

White Paper

Patient-centric and ecosystem insights into hepatocellular carcinoma across Asia-Pacific

Liver Ecosystem Advancement Program (LEAP)—expediting action to reduce incidence and mortality of hepatocellular carcinoma

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Executive summary

Hepatocellular carcinoma (HCC) is largely preventable, with decades of time to intervene, yet millions still die from it. It is however not incomprehensible why this happens. The journey from liver disease to liver cancer is complex—a myriad of broken healthcare systems, patient behaviors, cultural influences, stigma, funding, and limited healthcare professional (HCP) capacity. At first glance, it seems overwhelming, leaving us with the question—where should we intervene?

It is not practical or necessary to tackle every painpoint in the system; rather, the strategy to tackle system problems is about identifying influential levers and iterating. The very nature of ecosystems is that they change as soon as you intervene. Therefore, we look for small pragmatic steps that have the potential for large rippling impact.

This White Paper intends to facilitate concerted action among HCPs, patient advocacy groups, payers, and policy makers to reduce liver cancer incidence and mortality in APAC. It shares both holistic ecosystem and detailed human-centric insights as a starting point for change. Working with Key Opinion Leaders (KOLs) we provide tangible examples of active initiatives, and recommendations for taking the next steps.

From the research, a central theme emerged – ultrasound used in HCC surveillance is a major bottleneck. It is the cause of delayed or even missed diagnosis, and stark inequities in care. Biomarkers such as PIVKA-II show promise in lessening this problem while also offering improved sensitivity and specificity for HCC detection. Given the shifting etiology with rising fatty liver disease, there is a pressing need to re-assess risk factors and stratify patients to ensure we are not failing to detect. Being able to optimize surveillance protocols based on patient risk will improve efficiency and ability to catch early HCC and drastically improve survival.

To further maximize the benefit of a surveillance program, or any other initiative, it is important to consider surrounding opportunities up- and down-stream. For example, surveillance programs will benefit from up-stream awareness efforts to improve throughput, and down-stream availability of treatments. This paper provides an appreciation for the end-to-end patient journey and their needs along the way. Fundamentally, it advocates for the improvement of human life in the midst of receiving liver care, both clinically and experientially.

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Introduction

The state of chronic liver disease and cancer in Asia-Pacific

It is estimated that 1.3 million deaths will arise from liver cancer in the next 20 years to become the 3rd leading cause of cancer death worldwide¹. This upward trend follows obesity, and metabolic diseases such as Type 2 diabetes. Currently, the main cause of hepatocellular carcinoma (HCC)—the predominant type of liver cancer to which this paper refers to interchangeably, starts from incurable hepatitis B. Chronic hepatitis as a whole accounts for around 78% of the liver cancer cases globally, with Asia-Pacific (APAC) accounting for 63% of that global burden of disease². In fact, according to the World Health Organization (WHO), hepatitis kills more people than acquired immunodeficiency syndrome (AIDS), tuberculosis, and malaria combined³. Yet, the liver remains a forgotten organ with little attention from the public and governments.

Asia-Pacific accounts for over 60% of global liver cancer mortality and global deaths are set to rise by 55% by 2040¹.

What makes liver care a unique and complex challenge to solve?

Some cancers like breast cancer have high incidence but comparatively low mortality⁴(Figure 1). Liver cancer is the opposite; it goes undetected until late stage, resulting in dismal prognosis. Late presentation is a top issue in liver cancer. Without pain receptors, the liver has minimal symptoms until it is damaged beyond cure. Low perception of risk also feeds a perpetual cycle of limited public awareness. People usually die within 6.6 to 21.8 months of a late-stage HCC diagnosis⁵ and storytelling is stopped in its tracks.

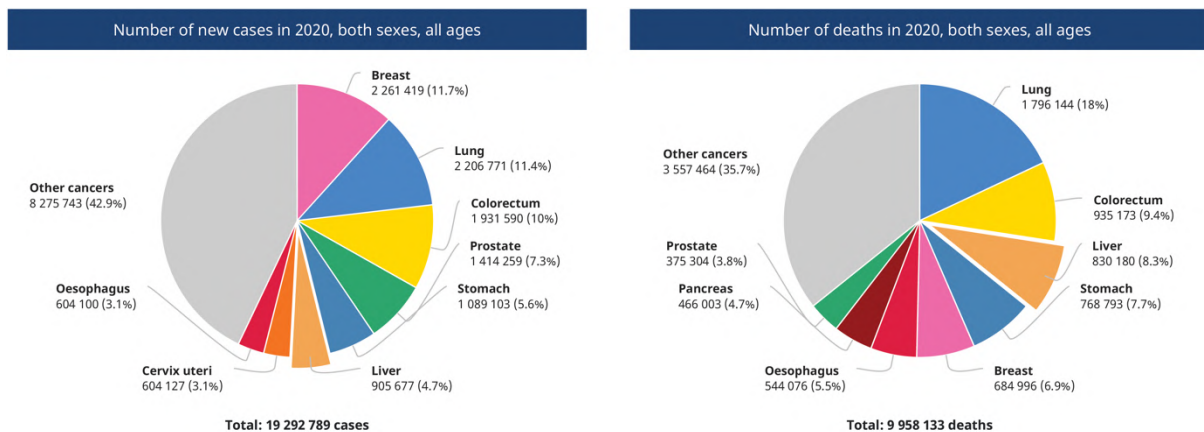


Figure 1: Worldwide incidence and mortality of cancer, 2020⁴. Chart showing which cancers have the highest incidence, and which cancers are the leading causes of death. Source: Globocan 2020.

Additionally, many real-world factors hinder screening and surveillance program success. They include patient affordability and stigma, healthcare professional (HCP) variance in how they conduct tests, culture, and individual lifelong habits. These are complicated and often overlooked in solution development.

To complicate matters further, etiology is shifting. Liver cancer is predominantly caused by chronic viral hepatitis that turns cirrhotic. But now, non-alcoholic fatty liver disease (NAFLD) has been rising exponentially over the last 3 decades⁶. In Malaysia and Singapore, HCPs reported rising cases of nonalcoholic steatohepatitis (NASH), and plateauing levels of viral hepatitis in their transplant patients. NAFLD associated HCC is even harder to detect on routine screening (e.g., through ultrasound) due to increased echogenicity of the liver, among other reasons^{7,8}. This means detection protocols need updating. Treatments exist for most viral causes, however, NAFLD and alcoholic liver disease (ALD) patients remain undiscovered and unsupported.

Non-alcoholic fatty liver disease has been rising exponentially over the last 3 decades⁶.

An ecosystem approach is needed

Given the complexity, there is no single solution. Rather, it will take concerted action from multiple stakeholders in the system to bring about positive change. That said, there are logical places to start. First, we need to understand the ecosystem. An ecosystem represents factors required to deliver a service, in this case, liver care. It helps identify solution, scope, and strategy by providing a holistic view of actors, processes, flow, influence, and relationships (Figure 2).

