nucleic acids or metabolites from various sources, such as the liver, blood and urine.

It is also a strong consideration in differential diagnosis when abnormal liver-related chemistries are identified in persons with minimal or no symptoms. There is presently no specific diagnostic test for DILI, or a means of confidently singling out an implicated drug. The overall frequency of hepatotoxicity for all drugs has not decreased in the last 15 years despite improvements in toxicological studies and in the safety analyses of clinical trials. Furthermore, the early detection of drug hepatotoxicity remains very difficult. Hundreds of agents can lead to liver injury. LiverTox (http://www.livertox.nih.gov/), an online database that provides detailed information on more than 600 such agents, indicates that antibiotics are the most common cause of DILI, followed by neuropsychiatric drugs, immunomodulatory agents, antihypertensives, analgesics, antineoplastic drugs, and lipid-lowering agents. The use of multiple drugs (polypharmacy) further increases the risk of developing DILI.

If an elderly patient takes several medications at the same time, they are at high risk for drug related problems. Elderly patients are particularly susceptible to polypharmacy issues because aging affects how their body handles medications, and they take more medications than younger patients: In most countries, people over 65 make up approximately 13% of the population but use about 30% of all prescriptions written. At any given time, an elderly patient takes, on average, four or

five prescription drugs and two over-the-counter pain management medications. An elderly patient is also more likely to be taking a medication that has been prescribed inappropriately (one that's unnecessary, ineffective, or potentially dangerous) and to suffer an adverse drug event (ADE). Most ADEs are the result of drug interactions; the more drugs a patient takes, the higher the risk of interactions. The estimated incidence of drug interactions rises from 6% in patients taking two medications a day to as high as 50% in patients taking five a day.

MiRNA122 has been shown to be a very early and sensitive biomarker of DILI. The earliest studies of serum miRNA in Acetominaphine (active component found in paracetamol) hepatotoxicity found that even subtoxic doses of APAP could increase miRNA122 levels in serum of mice while standard liver protein levels were unaltered. Similarly, it was reported in a particularly interesting case study that miRNA122 levels were elevated in a very early-presenting patient who lacked any other clinical evidence of liver damage. The patient returned to the hospital two days later with elevated liver enzymes and evidence of impaired blood clotting. These data suggest that serum miRNA122 measurement may be useful during early phase human trials to identify drugs that cause subclinical liver cell stress and therefore have the potential to cause hepatotoxicity (including idiosyncratic hepatotoxicity) once on the market.

Primary liver cancer (Hepatocellular carcinoma)

Hepatocellular carcinoma (HCC), accounts for 70–90% of primary liver cancers. Without any treatment, HCC is rapidly fatal, with a 5-year survival rate of around 5%. When liver resection with curative intention is performed, 5-year survival rates reach 26-40%. The management of HCC is complicated by the presence of liver cirrhosis in more than 80% of patients. Liver cirrhosis is often the direct cause of death and may hinder cancer treatment. Over half a million new cases of HCC are diagnosed each year worldwide. In recent years decreasing incidence has been reported in some high incidence countries due to preventative and educational actions, while significant increases have been reported in several low incidence countries. The latest data from the EU has indicated that liver cancer incidence was 10.6 and 3.6 per 100,000 persons for men and women, respectively. As expected, estimated mortality rates were very close to incidence rates. Outside of Europe, the situation is much worse: in the USA the estimated number of patients under effective surveillance for liver cancer are around 620 000, some have speculated that this is less than 20% of those that are thought to be requiring it.

The World Cancer Research Fund International, has estimated that over 780 000 new cases of liver cancer are diagnosed each year; it is the 6th most common cancer. Given the link of liver cancer to Hepatitis infections and to alcohol consumption, they estimated that 83% of these new liver cancer cases are occurring in less developed countries, with the highest incidences in Asia and Africa. The value of the global liver cancer diagnostic market has therefore been estimated at $8 billion.

Within HCC, numerous clinical analyses have revealed that loss of miRNA122, to levels lower than healthy individuals has been observed in patients with this disease. Furthermore, decreased miRNA122 levels have been associated with poor prognosis and metastasis of liver cancer.

Liver damage from Hepatitis (A, B, B+D, and C types) infection

Hepatitis in all forms results in liver damage; in addition to diagnostics to assses if a patient has hepatitis, there is also a drastic need to understand if there is liver damage. This damage can occur over long periods of time, therefore sensitive early stage assays are critical, especially in developing countries.

Hepatitis A is caused by infection with the hepatitis A virus (HAV). About 0.5 % of cases of hepatitis A will result in acute liver failure and death, but mortality reaches up to 2.1% in adults over 40. The yearly incidence rate of hepatitis A in Europe today is between 0.55 and 1.5 cases per 100,000 inhabitants, based on data from epidemiological surveillance systems. However HAV still poses a serious threat to public health in Europe, despite declining incidence, because reduced population protection leads to more symptomatic cases and to outbreaks.

Chronic Hepatitis B (HBV) is a highly infectious disease most common in India, the Middle East, South East Asia, China and eastern European countries. Only 5% of infections become chronic. In the UK > 90% of new cases are patients who have arrived from endemic areas where vertical transmission is common. 25-30% of patients will eventually develop cirrhosis. World-wide HBV is the commonest cause of HCC. Chronic HBV infections translate into a heavy disease burden; Cirrhosis occurs in 20 to 30% of infected patients with about 25% at risk of developing HCC, thus HBV is responsible for 10-15% of primary liver cancers. HBV infections also translate into excess mortality risk. Estimation from mortality registers suggests that HBV infected patients have an excess risk of all-cause mortality and liver- related mortality. In 2014, out of the 360 Million people infected with HBV, around 1 million people died of the disease or other complications associated with it. However, there has been a significant decrease in incidence of hepatitis B after introduction of hepatitis B vaccine.

Linked to HBV infection is the influence of Hepatitis delta virus (HDV) which can infect only an individual who has also been infected by HBV, either after concomitant transmission of the two viruses (so called co- infection), or via a subsequent infection of a HBV infected patient (so-called super-infection). It has been consistently shown that most patients with HBV and HDV co-infection develop chronic infection and have more severe liver disease, more rapid progression to cirrhosis and increased jaundice, and death compared with patients who have chronic HBV infection alone. The highest prevalence is seen in central Africa, the Horn of Africa, the Amazon basin, eastern and mediterranean Europe, the middle east, and parts of Asia.

Hepatitis C (HCV) is transmitted through infected blood products, and in a small percentage by sexual contact. Worldwide up to 3% of the population are infected with HCV. There is currently no vaccine. Untreated 25% of cases will clear spontaneously, about 5% will go on to develop cirrhosis. A small group of those with cirrhosis progress to HCC. Cure is now possible in over 90% of individuals by elimination of the virus.

In Hepatitis A infection, the sequential liver failures result in increased miRNA122 circulating in the serum. In Hepatitis B infection, miRNA122 levels drop to below normal, as the virus nucleic acids sequesters it; this has been shown to be linked to liver inflammation due to liver cell death and liver cancer following viral infection. Patients with Chronic Hepatitis C have normal liver enzyme levels but elevated miRNA122 levels similar to those seen with severe hepatic injury and that this elevated expression is associated with liver damage.

Clinical development of therapies

There is the potential application of the product within the clinical testing and development of novel therapeutics.

The worldwide market for liver diseases therapeutic prescriptions was estimated to be worth $6.5 billion in 2011, will reach $10.9 billion in 2018, and is projected to reach $19,536 million by 2022, registering a CAGR of 10.5% from 2011 to 2022. There are, therefore, significant efforts being made in the development of novel therapeutics.