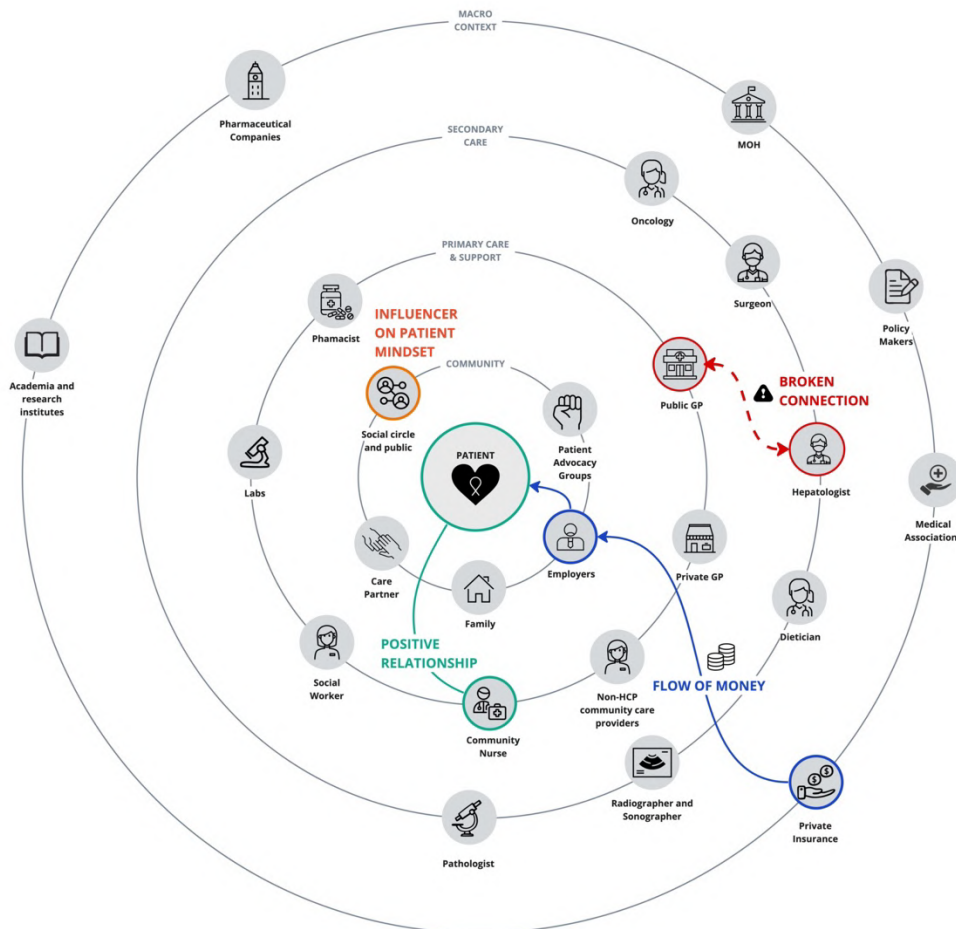


Figure 2: Example of types of actors and connections within the liver care ecosystem, image by author.

Actors and connections

Liver care ecosystem ‘actors’ include general practitioners (GPs), specialists, patients, caregivers, non-HCP community care providers, nurses, industry, academic researchers, government, payers, and policy makers. There are many actors in the community who play a large role including non-HCPs involved in testing, treatment, and monitoring; and community nurses that work in mental health, corrections, addictions, and homeless outreach for example. Each actor impacts, and is impacted by, each other. For example, in New Zealand we found a strong positive relationship between nurses and patients. These nurses also were well connected to a multi-disciplinary team (MDT) of specialists. They formed the heart and glue of patient navigation contributing significantly to improved patient outcomes. Equally, we saw disconnected actors in the system, for example GPs who were often bypassed because patients presented straight to the emergency room (ER) making early prevention or detection efforts difficult. Understanding connections helps focus efforts.

Levers for change

Like all system problems, the starting point is to identify critical levers for change. Levers are similar to the principle of identifying 20% of action that leads to 80% of change. In this research, the lever identified was HCC stratification: assessing a patient's level of risk for developing HCC which can allow optimized surveillance. It has potential to reduce costs through better management of high-risk patients, reduce patient burden by not over-testing, improve clinical outcomes, and increase public and patient engagement by giving audiences information that is more relevant to their individual risk factors.

Breakpoints

To make levers tangible, pinpointing breakpoints can further help prioritization and action. In the liver disease to HCC journey, major breakpoints include:

- Public awareness and education
- Support for primary care to play an active role in early detection
- Lack of registries to improve monitoring of patients at risk for HCC, including linkage to care
- Referrals and confusing reimbursements
- Logistical access to care
- Radiology bottlenecks
- Lack of funding for diagnostics and treatments

Key drivers reinforcing the status quo

Breakpoints do not exist in isolation. There are drivers that reinforce causes and effects. For liver care, these include:

- Public and patient perceptions of risk
- Stigma
- Under-resourced care providers
- The changing etiology
- Geographical distances
- Lack of cost effectiveness data

Opportunities

Lastly, zooming out, macro forces can change the situation at scale. These can be opportunities or threats, depending on if we notice and take action. For liver care, some examples include:

- **Other rising health threats such as metabolic conditions like Type 2 diabetes.** This *threats* to increase liver disease incidence, but, since this group are usually already plugged into the healthcare system, it is an *opportunity* for improved screening.
- **Availability of diagnostics.** The *threat* is that diagnostic tools are failing to keep up with the changing etiology. Conversely, a wakeup call to review diagnostic tools reveal the *opportunity* to really shift the story from palliative care to cure through better specificity and sensitivity.
- **Growing private sectors.** The *threat* to patient outcomes is coming from the fact that patients are getting lost in the system because of their increase in choices. However, there lies great *opportunity* to address gaps in service delivery through public-private partnerships.

Upstream and downstream influencers

Payers are, and should be, interested in maximizing the outcomes of programs they choose to fund. Without knowing what comes before or after an intervention, solutions will be short-sighted and sub-optimal. In the example intervention of *introducing biomarkers for surveillance* (Figure 3), improving upstream public awareness and patient education should be considered to increase the number of patients that enter

surveillance programs and reduce drop-out. Downstream, more surveillance will increase demand for treatments, therefore considering how the system will cope, and ensuring availability and affordability is key.

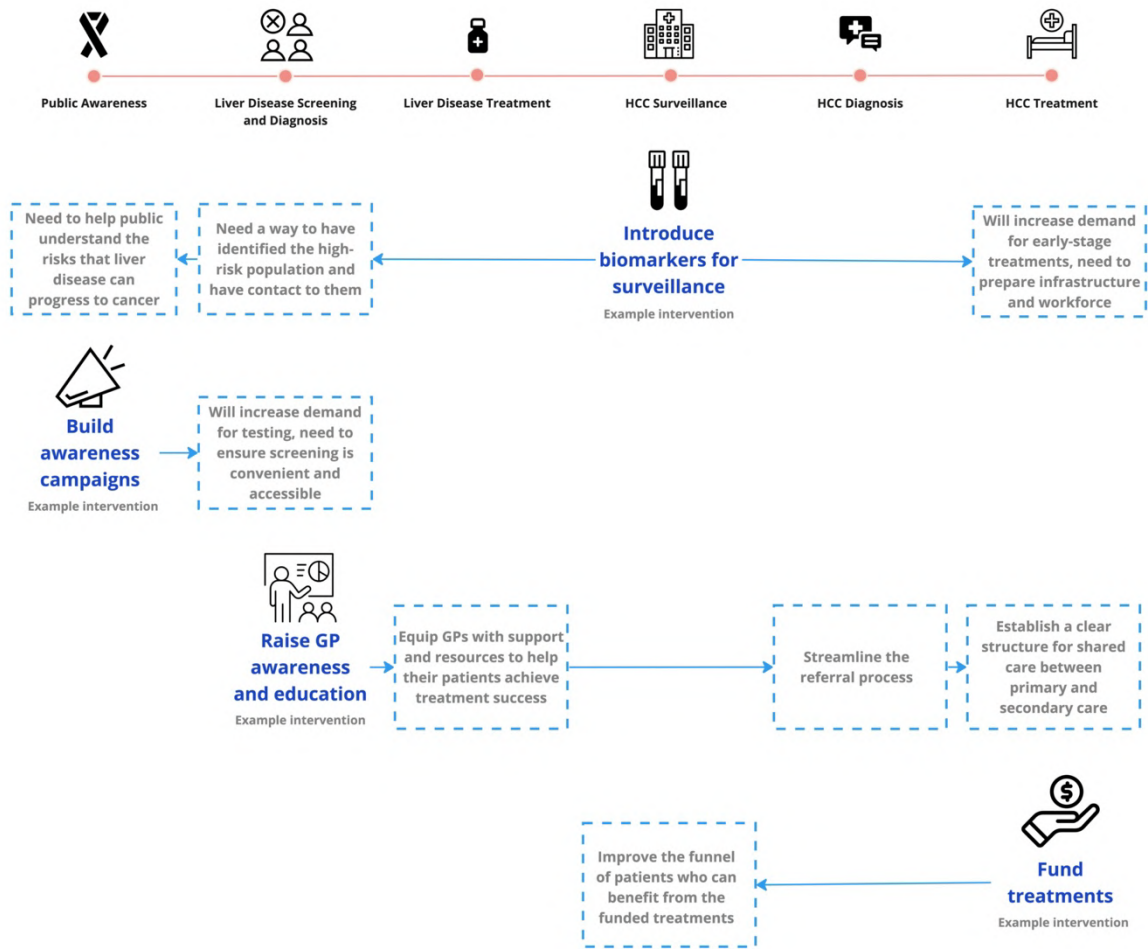


Figure 3: Example of up-stream and down-stream considerations surrounding an intervention, image by author.

Without knowing what comes before or after an intervention, solutions will be short-sighted and sub-optimal.

Primary research methodology for ecosystem insights

The research's objective was to uncover how to reduce liver cancer incidence and mortality in APAC. Knowing that outcomes are influenced by healthcare systems, cultures, religion, geographical spread, and economic state, 6 countries were chosen to give a variety of perspectives on trends and nuances. These were Singapore, Thailand, South Korea, Malaysia, Indonesia, and New Zealand. Research took place between 2021 to 2022 and involved over 100 participants.

System problems are often influenced by reasons people struggle to articulate. Without these insights, interventions fall flat. Therefore, Human-centered Design (HCD) methods were used. They included designing stimuli and probes we could give to participants to help them share their lives and experiences with us. These help us understand what people do, not just what they say they do. They also signal what is meaningful and important to them in their journey.

Human-centered design helps us understand what people do, not just what they say they do.

From a pragmatic lens, understanding what matters to people is not just nice to have. It helps identify moments that weigh heavily on actual outcomes so we can better invest funds to solve them.

“The human-centered approach is core in not just understanding, but also navigating the liver ecosystem. More importantly, taking action requires efforts from multiple stakeholders in the ecosystem.” – Prof. Dr. Yeong Yeh Lee, Consultant Hepatologist

Recruitment of participants

To understand the ecosystem, we gathered perspectives from the following groups:

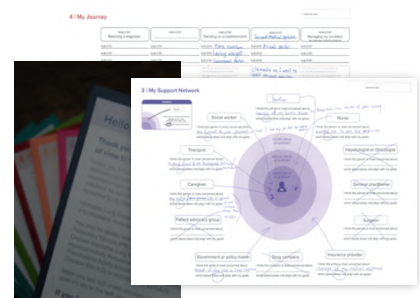
- HCPs N=50 Mix of public and private Primary Care Providers (PCPs), Hepatologists, Radiologists, Pathologists, Oncologists, Nurse Practitioners, Social Workers
- Patients and Care Partners N=35 hepatitis b virus (HBV)/hepatitis c virus (HCV), NAFLD, NASH, cirrhosis diagnosis, and HCC (early, intermediate, and advanced stage)
- Payers and Policy Makers N=18 Ministry of Health (MOH) representatives, private insurers, policy makers
- Academia and Think Tanks N=3 Research Universities, Patient Advocacy Groups (PAGs)

Methods

To understand both detail and big picture, a variety of methods were used; mainly ethnographic.

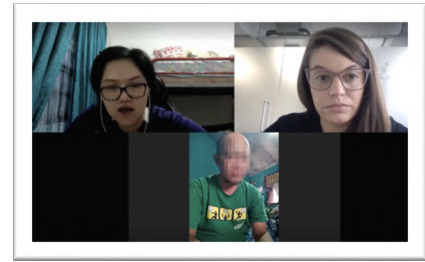
Design probes

Discovery Kits were deployed via mail to participants so they could share with us, over a week, the realities of living with a liver condition. The probes were designed specifically to uncover workarounds, meaning, significance, impact to quality of life, and external influencers of patients with liver disease. These discovery kits allowed us to further the HCD approach and extend the time we had with patients. They involved activities such as video diary entries, mapping one's support network, show and tell photo assignments, and role playing.



In-depth interviews

The Covid-19 pandemic led us to conduct interviews via online video calls. These were 1-hour, semi-structured, with simultaneous translation used in some regions. They enabled us to probe deeper into certain breakpoints and drivers.



Journey mapping

For some countries, we created Journey Maps with bright spots, gaps, quotes, processes, people, tools, and information used along the disease continuum. Other countries were further along in their understanding and did not require this.

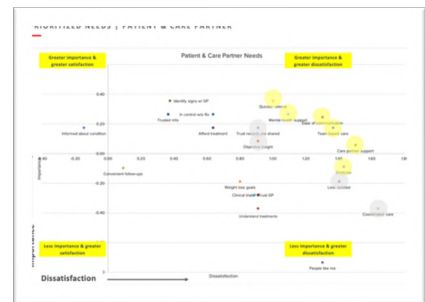


Roundtables

For Malaysia, we ran a roundtable discussion after the in-depth interviews with Key Opinion Leaders (KOLs) and the MOH to collaborate moving forward; this resulted in a report of recommendations some of which are shared in this paper. We also ran an APAC wide roundtable involving 6 KOLs to further share knowledge and help the transferability of insights locally.

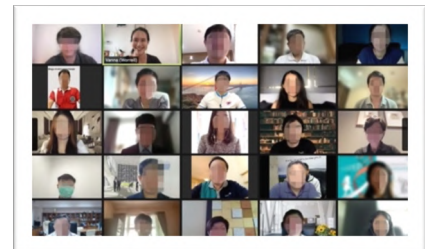
Surveys

To prioritize painpoints, surveys were sent to participants asking for their rating on how important and how dissatisfied they were with each theme. What HCPs and patients wanted resolved formed the themes of this White Paper.



Co-creation workshops

In ethnographic work like this, it is easy to get caught up in the problem. It is helpful to take another lens and reimagine ideal futures. Singapore, Thailand, and South Korea participated in online co-creation workshops allowing small groups of patients and HCPs to generate ideas. The outputs that resulted revolved around leveraging digital technology to improve access, finding new ways to connect patients, and exploring ways to address the radiology bottleneck. These themes are elaborated on shortly.



Since system problems have many variables, making ideas tangible early is beneficial so they can be tested. Designing for an ecosystem means as soon as you intervene, the system is changed again⁹; it is therefore an iterative and active process. We encourage you to take the insights from the next section and run low-fidelity pilots for this reason. The key is to just start small.

Overview of findings

Shared country issues and common root causes

Table 1 below summarizes contributors to rising liver cancer. Country nuances are covered on the following page. It is worth noting, some people are more affected by particular root causes which highlights how inequity arises. The ecosystem approach surfaces financial and social impacts that go beyond healthcare itself.