Additionally, for all therapeutic development for all diseases, over 35% of novel therapies fail in phase I testing due to drug toxicity: Phase I is in which drug safety is tested for the first time in a limited number of healthy individuals. This significantly increases the costs of drug research. Lower down the value chain, the conservation of the miRNA122 sequence, and known changes of expression in pre-clinically relevant animal models following liver damage presents the opportunity to use this device within early therapeutic development.

Within the liver disease therapeutic market, we can anticipate it being used preclinically for evidence of therapeutic efficacy, while in the non-liver therapeutic market, we can anticipate application in providing evidence pre-clinically and during clinical trials that the novel therapeutic does not induce liver toxicity. More importantly during human testing, for those patients and volunteers who are receiving novel therapeutics, early stages of liver damage will enable the protection of them and prevent further liver damage.

8. Competing products and services

Diagnostic tests presently performed for liver damage

Liver Test type	What it measures	Technology required	Strengths	Weaknesses
Enzyme and serum protein (ALT)	Levels of specific proteins and enzymes in the blood, including Albumin, Glutamyl Transpeptidase, Alkaline phosphotase and Amino-transferases	Complex biological reactions and associated infrastructure needed to extract and measure molecules, requiring high specialised personnel	non-invasive, helpful to recognize the pattern of liver disease. Like being helpful in differentiating between acute viral hepatitis and various cholestatic disorders and chronic liver disease.	Measurements not specific for liver diseases and all the parameters may be elevated for pathological processes outside the liver. Serum albumin may be decreased in chronic disease and also in nephrotic syndrome. Aminotransferases may be raised in both cardiac diseases and hepatic diseases.
Functional	Molecules produced by the liver which are excreted or can be extracted from the blood	Complex chemical reactions and associated infrastructure needed to extract and measure molecules, requiring high specialised personnel	non-invasive, Useful for diagnosing acute hepatitis infection and severe hepatic failure	Lack sensitivity; levels maybe normal in certain liver disease such as cirrhosis, noncongenital hepatic fibrosis, non cirrhotic fibrosis
Imaging	Provides images on the liver itself, potentially indicating scarring, inflammation or liver structure abnormality	Ultrasound, computerized tomography (CT) Magnetic resonance imaging (MRI) Endoscopic retrograde cholangiopancre	Can detect specific forms of liver disease	Cannot detect all forms of liver disease; requires very expensive equipment, with high maintenance requirements and specially trained staff. Can involve

		atography (ERCP) Magnetic Resonance cholangiopancreatography (MRCP		imbibing liquids which contain radioactive substances to enable imaging.
Biopsy	Liver cell biology and disease specific changes to the cells	Involves a surgeon inserting a thin needle into your liver to remove a small piece of tissue which is then examined under a microscope.	Very precise information on the cells extracted	A painful, expensive and potentially risky test. Its accuracy is also limited as it draws just a tiny piece of the liver, which may not be affected uniformly by disease.

Novel tests either on the market or being developed

Product (Proprietor)	What it does	Weaknesses
non-radioactive hydrogen molecule label **(KineMed)**	Binds to collagen within tissues to provide 3D enhanced imaging (Collagen large component of fibrotic tissue)	Does not measure early stage disease Needs medical imaging equipment i.e. patient mobility, and highly trained personnel Only measures fibrosis
Liver multiscan **(Perspectum)**	Imaging test software for characterisation of liver tissue	Needs medical imaging equipment i.e. patient mobility, centralised testing and highly trained personnel
Contrast agent for imaging that binds to collagen **(Collagen Medical)**	Binds to collagen within tissues to provide 3D enhanced imaging	Does not measure early stage disease. Needs medical imaging equipment i.e. patient mobility, and highly trained personnel: Only measures fibrosis
Reflotron plus/Sprint system **(Cobas)**	Single-test clinical chemistry system which allows the measurement of 17 parameters from whole blood, plasma or serum including: - liver and pancreas enzymes - metabolites - blood lipids- hemoglobin - potassium	Does not measure early stage disease and therefore resolve associated long term healthcare costs.
Piccolo Liver Panel plus	The panel has to be used with the Piccolo Blood Chemistry Analyser or the	Does not measure early stage disease and therefore resolve associated long term

(POCT /Abaxis)	Piccolo Xpress® Chemistry Analyser, provides in vitro quantitative determinations of Liver proteins, enzymes and excreted liver products	healthcare costs. Has a statistically significant bias for measurements of three excreted liver products.
Paper based test for measurement of liver enzymes/proteins (BCH)	Liver proteins, enzymes and excreted liver products	Does not measure early stage disease and therefore resolve associated long term healthcare costs.
HepQuant test **(HepQuant)**	Measures liver function via specifically targeting the hepatic uptake of cholate. Uses a single noninvasive test to quantify the systemic and portal circulation, and portal-systemic shunt and to derive a DSI in intact human subjects	Does not measure early stage disease Requires a fully equiped clinical laboratory

9. Possible products, markets, and innovations

Based on the above market opportunities, global application and competing solutions, it is highly feasible that Genechron, with the correct manufacturer can generate a market viable product based on miRNA122 measurements. The potential products include:

Drug-drug interaction kit: known to be in development, with extensive application in early stage therapeutic design and screening

CE marked microRNA122 detection kit, which can be used in any certified laboratory (international market certification maybe required or ideally, as indicated above, the Original Equipment Manufacturer (OEM) is centrally located with easy access, both market and regulatory, to as many markets as possible).

- Clinical therapeutic validation product : to be used within clinical trials as part of standard toxicity

- All levels of healthcare: primary to tertiary, the kit could be used within any healthcare infrastructure that has access to high technology molecular biology equipment, either within its existing infrastructure, or via a local medical laboratory.

- Point of care kit/device for markets without strong healthcare infrastructure: there is the potential to consider the use of the kit in a Point of Care setting if the mobile medical centre has a molecular biology infrastructure in place. Such devices have already been manufactured, such as the Roche Cobas Liat,

Given the species conservation, the direct application of the product within the animal health space is also a lucractive possibility.

10. Partners needed to make internationalisation of these products possible

Prior to being able to internationalise Genechron's products, it will need an EU product footprint of data to be leveraged into new markets: specifically clinical data and real world outcomes.

Ideally the manufacturer of the kit will be able to manufacture the CE kit as well as have significant mutual recognition agreements (MRA) in place that will enable exporting of the kit to additional markets.

A MRA is an agreement (a recognition) between countries by which the manufacturing and quality standards of one country are considered good enough that any product that is made in that country can also be exported to and sold in another country without further standards required. They are typically generated by specific product class or type. MRAs for medical devices already exist between the EU and New Zealand, Australia, and Switzerland. There is also one with Canada providing it is only used within the context of a clinical trial. For entry into the US market, the device would have to received a 501K certification, requiring a US manufacturer, and then identification of entities to distribute as well as identifying reimbursement routes.

When implemented, the result is to permit a product to be sold and used in any country that adheres to the regulation: for example the CE mark permits a product to be sold to the total 450 million people within the EU.

CE kit OEM: ideally already experienced in the sector, based in a central geographic location which will enable both sales in Europe and non European countries without additional bureaucracy.

Clinical partners: Genechron already has local clinical partners whom are willing to collaborate and clinically validate its products. In the instance that a non European market requires additional 'local' clinical evidence to be able to present data to the local reimbursement entities, a suitable Key Opinion Leader in that geography will need to be identified and partnered with.