	Liver disease screening & diagnosis	Liver disease treatment	HCC surveillance	HCC diagnosis	HCC treatment
Main issues & root causes	<p>Lack of patient awareness and engagement due to:</p> <ul style="list-style-type: none"> • People not knowing to ask for liver tests • Few symptoms until late-stage downplaying the patient’s perceived importance of getting checked up • Lack of awareness (GPs have no time to educate and there is no formalized ownership for patient education) • Stigma deterring people from getting checked <p>Inadequate liver disease screening at primary care due to:</p> <ul style="list-style-type: none"> • Screening not a routine practice amongst GPs. Especially for people with Type 2 diabetes getting missed because of outdated clinical guidelines • Cost to patients not always covered by health insurance; some get through employer health schemes • Failure to diagnose upon presentation • Most patients with compensated liver disease (irrespective of etiology or cirrhosis status) having no symptoms • Symptoms mistaken for general gastrointestinal (GI) issues • Cost of diagnostics reducing or limiting the tests GPs use 	<p>Not reaping the benefits of available medicines for hepatitis due to:</p> <ul style="list-style-type: none"> • Cost to patients, particularly for life-long medicines • Lack of compliance because patients don’t realize HBV anti-viral medication needs to be taken for life • Patients not seeing the value / importance since they are not feeling unwell <p>Lack of lifestyle change support due to:</p> <ul style="list-style-type: none"> • Lack of GP time and skills to give bespoke advice • Patients feeling demotivated when they attend check-ups and are told off for not losing weight • Shame that causes patients to avoid appointments because they haven’t managed to stop drinking alcohol 	<p>Inadequate surveillance in high-risk populations due to:</p> <ul style="list-style-type: none"> • Patients getting lost in referrals • Patients not going for surveillance due to the cumbersome logistics involved in getting to ultrasound appointments • Radiology and scanning equipment bottlenecks which increase wait times in the public sector and leads to strict referral and appointment policies • Poor utilization of a country’s resources because while some private GP practices have ultrasound machines, they lack the training to conduct the specialized liver surveillance scans with it 	<p>Delayed diagnosis due to:</p> <ul style="list-style-type: none"> • Patients wanting second opinions • HCPs doing scans again because they don’t trust the results from referred patients • Cost of diagnostics which mean cheaper, less definitive tests are used first regardless of patient risk factors, which lead to prolonged processes depending on a patient’s insurance cover <p>Difficulties reaching definitive diagnosis due to:</p> <ul style="list-style-type: none"> • Early symptoms mistaken for generic GI issues leaving liver disease untreated • Lack of specialists • Lack of specificity in diagnostic methods • Lacking or inconsistent access to MDTs for support in diagnosis decisions 	<p>Late presentation means many good therapies are no longer suitable or effective, this is due to:</p> <ul style="list-style-type: none"> • The diagnosis issues already mentioned • Lack of specialists available to conduct HCC treatment • Low knowledge sharing for techniques like transplant <p>Unaffordable treatments due to:</p> <ul style="list-style-type: none"> • Lack of cost effectiveness data evidence to fund targeted therapies even though most patients discovered are late-stage HCC <p>Insufficient patient education and support due to:</p> <ul style="list-style-type: none"> • Lack of communication channels for patients to ask questions about treatment side-effects and other concerns • Lack of HCP time to educate and prepare patients to know what to expect because of short appointment times <p>Poor palliative care due to:</p> <ul style="list-style-type: none"> • A lack of awareness and education for HCPs and caregivers to know about specific HCC symptoms at the end-of-life which leads to impatience and inappropriate care

Table 1: Shared challenges and common root causes across all researched countries.

Individual country snapshots—challenges and nuances

Although there were similarities between geographies, there were also unique challenges faced. These differences were often influenced by themes such as funding, healthcare systems, predominant etiology, religion, and culture. Countries should note these when tailoring locally.



Singapore

The challenge in Singapore is two-pronged—fatty liver disease and affordability. Fatty liver disease is the rising etiology of concern and patients lack support in understanding the severity of their diagnosis and help to achieve diet and exercise goals. Singapore has a good surveillance program in place for chronic hepatitis B, but not for high-risk NASH patients. HCPs are dissatisfied with poor specificity and sensitivity of diagnostic tools which hinder stratification efforts. In the field, there is a focus on supporting primary care to be more involved in early diagnosis by educating GPs on what risk factors to look for. Co-pays were implemented to avoid overutilization of health services, but they are proving to be a barrier to patients receiving tests or treatments, especially for patients with chronic viral hepatitis whose long-term costs add up.



Thailand

Patients face lengthy delays in diagnosis caused by a lack of scanning tools in many parts of the country. They want, but lack, a way to communicate with HCPs about questions between appointments. In addition to differences in nationwide resources, there is inconsistent use of clinical guidelines which further the disparities in care across the country. On the other hand, radiology resources in the private sector are under-utilized and there is an opportunity for public-private partnerships.



South Korea

Patients are comparatively engaged in their self-care but report being unaware of what is available to them. They desire more information about what's happening to them, particularly knowing what to expect regarding side-effects. Uncertainty is coupled with social isolation brought about by shame. HCPs are equally unclear on what diagnostics and treatments are covered and are frustrated with lengthy reimbursement times. South Korea is one of the only countries in this study that has both PIVKA-II biomarker diagnostics and targeted therapy Tecentriq and Avastin reimbursed. However, usage is low due to lack of awareness of clinical utility and availability amongst both HCPs and patients. South Korea's existing HCC surveillance using AFP and ultrasound is insufficient in sensitivity meaning early-stage cases are getting missed. Having PIVKA-II included as a recommendation in clinical guidelines for HCC surveillance would improve patient outcomes and make full use of the diagnostic tools available.



Malaysia

Patients can quite easily move between public and private care providers, but consequently, HCPs report that they tend to get lost while “shopping around”. The referral process is not always clear for HCPs either—GPs in more remote areas find referrals unclear due to rotational specialists in those areas. There are also notable differences in patient behavior and attitudes between East and West Malaysia. Like Singapore, fatty liver disease is also a big concern, although their guidelines are one step ahead and now include screening of people with Type 2 diabetes. Overall, their strong private sector is an opportunity to form public-private partnerships to improve care gaps.



Indonesia

Many patients were misdiagnosed with having gastrointestinal issues at the primary care level due to a lack of local specialists. Despite their convoluted journey to diagnosis, most patients had high trust in their PCPs (often internists) and described them to be caring, patient, and kind. Fundamentally, Indonesia struggles with more basic healthcare problems causing liver cancer to be deprioritized against infectious disease control. This low prioritization means most regions are under-served and funding is lacking. Additionally, private insurance has complicated policy which delays diagnosis and often forces patients to stop treatment mid-way.



New Zealand

New Zealand has the Hepatitis Foundation which hosts a nationally connected and well-functioning registry of all New Zealanders living with chronic hepatitis B. However, GPs struggle to get involved in early detection due to lack of patient engagement, especially due to distrust in the healthcare system by Māori who are disproportionately represented in HCC incidence and mortality. Many patients fall out of surveillance programs due to geographical and logistical barriers in getting to ultrasound appointments. Coupled with a strict ‘did-not-attend policy’ which requires patients to obtain new referrals, there was said to be a “postcode lottery of care” that disadvantages those less able to navigate the healthcare system. To reduce inequities, Māori cultural aspects such as family involvement in health decision-making, social practices around food, and how shame and stigma resonate are all considerations for change efforts.

Flag images by @ Waree Design

In-depth insights

Healthcare is ultimately about improving human life. This next section shares how liver disease is experienced in daily life and impacts much more than one’s physical body. We invite you to immerse yourself in the stories and remember them when developing solutions. It is arranged into key themes that span across the journey from liver disease screening through to HCC treatment. Notice how painpoints are felt by multiple actors in the system; our interventions need to consider how we design for HCPs and payers as much as we do patients.

Summary of themes and implications

#	Theme	Implications
1	People are not just unaware of liver disease screening, they are unconvinced.	Awareness and education campaigns must consider motivation. People don’t feel ‘at-risk’, nor do they perceive screening to be worth the hassle when they have no symptoms. Designing and iterating messages with public feedback is recommended. Coupling this with a national screening program can help with momentum.
2	The shifting etiology demands a change in early detection approach.	Clinical guidelines may be out of date and primary care not aware. Patients with fatty liver disease are a different demographic with unique challenges and needs. Both detection and management protocols need review.
3	Viral hepatitis treatments are good, but uptake and adherence are poor.	Existing treatment outcomes can be improved. This is largely overlooked yet has good potential. Advances in digital technology offer exciting potential to expand reach and achieve scalability. Improving patient education also includes training public health workers. National guidelines for initiating Nucleos(t)ide analogues (NUCs) therapy for HBV is advised.
4	HCC surveillance via ultrasound is a major system bottleneck.	Tackling the radiology bottleneck by adding more resources is not always feasible, investigation into the potential of biomarkers such as PIVKA-II to compliment AFP as a first line approach to triage patients before ultrasound is worth exploring. The benefits would be multi-fold, including improved patient experience and outcomes, and more targeted surveillance resulting in better budget spending.
5	Difficulties making a differential diagnosis reduces treatment options.	Non-specific symptoms make it difficult for primary care to diagnose HCC in early stages. It is recommended to empower primary care by connecting them to MDTs, improve access and use of more sensitive diagnostics, simplify referrals, and raise awareness and education.
6	Stratification of high-risk patients is pivotal to a pragmatic strategy.	6-monthly ultrasound is not available in many rural areas, unaffordable in many low-income countries, and may not be suitable as the sole method for all patient risk groups, particularly in its poorer ability to detect early HCC. It is worth stratifying by reviewing risk algorithms and protocols according to local circumstances.
7	Unaffordable HCC treatments are still the reality for most.	A short- and long-term approach is needed for chronic disease. While addressing early detection, treating those who already present late is a significant unmet need. It is only responsible for payers to request data to make decisions – this is lacking and needs to be collected by HCPs.
8	Navigating the healthcare system is confusing for patients.	Patient navigation is half the battle in successful liver care interventions. Streamlining, signposting, and simplifying through collaboration is necessary. Improving the HCP experience of referrals and reimbursements is part of the upstream process.
9	Consider human life when designing interventions.	Uncertainty, financial pressure, lack of feedback, life stage, and stigma are all key drivers behind motivation, compliance, and wellbeing. Countries must look at how these particularly resonate for their populations, otherwise programs may fall short.

Table 2: Summary of themes and implications

Theme 1: People are not just unaware of liver disease screening, they are unconvinced.

Catching liver disease early significantly increases the chance of cure. However, public engagement in screening is low. Standard approaches to awareness and education are not sufficient. People's perception of risk needs to be understood and addressed.

“It's not that I didn't know anything at all. If I could turn back time, I wouldn't do these things, and I've received this kind of information already from campaigns or something like that. I've read them before, but I've never paid attention. I think everyone's like this.” – Patient, HCC, Thailand

“There are a lot of people with Hep B in my generation, most people don't progress to cirrhosis, I didn't think it was a big deal.” – Patient, hepatitis B cirrhosis, Singapore

Social circles are key actors in the system. The problem mentioned earlier was that stories of liver disease progression are not often shared since people generally jump straight to late-stage and die shortly after. Early stages of liver disease are not taken seriously by patients until the liver becomes cirrhotic and the fear of cancer sets in. Many end up regretting not taking action earlier. There could be benefit in sharing these types of stories. Given the various etiologies, the messaging will need to be different depending on risk factors and life stage.

No symptoms, no perceived risk; and screening is not routine

Without symptoms, patients are unmotivated to go for liver disease screening. Even when they knew family members died from liver cancer, the risk was not sinking in. There needs to be a disassociation between 'feeling well' and 'having risk factors'. Currently, pain is the only signal for a patient to go to their doctor; by then disease has progressed.

In the countries we studied, liver screening is not routine and requires unrealistic public proactivity. Furthermore, Liver Function Tests (LFT) are often out-of-pocket. Those fortunate enough to have private health insurance through their employers were usually covered, however, in those cases, people did not know that they could, or should, ask for it during their health check-ups.

Relying on the public to be proactive and pay out-of-pocket is an unrealistic ask given their current lack of perceived risk. At a higher level, population-level mindsets are also influential, especially in more developing countries where preventative healthcare screening is not a concept people are accustomed to—such as what we heard in Indonesia.

National screening programs initiated by governments can reduce these barriers. They can also be highly targeted since we know the age groups that would have missed vaccination and screening in earlier efforts. We also have better information on current risk factors than when those initial programs were rolled out. The case study presented by Prof. Dr. Ed Gane below demonstrates the effectiveness of such programs.

“Most cases of HCC in APAC can be prevented by earlier diagnosis and treatment of chronic hepatitis B and C and NAFLD. Although universal neonatal immunization will eventually eliminate the hepatitis B virus, this will take another 70 years and another 50 million people will die. We need to consider universal testing; for HBV in all adults born prior to neonatal vaccination, targeted testing for HCV in people who inject drugs (PWIDs), and for NASH in diabetic clinics.” – Prof. Dr. Ed Gane, Chief Hepatologist

APAC in Action: New Zealand—The benefit of a national hepatitis B screening and HCC surveillance follow-up program

Prof. Dr. Ed Gane, Chief Hepatologist, Auckland City Hospital, New Zealand

In 2000 the New Zealand government funded a national hepatitis B testing program which actively targeted those at high-risk including Asians, Pacific Islanders and Māori. This was done in the community, not in hospitals. The testing program ran for only 3 years, after which all identified hepatitis B surface antigen (HbsAg) positive patients were offered recruitment onto a national hepatitis B registry linked with lifelong monitoring for HCC. Both the national HBV registry and HCC surveillance program are conducted by the Hepatitis Foundation—an NGO funded by the government. Since the hepatitis B testing program closed in 2002, GPs have been encouraged to continue offering opportunistic screening (existing patients during appointments) for hepatitis B for all Asians, Pacific Islanders, and Māori patients. Newly diagnosed cases are referred to the foundation for enrolment in the HCC surveillance program. The Hepatitis Foundation staff work with the primary care team to ensure that patients do not drop out of surveillance programs.

The success of the New Zealand HCC surveillance program speaks for itself in terms of outcomes of patients diagnosed with HCC. 80% of new cases of HBV-HCC detected in patients enrolled in the surveillance program received curative treatment because most were detected at an early stage, compared to only 7% of new cases of HBV-HCC detected in patients who were not in the program¹⁰. Since 2000, the number of New Zealanders diagnosed with hepatitis B and enrolled in the HCC surveillance program has increased steadily and this has translated to better outcomes—a significant improvement in survival, with 66% of those with HBV-HCC diagnosed in patients enrolled in the screening program surviving more than 10 years, compared to only 9% of those not in the screening program¹⁰. Between 1996-2000, 68% of new cases of HBV-HCC were palliative at diagnosis, compared to only 26% in 2021-23¹⁰. **Could it be time to re-commission national screening programs to pick up the large and growing undiagnosed and untreated cases of liver disease?**

“The only means to reduce the huge health burden associated with HBV-HCC in New Zealand will be to relaunch the national HBV screening program for all adult Asians, Pacific Islanders and Māori born before 1990 and recruit all new HBV diagnoses into the national HBV registry and HCC surveillance program.”

– Prof. Dr. Ed Gane, Chief Hepatologist

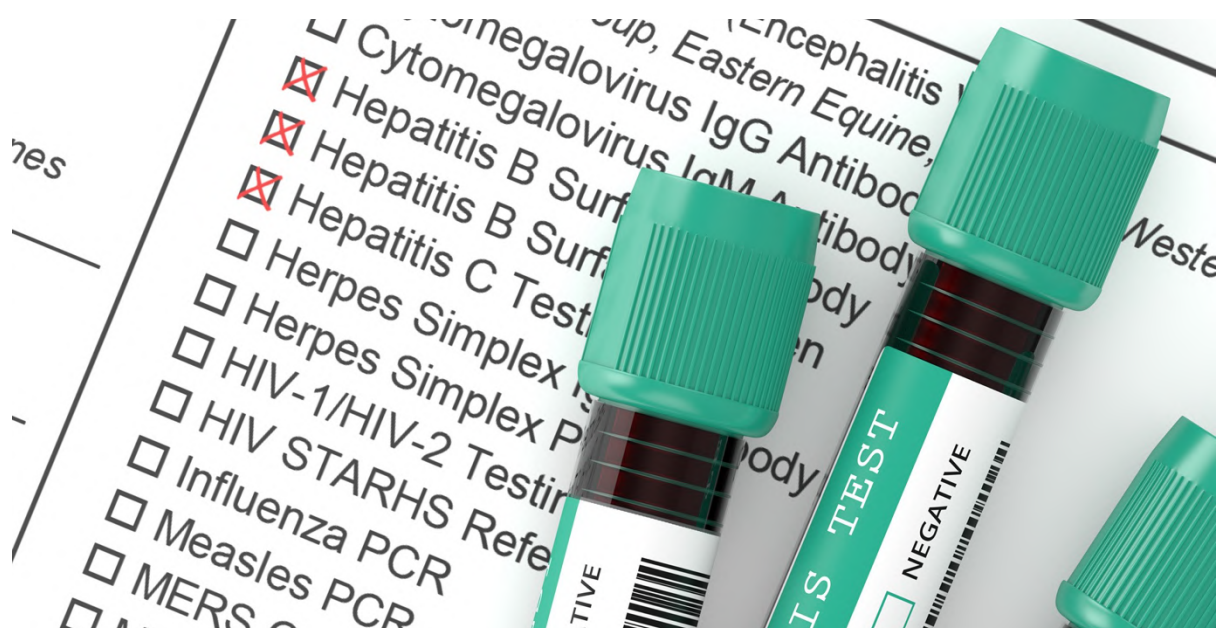


Image by @Aleksandra Gigowska

Theme 2: The shifting etiology demands a change in early detection approach.