Notified bodies (conformity assessment bodies) in relevant geographies: in the instance that extensive export occurs within a defined 'free trade' or 'harmonised market' area, it is likely that notified bodies will be required in each geography, however as presented below, endeavours are presently underway in large market geographies focusing on mutually recognising standards in medical devices

Distribution partners: ideally distribution partners will already be linked to the OEM and networked with the local health care community.

11. Medical Device quality control in key international markets

A key characteristic identified in our analysis is that Liver disease in all its manifestations is a global problem and is growing continually; this implies that once a reliable and high quality diagnostic product has been developed based on international standards, there is the possibility to penetrate a global market, principally through distribution agreements. An additional point is the cost:benefit of the product and who actually pays for or reimburses the measurement. cost:benefit is presented in the Business Case section below.

Given the spectrum of Liver based diseases, their growth in frequency and the changing political climate, it is our estimated opinion that the better markets to target are the Asian, partial Middle-East, Asian Pacific and then, secondarily the South American markets. It is noteworthy that the BRIC economies which include some of the target markets indicated here have been indicated to have a CAGR of 8.22% for the next 4 years reaching a total market value of over $15bn. This is due to the combination of how healthcare is reimbursed in these geographies and their initiatives to harmonise standards in medical devices and diagnostics, which means by manufacturing in one geography, automatically gives direct market access to the whole region. There is also an overlapping country within the Asian initiatives, through which the total Asian market should become accessible. The details of this are as follows:

Agreements on IVD
In Asia, there are two large economic integration agreements being developed which will enable access to a significant client and patient market in overlapping geographies:

Asian Harmonisation Working Party (AHWP): AHWP is a non-profit making organization that is working in association with member countries and the GHTF to harmonize medical device regulation in Asia. The current membership includes Abu Dhabi (UEA), Brunei Darussalam, Cambodia, Chile, China, Chinese Taipei (Taiwan), Hong Kong SAR, India, Indonesia, Jordan, Saudi Arabia, Korea, Laos, Malaysia, Myanmar, Pakistan, Philippines, Singapore, South Africa, Thailand, and Vietnam.

AHWP is currently working on producing a Safety Alert Dissemination System (SADS) based on experience in USA, EU, Australia and Japan. The aim is to have a single data system that can be shared by member nations.

Association of Southeast Asian Nations (ASEAN): ASEAN was established in 1967 with the signing of the Bangkok declaration by Indonesia, Malaysia, Philippines, Singapore and Thailand. Since then Brunei Darussalam, Vietnam, Laos, Myanmar and Cambodia have joined to make up what is today a ten member organization which is working towards a single market and production base by 2020 through elimination of technical barriers to trade posted by standards, technical regulations and conformity assessment in ASEAN Member Countries. Harmonisation on medical devices has already been reached. The group of countries are also active members of the AHWP.
The ASEAN Medical Device Directive (AMDD) was signed by the 10 member countries in August 2014. The directive is expected to be rolled out by the end of 2015 and will require ASEAN members to adopt uniform classification criteria for medical devices. For medical device companies, this means that they will be able to more easily access a common medical device market with a market size of more than 600 million people.

One should anticipate that the AMDD is the blue print for an agreement between the members of the AWHP. The AHWP has already posted guidance on the preparation of a common submission dossier template for the region. AHWP views the guidance as a step toward eliminating the need for medical device manufacturers to create individually formatted dossiers for submission in China, India and its other member countries. As it stands, companies pursuing the approval of medical devices in multiple Asian countries have to prepare different dossiers to each national regulatory body. The differences between the dossiers are primarily to do with formatting, not content, and as such AHWP sees value in harmonizing styles. As well as China and India, regulators from Hong Kong, Singapore, Korea and 19 other countries, including some such as South Africa that are located outside Asia, are members of AHWP.

In the guidance proposed by AHWP, the working group sets out its vision for a Common Submission Dossier Template (CSDT), from the definitions that underpin its approach through to specifics of how to present the device description and features. The CSDT is designed to present all the information that is needed to comply with the essential principles of medical device safety and performance that were established by the Global Harmonization Task Force.

An important consideration for medical device companies entering the Asian market is the lack of domestic competition in the region. For example, in China and India, global firms often have to contend with well-established domestic medical device companies, especially in the low-to-mid end market segments. In comparison, there are limited numbers of indigenous medical device manufacturers in the Asian member countries, except for notable surgical glove makers in Malaysia and Thailand, as well as a few small to mid-sized device manufacturers. Overall, Asian is a net importer of medical devices. Vietnam for example, currently imports 90% of all the medical devices used in the country.

There is a third organisation, which is the Asia-Pacific Economic Cooperation (APEC). APEC was established in 1989 by Australia, Brunei Darussalam, Canada, Indonesia, Japan, Korea, Malaysia, New Zealand, the Philippines, Singapore, Thailand and USA and now has a membership to 21. However it has not generated a mutual recognition for medical devices or diagnostics, which limits applicability, and the present US foreign policy may scupper any future plans.

In South America, the Mercado Común del Sur (MERCOSÚR), the common market of the south, was set up in 1991 by Argentina, Brazil, Paraguay and Uruguay under the Treaty of Asuncion. The 1994 Treaty of Ouro Preto gave the organization a wider international status and formalized a customs union. The membership of Mercosur has now expanded and includes Venezuela and five associate members: Chile, Bolivia, Colombia, Ecuador and Peru. Negotiations for an inter-regional association agreement between Mercosur and the EU began in 1999. Harmonization of the regulation for medical devices within the Mercado area is one of the aims of the organization. Currently the group is working towards each country having the same regulatory requirements and a single quality management system. Medical devices still require approval in each member state, but the eventual aim is to have a single approval scheme similar to that of the EU.

For products that may already have a CE mark approval, an independent approval process has been established in South America. A Free Sale Certificate (FSC) or a Certificate to Foreign Government (CFG) obtained from the country of origin confirms that a product is approved for sale there. These certificates include a product description with specific product numbers and identify the manufacturing site. They can enable medical devices to be exported to South America without restriction.

12. Healthcare provision and reimbursement in the target geographies

United Arab Emirates

Standards of health care are considered to be generally high in the United Arab Emirates, resulting from increased government spending during strong economic years. According to the UAE government, total expenditures on health care from 1996 to 2003 were AED 1,601,384,360.05 [US$436 million]. According to the World Health Organization, in 2004 total expenditures on health care constituted 2.9 percent of gross domestic product (GDP), and the per capital expenditure for health care was US$497. Healthcare currently is free only for UAE citizens.

The UAE now has 40 public Hospitals, compared with only 7 in 1970. The Ministry of Health is undertaking a multimillion-dollar program to expand health facilities and hospitals, medical centres, and a trauma centre in the seven emirates. A state-of-the-art general hospital has opened in Abu Dhabi with a projected bed capacity of 143, a trauma unit, and the first home health care program in the UAE. To attract wealthy UAE nationals and expatriates who traditionally have travelled abroad for serious medical care, Dubai is developing Dubai Healthcare City, a hospital free zone that will offer international-standard advanced private healthcare and provide an academic medical training centre; completion is done and finished on 2010. 12 million people visit Dubai every year for healthcare services.