Metabolic disease is increasing worldwide, coupled with this trend is rising fatty liver disease. While diet and exercise are the treatment to curb progression from fatty liver disease to cirrhosis, the sentiment is that without medicines it can't be that serious. As one surgeon in Singapore put it: "Fatty liver is one of the most common undervalued problems in developed countries. Because of fatty diet, and lack of exercise, they don't view this as a disease". Not only are this cohort under-served by way of exercise and diet treatment support, but they are also going undetected due to outdated clinical protocol and primary care awareness. Furthermore, patients with NAFLD can concurrently have chronic hepatitis B which is another rising complexity. Overall, this shift in etiology demands a new approach to the liver cancer prevention strategy, especially considering how to manage co-morbidities. With both Malaysia and Singapore already seeing fatty liver disease hit their shores, we share examples of how KOLs are taking action.

"Fatty liver disease is one of the most common undervalued problems in developed countries because of fatty diet and lack of exercise, they don't view this as a disease." – Surgeon, Singapore

APAC in action: Malaysia—Facilitating the detection of fatty liver disease as new routine practice to identify those at risk of HCC

Prof. Dr. Rosmawati Mohamed, Consultant Hepatologist, Hospital Canselor Tuanku Muhriz, National University of Malaysia

Malaysia faces the problem where individuals with fatty liver disease are not getting picked up, and surveillance is low for this group compared to chronic viral hepatitis patients. Data indicates the shortfall is happening in primary care—only 29.5% of people picked up in primary care are being actively surveilled, compared to 73.7% once engaged in GI/Hepatology clinics¹¹. As such, Prof. Dr. Rosmawati Mohamed and her team have started a program in 3 states across Malaysia to support primary care surveillance efforts.

The program helps implement new clinical guidelines in Malaysia that now recommends screening people with Type 2 diabetes—an important risk factor for fatty liver disease¹². It uses blood tests for alanine transaminase (ALT) and aspartate aminotransferase (AST); screening intervals are tailored depending on those results and FIB-4 scoring. FIB-4 is a non-invasive blood test marker for liver fibrosis in patients with NAFLD and is a pragmatic initial stratification method which can be followed by confirmatory tests where needed. Patients with a FIB-4 level of 3.25 or higher are surveilled for HCC. At the same time, patients are tested for viral hepatitis and the possibility of alcohol induced factors.

Since screening has not been a routine practice previously, GPs are unfamiliar with the protocol and need support in getting up to speed with the changing etiology. Using the ECHO (Extension for Community Healthcare Outcomes) model, Prof. Dr. Rosmawati Mohamed initiated a program to reach rural HCPs. It supports this transition and the scaling-up of detection across the country by providing digital access to knowledge and tools. Other countries would benefit from adopting updated guidelines and coupling it with an implementation support initiative such as this. The ECHO model is worth looking into as a way of leveraging digital technology to combat geographical disparities. **How might we collaborate to scale efforts at an APAC level?**

"Liver disease screening and stratification to identify those at high risk can optimize HCC prevention and early detection." – Prof. Dr. Rosmawati Mohamed, Consultant Hepatologist

APAC in action: Singapore—Empowering primary care to become more active in liver cancer prevention

Dr. Mark Muthiah, Consultant Hepatologist, National University Hospital Singapore and Medical Director, Adult Liver Transplant Program, National University Centre for Organ Transplantation

Singapore is also feeling the rising wave of NAFLD. In response, Dr. Mark Muthiah and team are proposing a new two-stage workflow that follows the American Association of Clinical Endocrinology (AACE) guidelines—initial FIB-4 screening, primarily for patients at high risk of metabolic-related liver disease that can be done at GPs, followed by a FibroScan in patients with indeterminate risk with FIB-4 which has already gained momentum in the USA.

In addition, a number of surrounding efforts are being made to empower primary care and service delivery from multiple angles across the ecosystem. Starting at the foundations, fatty liver disease testing protocols are now embedded into medical school examinations, and continued education ensures HCPs can learn about the changing needs of the country.

To increase throughput for screening programs, they are raising awareness among cardiovascular and Type 2 diabetes research programs, so that they can select patients that are high risk and proceed to screen them for liver disease. To avoid anticipated bottlenecks, FibroScan access is being improved by helping to develop pathways and instructions on how to run open access FibroScans within the government hospital system as well as private sector. Looking broader within the ecosystem of liver care, advanced practitioner nurses are being trained to ease the load on specialists and reduce the costs in service delivery.

Identifying that cases were getting lost in complicated referral pathways, work has been done to ease access by simplifying the process. Importantly on the reimbursement side, the government now funds imaging and bloods which are now claimable under national insurance. To support scaling of all these efforts, a grant funded research project is being run with a population-based cohort to generate cost effectiveness data for the value of screening that can be used to present to policymakers.

Thinking ahead and leveraging technology, Dr. Mark Muthiah and his team are pushing for all patients with Type 2 diabetes and metabolic diseases to have their FIB-4 automatically calculated and put on their electronic medical records. This would be a huge step forward towards a sustainable approach through automation and standardization. This work inspires us to look at multiple actors in the system for a concerted and sustainable approach. **What are the interdependencies for successful service delivery in your country?**

“Early recognition of patients at increased risk is key to reducing morbidity and mortality from end stage liver complications and HCC.” – Dr. Mark Muthiah, Consultant Hepatologist



Image by @Blue Planet Studio

Theme 3: Viral hepatitis treatments are good, but uptake and adherence are poor.

Unlike the lack of treatments available for fatty liver disease, good medications are available that make hepatitis C around 90% curable with an 8-week course of antivirals¹³. And for chronic hepatitis B that is incurable, there are still effective pills with little side effects that slow progression to cirrhosis. We recommend referring to the latest China clinical guidelines where HBV DNA level and age determine treatment initiation irrespective of ALT and fibrosis stage¹⁴. This approach has been possible due to access to low-cost generics and supported by studies showing not only reduced HCC incidence in these patients over 10 years, but also rapid reduction in viral genetic material integration burden¹⁵. Unfortunately, they are failing to stop disease progressing to cancer because uptake and adherence is poor.

In a 2019 study by the WHO, only 19% of people with hepatitis B were aware of their infection status, of those, a mere 15% received treatment in the same year as their diagnosis¹⁶. Patients often stop taking HBV antiviral medication because they do not realize they need to take it for life. Without a gauge or understanding of how their medicines work, they do not understand how to manage their disease appropriately. For example, in New Zealand, a patient thought that because a liver resection cured his cancer, that the hepatitis B was also gone. He stopped taking medications because he thought he didn't need to anymore; however it is important continue medication to avoid the high risk of relapse, jaundice, and death¹⁷. For others, non-compliance was due to long-term costs.

“She [doctor] has recommended me some sort of treatment a few times now, I kept saying no, as I don't want to pay for an additional therapy. I can't recall the name or the purpose of it.” – Patient, hepatitis B cirrhosis, Singapore

Only 19% of people with hepatitis B were aware of their infection status, of those, a mere 15% received treatment in the same year as their diagnosis.¹⁶

Patients lack the information they need to realize the seriousness of their condition

Concerningly, the risk that liver disease is chronic and can progress to cancer is not always being effectively communicated. While much generic information can be found online, patients do not always know what to search for. Neither do they know what specific questions to ask during appointments. Physicians are constrained by time, and although they do try to explain everything during consultations, there is a limit to how much they can cover. Often the diagnosis is so unexpected that patients are in shock and cannot remember what their physicians tell them. Sometimes more tech savvy patients will Google the terminology on their test results, though there may be a generational difference in this behavior.

“I was not aware of HCC before the diagnosis, I was aware of hepatitis but didn't know it could lead to cancer.” – Caregiver, Thailand

“Now that the information is so readily available on the internet, I think they can find what they want to know.” – Hepatologist, Singapore

“My specialist never explains to me, nor about the test result or treatment. They only answer if I ask very specific questions. But I am not a medical expert, how would I know all the questions to ask about my condition?” – Patient, hepatitis B cirrhosis, Singapore

While much generic information can be found online, patients do not always know what to search for.

In these situations, early detection efforts are wasted; the benefits are not being fully realized. Below, we share what Prof. Dr. Pisit Tangkijvanich in Thailand is doing to not only empower patients through education, but also tackle the accessibility aspect of patient screening.

APAC in action: Thailand—Scaling up the ability to screen and treat hepatitis B

Prof. Dr. Pisit Tangkijvanich, Consultant Hepatologist, Chulalongkorn University, Thailand

Thailand struggles to screen its population for hepatitis B, especially in rural areas due to lack of staff and resources. While people may know they have hepatitis, they don't know how to manage it. The challenge is, there is no online database that holds sufficient epidemiological data to allow tracking of these patients. Nor is there an eLearning platform or way to track patient education efforts.

A pilot project is being conducted by the Center of Excellence in Hepatitis and Liver Cancer at the Faculty of Medicine Chulalongkorn University, in collaboration with the Thai Association for the Study of Liver (THASL) and the Department of Disease Control (DDC), Ministry of Public Health to facilitate hepatitis B elimination in Thailand. They are modelling a way to get better online populational data, increase awareness, and improve education by leveraging technology to reach patients and HCPs en masse. The scope of this project is 80,000 to 100,000 people from the general population in 20 provinces, over the age of 30—which was just before the immunization program. Currently, HBV screening in Thailand is implemented for free only to people who donate blood, HIV-positive individuals, and pregnant women.

To make testing more accessible, they are using rapid hepatitis B surface antigen (HBsAg) test strips. These are cheap, simple diagnostics that can be used in primary healthcare settings and district hospitals without much training. The accuracy is more than 90%¹⁸; not a perfect test but a very pragmatic tool for overwhelmed healthcare settings. Individuals who are confirmed HBsAg-positive will be evaluated for additional relevant blood tests and linked to care by HCPs.

Those patients will then receive 30 minutes of eLearning via a mobile app using video for easy consumption. Before and after self-learning, the patients are asked “Yes”, “No”, or “Do not know” questions to test their understanding of facts like ‘can I get it via sharing food or drinks?’. These are simple but provide important confirmation of knowledge about HBV infection. Topics were chosen to empower patients to understand and manage their disease with confidence. Topics they are focusing on are the load of transmission, treatments, and medications available, and how to understand their risk factors.

HCPs involved in running the study with patients also receive access to an online training program. Pre- and post-intervention surveys will be used to compare changes in knowledge, attitudes, behaviors, and practice of HCPs. The study is due to conclude in November 2023. So far, the challenge was to get HCPs onboard. They had questions such as ‘why are we doing this?’ and ‘why do we need to change the way we do things?’. To overcome this, a coordinator role was created who works with the government, has contacts at each of the pilot sites, and puts the project team in touch for online video calls to explain the background and goals; this has helped to smooth that upfront barrier in adoption. HCPs involved are also compensated to run the program. If this proves to be effective, the next step would be to seek funding to scale nationally—from government but also privately from people and companies interested in supporting this cause. **Could rapid HBsAg testing be utilized in other countries as a pragmatic first pass method of hepatitis b screening?**

“Point-of-care (POC) testing such as rapid HBsAg can improve the rate of HBV diagnosis and linkage to treatment, especially in primary healthcare settings. In addition, digital health platforms have the potential to increase awareness and knowledge, as well as facilitate HBV care that leads to the prevention and early detection of HCC.” – Prof. Dr. Pisit Tangkijvanich, Consultant Hepatologist

Theme 4: HCC surveillance via ultrasound is a major system bottleneck.

One of the major patient painpoints mentioned, in all regions apart from in South Korea, was the burden of having to go to hospital rather than a local clinic for scans. This applied to confirmative diagnostic tests such as MRI and CT, and ultrasound in HCC surveillance. In surveillance, patients are much less motivated to attend since they don't perceive the benefits as we have discussed. This is the main reason patients do not get onto surveillance programs, or eventually drop out. We found several contributors to this poor experience:

- Under-resourced radiology departments leading to months of waiting for an appointment (all countries)
- Unavailability of convenient appointment slots with patients needing to stay up late to log onto the booking system for a better chance of securing a peak time (SG)
- Strict did-not-attend policies which require patients to obtain a new referral from their GP if the appointment is missed or not able to be booked within a certain time period (NZ)
- Distance to hospital (TH, IN, MY, NZ)
- Difficulty and expense of finding a parking spot at the hospital (NZ)
- The need to return just to hear the results—patients wished at least to get their results more locally (all)
- The need to take at least a half day off work (SG), or more often the full day (TH, IN, MY, NZ)

Radiology departments are under-resourced in terms of staff and equipment and are usually located in major city hospitals. Their wait-times are lengthy since they serve such large areas and multiple other disease areas. In Thailand for example, this wait can be 7 months. Countries are missing their cancer control targets due to this system bottleneck.

“Thailand lacks equipment, at my hospital the wait for MRI & CT could be 7 months.” – Pharmacist

“We can't cure shortage by just increasing supply but should consider the roots behind the shortage.” – Prof. Dr. Yeong Yeh Lee, Consultant Hepatologist

Liver cancer exacerbates health inequity

In APAC, liver cancer is the top cause of cancer related deaths in the lower-middle- and low-income bracket¹⁹. It has disproportionately impacted those not fortunate enough to live near a major hospital. The problem is not only wait time, but convenience. Getting to a hospital for a scan is not easy, even for the most motivated of patients. Many countries in APAC have dispersed populations across multiple islands with rural communities. Journeys participants told us about were often around 4 to 10 hours, involving buses, ride shares, and even boats.



Image by @Rasmus

In East Malaysia, access is not just a matter of distance, it's a matter of the tides. "...he [patient] said... he can't come to the hospital... he needs to look at the moon. If it's a full moon, then you know, the water level rises, only then can he take the boat out from his village to come to us. So, when it's not full moon, the river water is so shallow that he cannot get out from his village." - HCP, Malaysia

"It is important to consider the overall cost of treatment when patients from the rural areas have to commute to get treatment at bigger city hospitals. There is generally a higher rate of recovery for urban patients vs rural patients due to this context." – Oncologist, Thailand

The inequities are also seen in quality of care due to the availability of specialists and treatments. While decentralized healthcare and 'close to home' care provides better access, the trade-off is 'best care'. There isn't enough resource to have a specialist in every region, hence the idea of Centers of Excellence. Although with advances in technology and communication channels, and the possibility of better-connected MDTs and/or public-private partnerships, this concept should be revisited and reimagined; below are two examples. Later we discuss the role of biomarkers in addition to ultrasound for early detection of HCC.

While decentralized healthcare and 'close to home' care provides better access, the trade-off is 'best care'.



Image by @Surachetsh

APAC in Action: Thailand—Connecting hospitals, primary care, and community labs. Opening access to a network of care.

Dr. Passakorn Wanchaijiraboon, Consultant Oncologist, Phrapokklao Cancer Center of Excellence, Phrapokklao Hospital, Chantaburi, Thailand

Thailand sees a wide range of treatment access disparities across its different regions. An overwhelming number of patients particularly in the east and west of Thailand are not receiving any specific treatment whatsoever, apart from around 5% being treated with TACE²⁰. This is compared to other regions such as Bangkok and the South where combination therapy and RFA is being used²⁰. Even then, patients treated with the same treatments in Bangkok will go on to have better survival rates than those treated in the periphery²⁰. This is thought to be due to better availability of specialists to deliver specific treatments in Bangkok, and more resources which further reduces wait time. Although patients with viral hepatitis can be diagnosed in community hospitals, the treatment needs to be started by a general or internal medicine doctor or GI specialist in a referral hospital. This leads to a gap between diagnosis and treatment and poorer survival as a consequence.