Brunei Darussalam

Brunei has one of the best publicly run health care systems in the world. Those who are citizens of the country are entitled to medical care free of charge and immigrants who are employed are entitled to health care at a small cost. Brunei has excellent hospital facilities in all four of its districts, the biggest of which is Raja Isteri Pengiran Anak Saleha, located in the country's capital. There are also two private hospitals for those who have private medical insurance. The five general hospitals are supplemented by the health clinics situated around the country.

The Flying Medical Services division is responsible for air lifting any citizens who require emergency medical assistance to the nearest hospital if they live in remote rural villages. The government has also been known to take care of the expense of sending citizens abroad for any special medical treatments.

The government in Brunei is continuously working to keep improving the health of its citizens and government funding for health care is considered to be an important investment in the country’s future.

Chile

Chile has maintained a dual health care system in which its citizens can voluntarily opt for coverage by either the public National Health Insurance Fund or any of the country's private health insurance companies. 68% of the population is covered by the public fund and 18% by private companies. The remaining 14% is covered by other not-for-profit agencies or has no specific coverage. The system's duality has led to increasing inequalities prompting the Chilean government to introduce major reforms in health care provision. Chile's health care system is funded by a universal income tax deduction equal to 7% of every worker's wage. Many private health insurance companies encourage people to pay a variable extra on top of the 7% premium to upgrade their basic health plans. Because of this arrangement, the public

and private health subsystems have existed almost completely separate from each other rather than coordinating to achieve common health objectives.

Health care in Chile is provided by the government (via Fonasa) and by private insurers (via Isapre). All workers and pensioners are mandated to pay 7% of their income for health care insurance (the poorest pensioners are exempt from this payment). Workers who choose not to join an Isapre, are automatically covered by Fonasa. Fonasa also covers unemployed people receiving unemployment benefits, uninsured pregnant women, insured worker's dependant family, people with mental or physical disabilities and people who are considered poor or indigent.

Fonasa costs vary depending on income, disability or age. Attention at public health facilities via Fonasa is free for low-income earners, people with mental or physical disabilities and people over the age of 60. Others pay 10% or 20% of the costs, depending on income and number of dependants. Fonasa beneficiaries may also seek attention in the private sector, for a designated fee.

Additionally, there are a number of high-mortality illnesses (currently 69) that have special attention guarantees for both Isapre and Fonasa affiliates, in relation to access to treatment, waiting times, maximum costs and quality of service.

China

China is undertaking a reform on its health care system, which was largely privatized in the 1990s. The New Rural Co-operative Medical Care System (NRCMCS), is a new 2005 initiative to overhaul the healthcare system, particularly intended to make it more affordable for the rural poor. Under the NRCMCS, the annual cost of medical coverage is 50 yuan (US$7) per person. Of that, 20 yuan is paid in by the central government, 20 yuan by the provincial government and a contribution of 10 yuan is made by the patient. As of September 2007, around 80% of the whole rural population of China had signed up (about 685 million people). The system is tiered, depending on the location. If patients go to a small hospital or clinic in their local town, the scheme will cover from 70–80% of their bill. If they go to a county one, the percentage of the cost being covered falls to about 60%. And if they need specialist help in a large modern city hospital, they have to bear most of the cost themselves, the scheme would cover about 30% of the bill.

On January 21, 2009, the Chinese government announced that a total of 850 billion yuan (US$127.5 billion) will be provided between 2009 and 2011 in order to improve the existing health care system.

At the end of 2008, the government published its reform plan clarifying government's responsibility by saying that it would play a dominant role in providing public health and basic medical service. It declared "Both central and local governments should increase health funding. The percentage of government's input in total health expenditure should be increased gradually so that the financial burden of individuals can be reduced," The plan listed public health, rural areas, city community health services and basic medical insurance as four key areas for government investment. It also promised to tighten government control over medical fees in public hospitals and to set up a "basic medicine system" to quell public complaints of rising drug costs.

The plan was passed by the Chinese Cabinet in January 2009. The long-awaited medical reform plan promised to spend 850 billion yuan by 2011 to provide universal medical service and that measures would be taken to provide basic medical security to all Chinese.

Chinese Taipei (Taiwan)

The current health care system in Taiwan, known as National Health Insurance (NHI), was instituted in 1995. NHI is a single-payer compulsory social insurance plan which centralizes the disbursement of health care dollars. The system promises equal access to health care for all citizens, and the population coverage had reached 99% by the end of 2004. NHI is mainly financed through premiums, which are based on the payroll tax, and is supplemented with out-of-pocket payments and direct government funding. In the initial stage, fee-for-service predominated for both public and private providers. Most health providers operate in the private sector and form a competitive market on the health delivery side. However, many health care providers took advantage of the system by offering unnecessary services to a larger number of patients and then billing the government. In the face of increasing loss and the need for cost containment, NHI changed the payment system from fee-for-service to a global budget, a kind of prospective payment system, in 2002.

According to T.R. Reid, Taiwan achieves "remarkable efficiency", costing ≈6 percent of GDP universal coverage; however, this underestimates the cost as it is not fully funded and the government is forced to borrow to make up the difference. "And frankly, the solution is fairly obvious: increase the spending a little, to maybe 8 percent of GDP. Of course, if Taiwan did that, it would still be spending less than half of what America spends."

Hong Kong SAR

Hong Kong's medical infrastructure consists of a mixed medical economy, with 11 private hospitals and 42 public hospitals. Hong Kong has high standards of medical practice. It has contributed to the development of liver transplantation, being the first in the world to carry out an adult to adult live donor liver transplant in 1993. There are also polyclinics that offer primary care services, including dentistry.

Hong Kong is one of the healthiest places in the world. Because of its early health education, professional health services, and well-developed health care and medication system, Hongkongers enjoy a life expectancy of 85.9 for females and 80 for men, which is the third highest in the world, and an infant mortality rate of 2.73 deaths per 1,000 births, the ninth-lowest in the world. The proportion of the population over 65 years old is expected to grow from 14% in 2013 to 18% in 2018, and the number of people with a long-term condition is expected to increase by 33% over the same period.

India

India's healthcare system is dominated by the private sector, although there are various public healthcare systems like Rajiv Gandhi Jeevandayee Arogya Yojana in Maharashtra that provides free healthcare to those below the poverty line.[39][40] Currently, the majority of Indian citizens do not have health insurance, and must pay out of pocket for treatment. There are government hospitals that provide treatment at taxpayer expense. Some essential drugs are offered free of charge in these hospitals.

An outpatient card at AIIMS costs a one-time fee of 10 rupees (around 20 cents U.S.) and thereafter outpatient medical advice is free. In-hospital treatment costs depend on the financial condition of the patient and the facilities utilized, but are usually much less than the private sector. For instance, a patient is waived treatment costs if their income is below the poverty line. However, getting treatment at high quality

government hospitals is very tough due to the high number of people needing healthcare and the lack of sufficient facilities.

Primary health care is provided by city and district hospitals and rural primary health centres (PHCs). These hospitals provide treatment free of cost, but only if they are functional. Primary care is focused on immunization, prevention of malnutrition, pregnancy, child birth, postnatal care, and treatment of common illnesses.[*citation needed*] Patients who receive specialized care or have complicated illnesses are referred to secondary (often located in district and taluk headquarters) and tertiary care hospitals (located in district and state headquarters or those that are teaching hospitals).[*citation needed*]

Now organizations like Hindustan Latex Family Planning Promotional Trust and other private organizations have started creating hospitals and clinics in India, which also provide free or subsidized health care and subsidized insurance plans.[*citation needed*]

The government-run healthcare suffers from a lack of hygiene; the rich avoid the government hospitals and go to private hospitals. With the advent of privatized healthcare, this situation has changed. India now has medical tourism for people from other countries while its own poor find high-quality healthcare either inaccessible or unaffordable.

The current Indian government is planning to unveil a national universal healthcare system called the National Health Assurance Mission, which will provide all Indian citizens with insurance coverage for serious illnesses, and free drugs and diagnostic treatments.

The Indian healthcare delivery market was estimated at US $34 billion and employed over four million people in 2008, making it one of the largest service sectors in the Indian economy. Total national healthcare spending stood at 4.1 percent of GDP in 2007 and is now 8 percent of GDP or $77 billion. The industry has grown at about 13 per cent annually in recent years and is expected to grow at 23 percent per year over the next few years. Growth has been mainly driven by rising incomes, growing propensities to spend on healthcare, shift to lifestyle-related diseases, and demographic factors.

The sector comprises many segments. Estimates and projections for the individual segments show promising trends in several segments such as clinical trials, diagnostics, hospitals, medical devices, and health imaging. Nevertheless, India's healthcare sector falls well below international benchmarks for physical infrastructure, manpower, and existing standards in comparable developing countries. It is estimated that investment of $78 billion is required in health infrastructure and an additional 800,000 physicians are required over the next 10 years. Considerable scaling up is required in the availability and quality of physical infrastructure and human resources.

One of the most important aspects of India's healthcare system is the significant role of the private sector, which accounts for over 75 percent of India's total healthcare spending. Private players account for 75 percent of dispensaries, 80 percent of all qualified doctors, and an estimated 95 percent of new hospital beds in recent years. Public health expenditure accounts for less than 1 per cent of GDP. Government spending on healthcare infrastructure (excluding land) is projected to rise only marginally, by 0.12 per cent of GDP and the private sector is expected to provide 88 per cent of investment requirements over the medium term. However, private healthcare delivery is highly fragmented with over 90 per cent of it being serviced by the unorganized sector according to a recent report, and suffers from huge variation in quality and standards.

Indonesia

Indonesia's community health system were organized in three tier, on top of the chart is Community Health Center (Puskesmas), followed by Health Sub-Center on the second level and Village-Level Integrated Post at the third level. According to data from the Ministry of Health of Indonesia there are 2454 hospitals around the country, with total of 305,242 bed counting 0.9 bed per 100,000 inhabitant. Among these 882 of these hospitals are government owned and 1509 are private hospitals. According to the Worldbank data in 2012, there are 0.2 physicians per 1,000 people, with 1.2 Nurses and Midwives per 1,000 people in Indonesia. Out of all the 2454 hospitals in Indonesia, 20 have been accredited by Joint Commission international (JCI) as of 2015. In addition there are 9718 government financed Puskesmas (Health Community Center) listed by the Ministry of Health of Indonesia, which provide comprehensive healthcare and vaccination for the population in the sub-district level. Both traditional and modern health practices are employed. A data taken from World Health Organization (WHO) of 2013 shows that government health expenditures are about 3.1 percent of the total gross domestic product (GDP).

Jordan

In comparison to most of its neighbours, Jordan has quite an advanced health care system, although services remain highly concentrated in Amman. Government figures have put total health spending in 2002 at some 7.5 percent of Gross domestic product (GDP), while international health organizations place the figure even higher, at approximately 9.3 percent of GDP. The country's health care system is divided between public and private institutions. In the public sector, the Ministry of Health operates 1,245 primary health care centers and 27 hospitals, accounting for 37 percent of all hospital beds in the country; the military's Royal Medical Services runs 11 hospitals, providing 24 percent of all beds; and the Jordan University Hospital accounts for 3 percent of total beds in the country. The private sector provides 36 percent of all hospital beds, distributed among 56 hospitals. On 1 June 2007, Jordan Hospital (as the biggest private hospital) was the first general specialty hospital who gets the international accreditation (JCI). Treatment cost in Jordan hospitals is less than in other countries.

Saudi Arabia

The Ministry of Health (MOH) is the major government agency entrusted with the provision of preventive, curative and rehabilitative health care for the Kingdom's population. The Ministry provides primary health care (PHC) services through a network of health care centers (comprising 1,925 centers) throughout the kingdom. It also adopts the referral system which provides curative care for all members of society from the level of general practitioners at health centers to advanced technology specialist curative services through a broad base of general and specialist hospitals (220 hospitals). The MOH is considered the lead Government agency responsible for the management, planning, financing and regulating of the health care sector. The MOH also undertakes the overall supervision and follow-up of health care related activities carried out by the private sector. Therefore, the MOH can be viewed as a national health service (NHS) for the entire population.

The MOH provides around 60% of the health services, free of charge, through 13 health directorates. Twenty per cent of the health service is delivered free through other government agencies and the remaining 20% is provided by the non-government sector, which is growing rapidly (the private sector provides health services through its health facilities including hospitals, dispensaries, laboratories,

pharmacies and physiotherapy centers throughout the kingdom. The following are the major indicators provided by the private sector:

- 100 hospitals with 8,485 beds, accounting for about 19 percent of the total number of hospitals beds in the kingdom.
- 622 dispensaries, 785 clinics, 45 medical laboratories and 11 physiotherapy centers.
- 273 pharmaceutical stores and 3,209 pharmacies.
- Increased investments in manufacturing of drugs and medical supplies of medical appliances, and pharmaceuticals, in addition to the operation of some governmental hospitals and maintenance and cleaning in all health facilities.
- Increased contribution of the private sector in the provision of health care services, where out-patient visits to its facilities increased from 12.1 percent of total out-patient visits in 1994 to 16.1 percent in 1998. In addition, in-patients in the Kingdom’s private hospitals as a percentage of total in-patients rose from 16.6 percent in 1994 to 27.1 percent in 1998.

Korea

South Korea's National Health Insurance programme is a compulsory social insurance system which covers the whole population. By law, any company that employs more than five foreign workers must enrol their foreign workers in a health insurance programme. The company is expected to pay half of their employees' health insurance premiums each month, while employees cover the other half.

National Health Insurance covers most day-to-day and emergency medical procedures, prescription medication and specialist visits. However, some procedures and medications, particularly those associated with chronic illnesses, such as cancer, are not covered and can become costly. Private insurance companies exist for this reason and many Koreans and expats who can afford it sign up for a chronic illness plan to guard against costs the NHI may not cover.

Malaysia

Health care in Malaysia is divided into private and public sectors. Doctors are required to undergo a 2-year internship and perform 3 years of service with public hospitals throughout the nation, ensuring adequate coverage of medical needs for the general population. Foreign doctors are encouraged to apply for employment in Malaysia, especially if they are qualified to a higher level.

Malaysian society places importance on the expansion and development of health care, putting 5% of the government social sector development budget into public health care – an increase of more than 47% over the previous figure. This has meant an overall increase of more than RM 2 billion. With a rising and ageing population, the Government wishes to improve in many areas including the refurbishment of existing hospitals, building and equipping new hospitals, expansion of the number of polyclinics, and improvements in training and expansion of telehealth. Over the last couple of years they have increased their efforts to overhaul the systems and attract more foreign investment.

There is still a shortage in the medical workforce, especially of highly trained specialists. As a result, certain medical care and treatment is available only in large cities. Recent efforts to bring many facilities to other towns have been hampered by lack of expertise to run the available equipment made ready by investments.

The majority of private hospital facilities are in urban areas and, unlike many of the public hospitals, are equipped with the latest diagnostic and imaging facilities.

Pakistan

Pakistan's health indicators, health funding, and health and sanitation infrastructure are generally poor, particularly in rural areas. About 19 percent of the population is malnourished – a higher rate than the 17 percent average for developing countries – and 30 percent of children under age five are malnourished. Leading causes of sickness and death include gastroenteritis, respiratory infections, congenital abnormalities, tuberculosis, malaria, and typhoid fever. The United Nations estimates that in 2003 Pakistan's human immunodeficiency virus (HIV) prevalence rate was 0.1 percent among those 15–49, with an estimated 4,900 deaths from acquired immune deficiency syndrome (AIDS). AIDS is a major health concern, and both the government and religious community are engaging in efforts to reduce its spread. In 2003 there were 68 physicians for every 100,000 persons in Pakistan. According to 2002 government statistics, there were 12,501 health institutions nationwide, including 4,590 dispensaries, 906 hospitals with a total of 80,665 hospital beds, and 550 rural health centers with a total of 8,840 beds. According to the World Health Organization, Pakistan's total health expenditures amounted to 3.9 percent of gross domestic product (GDP) in 2001, and per capita health expenditures were US$16. The government provided 24.4 percent of total health expenditures, with the remainder being entirely private, out-of-pocket expenses.

Philippines

In 2000 the Philippines had about 95,000 physicians, or about 1 per 800 people. In 2001 there were about 1,700 hospitals, of which about 40 percent were government-run and 60 percent private, with a total of about 85,000 beds, or about one bed per 900 people. The leading causes of morbidity as of 2002 were diarrhea, bronchitis, pneumonia, influenza, hypertension, tuberculosis, heart disease, malaria, chickenpox, and measles. Cardiovascular diseases account for more than 25 percent of all deaths. According to official estimates, 1,965 cases of human immunodeficiency virus(HIV) were reported in 2003, of which 636 had developed acquired immune deficiency syndrome (AIDS). Other estimates state that there may have been as many as 9,400 people living with HIV/AIDS in 2001.

Singapore

Health care in Singapore is mainly under the responsibility of the Singapore Government's Ministry of Health. Singapore generally has an efficient and widespread system of health care. It implements a universal health care system, and co-exists with private health care system. Infant mortality rate: in 2006 the crude birth rate stood at 10.1 per 1000, and the crude death rate was also one of the lowest in the world at 4.3 per 1000. In 2006, the total fertility rate was only 1.26 children per woman, the 3rd lowest in the world and well below the 2.10 needed to replace the population. Singapore was ranked 6th in the World Health Organization's ranking of the world's health systems in the year 2000.

Singapore has a universal health care system where government ensures affordability, largely through compulsory savings and price controls, while the private sector provides most care. Overall spending on health care amounts to only 3% of annual GDP. Of that, 66% comes from private sources. Singapore currently has the lowest infant mortality rate in the world (equalled only by Iceland) and among the highest life expectancies from birth, according to the World Health

Organization. Singapore has "one of the most successful health care systems in the world, in terms of both efficiency in financing and the results achieved in community health outcomes," according to an analysis by global consulting firm Watson Wyatt. Singapore's system uses a combination of compulsory savings from payroll deductions (funded by both employers and workers) a nationalized catastrophic health insurance plan, and government subsidies, as well as "actively regulating the supply and prices of health care services in the country" to keep costs in check; the specific features have been described as potentially a "very difficult system to replicate in many other countries." Many Singaporeans also have supplemental private health insurance (often provided by employers) for services not covered by the government's programs.

Singapore's well-established health care system comprises a total of 13 private hospitals, 10 public (government) hospitals and several specialist clinics, each specializing in and catering to different patient needs, at varying costs.

Patients are free to choose the providers within the government or private health care delivery system and can walk in for a consultation at any private clinic or any government polyclinic. For emergency services, patients can go at any time to the 24-hour Accident & Emergency Departments located in the government hospitals.

Singapore's medical facilities are among the finest in the world, with well qualified doctors and dentists, many trained overseas.

Singapore has medical savings account system known as Medisave.

South Africa

In South Africa, parallel private and public systems exist. The public system serves the vast majority of the population, but is chronically underfunded and understaffed. The wealthiest 20% of the population uses the private system and are far better served. This division in substantial ways perpetuates racial inequalities created in the pre-apartheid segregation era and apartheid era of the 20th century. In 2005, South Africa spent 8.7% of GDP on health care, or US$437 per capita. Of that, approximately 42% was government expenditure.

The public sector uses a Uniform Patient Fee Schedule (UPFS) as a guide to billing for services. This is being used in all the provinces of South Africa, although in Western Cape, Kwa-Zulu Natal, and Eastern Cape, it is being implemented on a phased schedule. Implemented in November 2000, the UPFS categorises the different fees for every type of patient and situation.

It groups patients into three categories defined in general terms, and includes a classification system for placing all patients into either one of these categories depending on the situation and any other relevant variables. The three categories include full paying patients—patients who are either being treated by a private practitioner, who are externally funded, or who are some types of non-South African citizens—, fully subsidised patients—patients who are referred to a hospital by Primary Healthcare Services—, and partially subsidised patients—patients whose costs are partially covered based on their income. There are also specified occasions in which services are free of cost.

The current government is working to establish a national health insurance (NHI) system out of concerns for discrepancies within the national health care system, such as unequal access to healthcare amongst different socio-economic groups. Although the details and outline of the proposal have yet to be released, it seeks to find ways to make health care more available to those who currently can't afford it or whose situation prevents them from attaining the services they need. There is a

discrepancy between money spent in the private sector which serves the wealthy (about US$1500 per head per year) and that spent in the public sector (about US$150 per head per year) which serves about 84% of the population. About 16% of the population have private health insurance. The total public funding for healthcare in 2012/3 was R21 billion. The NHI scheme is expected to require expenditure of about R336 billion.

Thailand

The majority of health care services in Thailand is delivered by the public sector, which includes 1,002 hospitals and 9,765 health stations. Universal health care is provided through three programs: the civil service welfare system for civil servants and their families, Social Security for private employees, and the Universal Coverage scheme theoretically available to all other Thai nationals. Some private hospitals are participants in these programs, though most are financed by patient self-payment and private insurance.

The Ministry of Public Health (MOPH) oversees national health policy and also operates most government health facilities. The National Health Security Office (NHSO) allocates funding through the Universal Coverage program. Other health-related government agencies include the Health System Research Institute (HSRI), Thai Health Promotion Foundation ("ThaiHealth"), National Health Commission Office (NHCO), and the Emergency Medical Institute of Thailand (EMIT). Although there have been national policies for decentralization, there has been resistance in implementing such changes and the MOPH still directly controls most aspects of health care.

Thailand introduced universal coverage reforms in 2001, becoming one of only a handful of lower-middle income countries to do so at the time. Means-tested health care for low income households was replaced by a new and more comprehensive insurance scheme, originally known as the 30 baht project, in line with the small co-payment charged for treatment. People joining the scheme receive a gold card which allows them to access services in their health district, and, if necessary, be referred for specialist treatment elsewhere. The bulk of finance comes from public revenues, with funding allocated to Contracting Units for Primary Care annually on a population basis. According to the WHO, 65% of Thailand's health care expenditure in 2004 came from the government, 35% was from private sources. Although the reforms have received a good deal of critical comment, they have proved popular with poorer Thais, especially in rural areas, and survived the change of government after the 2006 military coup. The then Public Health Minister, Mongkol Na Songkhla, abolished the 30 baht co-payment and made the UC scheme free. It is not yet clear whether the scheme will be modified further under the coalition government that came to power in January 2008.

Vietnam

The overall quality of health in Vietnam is regarded as good, as reflected by 2005 estimates of life expectancy (70.61 years) and infant mortality (25.95 per 1,000 live births). However, malnutritionis still common in the provinces, and the life expectancy and infant mortality rates are stagnating. In 2001 government spending on health care corresponded to just 0.9 percent of gross domestic product (GDP). Government subsidies covered only about 20 percent of health care expenses, with the remaining 80 percent coming out of individuals' own pockets.

In 1954 the government in the North established a public health system that reached down to the hamlet level. After reunification in 1976, this system was extended to the

South. Beginning in the late 1980s, the quality of health care began to decline as a result of budgetary constraints, a shift of responsibility to the provinces, and the introduction of charges. Inadequate funding has led to delays in planned upgrades to water supply and sewage systems. As a result, almost half the population has no access to clean water, a deficiency that promotes such infectious diseases as malaria, dengue fever, typhoid, and cholera. Inadequate funding also has contributed to a shortage of nurses, midwives, and hospital beds. In 2000 Vietnam had only 250,000 hospital beds, or 14.8 beds per 10,000 people, a very low ratio among Asian nations, according to the World Bank.

13. Key market players

Asia is home to some of the most successful private hospital operators in the world. These private hospitals provide healthcare services not only to local patients in their respective countries but often also to medical tourists from around the world. These hospitals are often among the first to deploy new healthcare solutions and devices that can make significant positive impacts on their patients' treatment outcomes. The following table describes a few of the major hospital groups in Asia.

Some of the larger Hospital Groups in Asia

Hospital Group	Country	Description
IHH Healthcare	Malaysia	World's 2nd largest hospital operator by market capitalisation, IHH is publicly listed on both the Singapore stock exchange (SGX) and the Malaysia stock exchange (Bursa). The group operates hospitals and medical centres in 9 countries including Singapore, Malaysia and Turkey. Website: www.ihh-healthcare.com
KPJ Healthcare	Malaysia	It is one of the largest private hospital company in Malaysia, operating hospitals in Malaysia and Indonesia. The company is listed on the Malaysia stock exchange (Bursa). Website: www.kpjhealth.com.my
Raffles Hospital	Singapore	The Raffles Hospital is a tertiary hospital belonging to the Raffles Medical Group, which operates the largest private group practice in Singapore and is also publicly listed on the Singapore stock exchange (SGX). Website: www.raffleshospital.com
Bumrungrad Hospital	Thailand	One of Asia's busiest and largest hospitals, Bumrungrad sees over a million patients a year. It caters primarily to higher income market segments in Thailand as well as expatriates and medical tourists. Bumrungrad is publicly listed on the Thailand stock exchange (SET) and is very profitable. Website: www.bumrungrad.com
Bangkok Dusit Hospital	Thailand	It is the largest private hospital operator in Thailand in terms of revenues and market capitalisation. It currently manages 40 hospitals under 6 hospital brands. Bangkok Hospital targets mainly the upper-middle to high income segment of the market, as well as expatriates and medical tourists. Website: www.bangkokhospitalgroup.com
Siloam Group	Indonesia	It is one of Indonesia's leading hospital operator and has been listed on the Indonesia stock exchange since September 2013. Its long term goal is to operate 40 hospitals by 2018 to cater to Indonesia's rapidly growing middle and affluent class. Website: www.siloamhospitals.com

Rumah Sakit Mitra Keluarga	Indonesia	Mitra Keluarga was established in West Java in 1993 and today operates 11 hospitals in Jakarta, Depok, Bekasi, Tegal, Sidoarjo, and Surabaya. It caters mostly to local patients. Website: www.mitrakeluarga.com (in Bahasa Indonesia only)

14. Best location for a partner OEM manufacturer to enter this market: Singapore

With effect from 1 April 2013, the Singapore Health Sciences Authority issues Free Sale Certificates (FSCs) to local product owners of finished medical devices that have been registered with them.

A Free Sales Certificate is issued to registrant companies requiring the certificate for finished medical devices that are registered and listed on SMDR. The Free Sales Certificate is valid for up to 2 years from the date of issue. Its acceptance is subject to the respective requirements imposed by the regulatory agencies of the importing countries. The Free Sales Certificate for the medical device is invalid if the medical device is no longer listed in the Singapore Medical Device Register (SMDR) unless except for Class A devices which are exempted from product registration.

By entering into partnership with a Singapore based manufacturer, and registering the diagnostic with their healthcare authorities, will result in access to the total Asian marketplace.

There is also the future option to establish a subsidiary there: Singapore's medical devices industry is currently aiming to hit SG $5 billion in manufacturing output. The government is targeting up to 1 million foreign patients a year, which will contribute SG $2.6 billion (US $1.55 billion), or about one percent, to Singapore's GDP. Already there are 30 global medical technology companies, including the industry's leading manufacturers, who carry out their operations and R&D in Singapore.

The ASEAN economy has maintained robust growth, particularly in the healthcare industry. Of the 10 ASEAN members, Singapore is by far the most developed and efficient healthcare provider and annually spends the most per capita on health. The country also possesses excellent transportation and communication infrastructure, making it an ideal base for further pushes into the ASEAN region.

Singapore's medical technology sector contributes about SG $4.3 billion and around 9000 jobs to the country's economy. To put this into perspective, 10 percent of the world's contact lenses, over 70 percent of microarrays, and roughly half of the world's thermal cyclers and mass spectrometers are currently produced in Singapore – numbers which are likely to rise. Medtech sectors which are already growing include cardiovascular, eye care, diagnostic, imaging, research tools, scientific instruments and orthopedics. This is largely due to the government's interest in supporting the medtech sector, exemplified in numerous incentive schemes. The EDB's Partnerships for Capability Transformation (PACT) was initiated in 2010 to develop the competencies of OEMs and to enable suppliers to meet manufacturing quality and certification requirements.

15. Business case

A diagnostic product which is able to inform primary care physicians that their patient is experiencing early signs of liver damage does not exist. Instead the patient is in the greater number of cases not referred for diagnosis and in the instances when they are, the diagnosis confirms often an advanced stage of liver disease, for which therapeutic or life style change options to correct the damage are limited. The patients that are not referred still develop liver disease, except they by default are treated when the disease is already advanced.

As existing diagnostics require highly skilled personnel and an expensive infrastructure requiring extensive national support any easy to use and point of care diagnostic will provide a valuable and viable solution.

The need for such a diagnostic is huge as indicated by the figures in the impacts section above; the numbers are simply mind-boggling, the medical need essential, and in light of the significant budget constraints that healthcare systems are facing a diagnostic that will reduce mortality, morbidity and all potentially unnecessary related therapeutic interventions related to liver disease are going to be essential.

The market volumes and clear levels of desperation in the medical community are incentive enough from a commercial perspective, however, given the budget constraints of health care systems Genechron must ensure that the product is very affordable, reliable, validated, quality standardized, easy to use and medically enabling. This will also deter competition from trying to enter the market.

The range of potential users for the Genechron products are global. The most obvious user group are general practitioners in developed countries who could offer liver testing as part of a routine check-up, especially if patients belong to certain high-risk groups (e.g. type 2 diabetes or obesity). Due to the changes in lifestyle in developing economies this problem now affects us all; liver diseases, which were totally absent, are now rapidly expanding and becoming almost epidemic in nature, and the potential primary care end-users of our product therefore global. These users will typically expect high-quality lab grade results and an easy to use system.

We have estimated the potential socioeconomic benefit and market size of the final clinical product. Our calculations are based on the diseases indicated below and does not include DILI/polypharmacy numbers, drug testing or other liver diseases, for which the products will clearly be applicable, so the initial business case estimates are conservative.

Liver Disease	Frequency of cases worldwide
Cancer	780 000/year
NAFLD	7 000 000/year
Viral induced	2 000 000/year

- Health care costs relate to non-diagnostic costs of hospital care, GP visits, and home care which cost €10000 for early stage, €40000 for mid staged and €60000 for advanced stage liver disease; our calculations do not include therapeutic/interventive costs.

- Diagnostic costs are based on an initial series of enzyme tests (the present comparable standard, even with accepted limitations incorporated) or combination

with miRNA122 tests, which cost €80/test/type, plus 2 visits to a hospital for more complex diagnostic, which costs on average €2000 per visit for advanced disease or €1000 for early disease.

- Our initial conversations with health agencies and medics have indicated that the nearest comparable product will be the enzyme assay; despite its limitations it would be the standard against which reimbursement agencies would make their evaluations. The standard enzyme assay costs €80 and has to be performed on average 4 times on an at risk patient. Any miRNA based solution should be performed at an equivalent price.

With this knowledge we have modelled the potential medical options that are:

A) Wait for the patient to present clinical symptoms, perform enzyme assays only, therefore all patients have liver disease and need hospital based diagnosis.

This is the model that would occur if all patients were never referred by their GP, which we know occurs 80% of the time. Our estimate does not include the capital investment by the hospital to put in place the infrastructure necessary to be able to implement this number of tests within a clinical setting.

- 4 enzyme tests = €320
- 2 x advanced tests needed= €4000
- Health care costs averaged for all stages = €36000

Model A Total cost 40320/year x 9 780 000 patients= €394 billion estimated in global health care costs every year.

B) Perform enzyme assays on everyone at risk, and as soon as enzyme levels elevate, perform advanced diagnosis to identify those as early as possible with advanced disease

This model corresponds to what happens 20% of the time. The doctor may be able to reduce health care costs by 50% because optimistically maybe they can cure or change the life style of the patient, the other 50% are going to need advanced health care as enzyme levels varies by disease with no clear correlation, but understanding that the disease is progressing. Estimates again do not include the capital investment necessary to be able to implement this number of measurements.

- 9 780 000 patients x €80 for enzyme level based diagnosis = €0.782 billion

All patients would be advised to change their lifestyle (food and drink and exercise) and be retested after 4-6 weeks.

- 9 780 000 patients x €80 for enzyme level based diagnosis = €0.782 billion

The patients with liver cancer and viral induced liver disease, will show no difference and will need to go for further medical care. For the patients with NAFLD a change in lifestyle will have an effect, however because the enzyme measurement tests indicate a later stage disease, 50% will need to go to hospital for full medical diagnosis. The remaining will continue to be monitored by their GP using enzyme assays.

- 2 000 000 viral induced, 780 000 liver cancer and 3 500 000 NAFLD patients will need hospital care and advanced diagnosis x €36000 in health care costs and €2000 for advanced diagnosis = €238 billion

- 3 500 000 NAFLD patients will need continued enzyme analysis x €160 = €0.56 billion

Model B Total cost = €240 billion estimated in global health care costs every year.

C) Genechron system performed in tandem with liver enzyme test on all 'at risk' patients (medics will insist on performing measurement against something they know)

Enzyme levels	MiRNA levels	Diagnosis
No change	No change	No disease
No change	Change in levels	Potential early liver disease
Change in levels	Change in levels	Liver disease

* Note that change in Enzyme, but no change in miRNA is known to imply very late stage liver disease

Screen at risk patients early using Genechron products and existing liver enzyme assay

- 9 780 000 patients x 1 microRNA test x €80 per test = €0.782 billion
- 9 780 000 patients x 1 enzyme test x €80 per test = €0.782 billion

If changes observed, recommend change in life style and re-measure after 4-6 weeks (first step in most non infectious origins of liver disease; for infectious diseases the patients are questioned on potential exposure to biohazards as part of diagnosis, but test is still repeated)

Repeat test:
- 9 780 000 patients x 1 microRNA test x €80 per test = €0.782 billion
- 9 780 000 patients x 1 enzyme test x €80 per test = €0.782 billion

Clinical reports have demonstrated that if identified early enough changes in life style reduce liver disease progression and restoration of liver function in 70% of NAFLD patients: it has been speculated that if it was possible to diagnose even earlier this could be increased to 90% of patients (BMC Med: The role of lifestyle in the management of chronic liver disease).

Those anticipated to require further diagnosis: 780 000 potential liver cancer patients, 2 100 000 NAFLD patients, 2 000 000 viral induced patients = 4 880 000 patients

- 4 880 000 patients will require early to mid staged patient care at €25000 average plus €4000 in diagnostics = €141 billion

Continued testing on remaining population of NAFLD twice per year

- 4 900 000 patients x 2 microRNA test x €80 per test = €1.56 billion
- 4 900 000 patients x 2 enzyme test x €80 per test = €1.56 billion

Model C Total cost = €147 billion estimated in global health care costs every year.

We know that Model B is not routinely performed and that the real arguable costs based on diagnosis and referral statistics would correspond to 20% of costs of Model B + 80% of costs of Model A = €363 billion total healthcare costs.

Therefore by integrating the Genechron product into the diagnostic and patient care process, which produces the Model C costs we estimate the potential to create a socioeconomic impact, which reduces healthcare related costs of liver disease by up to 60%.

The annual global market for Genechron products is also conservatively estimated at €3.12 billion (corresponding to the 4 miRNA liver tests that would be performed annually on the total patient population)

By validating and owning the diagnostic, through our commercial plan and identifying global distributors matched with its USPs we should anticipate owning the whole market.

If there is an initial global uptake of 10% by medical entities, which we believe is feasible, then this would generate €300 million in revenues for Genechron. This value would grow as the marketing and communication efforts continue after implementation of the marketing plan and innovation potentials.

16. Recommendations

From our analysis, we consider the development of a low cost miRNA122 detection kit, by a reputed OEM based in a central Asian location will enable Genechron to generate CE marked and Asian approved liver disease solutions in Europe and Asia, and importantly, that can be easily inserted into the South American market, once CE marking has been obtained.

We would suggest that Genechron identifies a renowned OEM in Singapore and establishes a working collaboration.

The short to medium term business model for internationalization would be, that after obtaining a CE mark and independent clinical and commercial validation of the kit in a European setting, to use this information to obtain regulatory approval in the different geographic markets and then identify the principal IVD suppliers and distributors and establish agreements with them.

The long term model would be to generate a subsidiary in one specific geography in which has Mutual Recognition Agreements with as many target geographies as possible and develop your own international sales force. We would only advocate this approach after a large enough market volume has been obtained AND the number of different Genechron IVD products has increased.

A significant part of our recommendation is founded on 3 concepts:

- That due to the budget constraints of healthcare systems the product must be applicable within the existing infrastructure

- The final product does not require extensive or costly training and must be based on science and SOPs that the end users are knowledgeable on and comfortable with.

- The product provides additional benefit to patients at the same or lower cost, or to provide equivalent benefit to patients at lower cost (this is now a standard for obtaining any form of reimbursement).

Signed by: Dr. Jonathan S Dando
CEO
Echino Ltd