To address this, a pilot project called the Liver Clinic System Model (Figure 4) was created. The aim is to help Thai people access effective screening and treatments on time, leading to a better quality of life and a higher chance of survival by connecting care across the country. With the multifactorial nature of this ecosystem problem in mind, there are 4 key elements designed to drive optimal success:

- 1) Proactive finding of high-risk groups**—improving targeting of efforts and healthcare budgets through public awareness and proactive searching.
- 2) Digital Health for HCC Surveillance**—leveraging technology to support accessibility in communicating and monitoring symptoms of liver disease, especially in high-risk patients.
- 3) Adding new biomarkers/algorithms for surveillance programs**—tackling the healthcare system bottleneck and improving the effectiveness and ease of surveillance through new protocols and diagnostic tools.
- 4) Health Information Exchange**—a health data platform that allows liver disease patients to receive care from anywhere, by sharing information between each hospital.

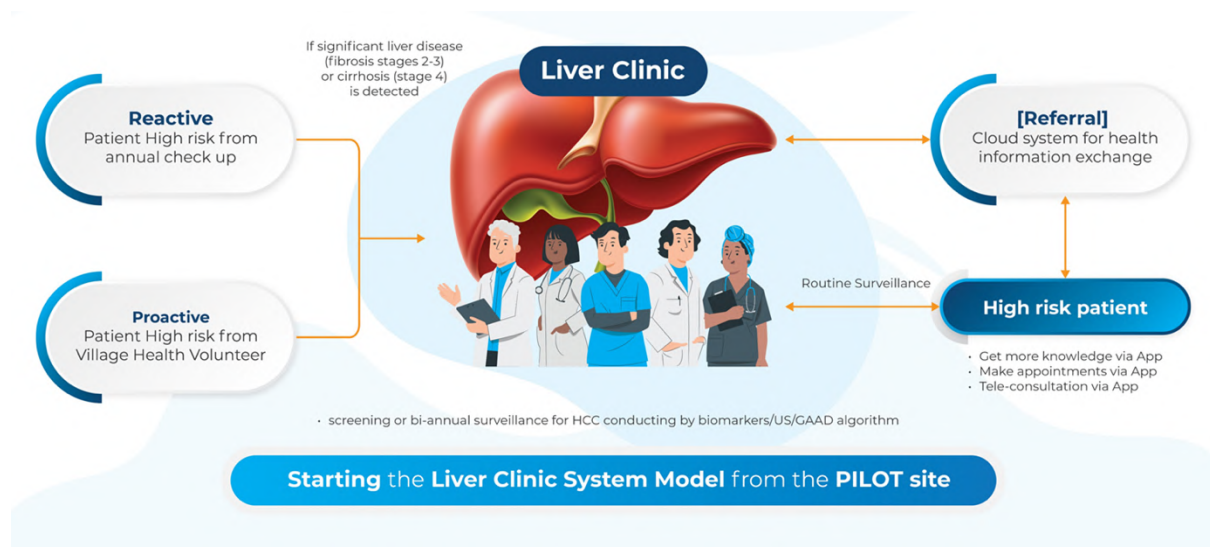


Figure 4: Model of Integration Liver Clinic System by Roche Liver Ecosystem Advancement Program core team Thailand.

In support of this system-based model, there are initiatives that provide bespoke solutions to Thailand's unique circumstances—for example, Health Link supporting the Health Information Exchange, and SurviLiver supporting Digital Health for HCC Surveillance.

Health Link is a cloud platform that is in development to store patient health information digitally. This overcomes the issue that shared care is difficult to provide in Thailand because health records are inefficient to exchange. This solution would connect community labs to referral hospitals and smooth the diagnostic-treatment transition. SurviLiver is an app that contains educational information, a patient diary, an appointment booking system, and ability for physicians to check on their patient's health between visits. The intention is to improve liver cancer survival chances by empowering critical actors in the system and bridging breakpoints.

This model demonstrates a holistic strategy to close the care gaps by acknowledging the ecosystem, macro trends of technology, and human-centered opportunities to improve care. To further this work, collaboration is needed between the Ministry of Public Health (MoPH) and The Ministry of Digital Economy and Society (MDES). The MDES is responsible for the Health Link project. But it's the medical personnel who are responsible for direct care of HCC and HVB patients in the MoPH. Joining these actors in the ecosystem is a critical link.

“Resolving breaks in the ecosystem cannot always be tackled by more resources, but we can look towards technology to connect the resources we do have.” – Dr. Passakorn Wanchaijiraboon, Consultant Oncologist

Spotlight: Public-Private Partnership discussion in Malaysia

Malaysia, like other countries, has the ultrasound bottleneck issue. Although several private GP clinics have ultrasound machines, clinicians are not trained to use them to detect liver abnormalities. There is therefore an under-utilization of a crucial resource. One clinician said, “We have no shortage of manpower, it's just that sometimes there's misplacement”.

Malaysia has a strong private sector that provides around 30% of care. Unlike in other countries where referrals are needed to access secondary and tertiary care, Malaysian patients are free to access healthcare at whichever level they want, it's just down to cost. Public-private partnerships are thought to be one avenue to improve resource shortages in the public sector. Its potential was demonstrated during the Covid-19 pandemic and has sparked interest.

“We have no shortage of manpower, it's just that sometimes there's misplacement.”- Private GP, Malaysia

Practical implementation considerations include ensuring private care providers are adequately reimbursed by the government. Private GPs also fear losing their patients to the public sector and specialists; a clear and fair agreement needs to be discussed around how to achieve shared care. Other countries that have this macro trend of growing private sectors may consider this type of partnership, including Thailand that have expressed interest.



Image by @pongmoji

Theme 5: Difficulties making a differential diagnosis reduces treatment options.

The next hurdle in the journey is difficulty making a differential diagnosis. Meanwhile disease progresses; again, diminishing the benefits of early presentation and reducing treatment options. There are multiple points where arriving at a differential diagnosis is a challenge:

- When patients present to their PCP and their symptoms are diagnosed as gastric acid or other gastrointestinal problems as we heard frequently in Indonesia
- When GPs order the wrong modality for imaging tests
- When radiographers differ in techniques
- When insurance policies request cheaper less precise tests are done first

“For more than half of CAT scans I receive, I need to order them again because GPs don't mention that patients need triple-phase.” – Hepatologist, Thailand

During this uncertainty, patients often mentioned they were scared, tired, and worried their disease was getting worse. Shuttling between the healthcare system was exhausting, and many had to stop work due to fatigue. Additionally, the financial cost of tests added to the pressure of unemployment.

During this uncertainty, patients often mentioned they were scared, tired, and worried their disease was getting worse.

Patient story—It took 7 months to arrive at a differential diagnosis of Stage 2 HCC



Image by @sitriel

Banyu is 48 years old and has 4 children between 3 months and 20 years old. He lives with his family, and his older sibling's family, under one roof in a village in rural Indonesia. Initially he experienced nausea, bloating, and vomiting and was given ailments for gastric acid problems by the community clinic doctor. But after feeling extremely fatigued, and this happening another 4 times in close proximity, he went to an internist who suspected it was a gallbladder problem. A CT scan for his stomach revealed a lump in his liver; a biopsy confirmed it was malignant. This whole process took 7 months; by now it was Stage 2 HCC. At first, he couldn't believe the diagnosis because he felt he was a healthy person. He used to go on hikes and long-distance tours on his motorbike without any problems all this time. Since his diagnosis, he had to leave his job because he didn't have the energy to keep it up. For check-ups, he tries to get to the hospital at 3am to avoid the queues which make him even more exhausted. His wife now must work extra hard to support the family and he worries about how much his condition is costing everyone. - Patient, Intermediate HCC, Indonesia

Multi-disciplinary teams are necessary for speedy diagnosis

Due to the complex pathology of liver cancer, MDTs are invaluable to achieve optimal patient outcomes. But PCPs are not usually connected. Without MDTs, treatments tend to be swayed by which specialty the PCP refers the patient to since each have different focal points and risk tolerances. What's needed is a clear process for shared patient care, for example, in New Zealand, all patients picked up in primary care are first referred to the Hepatitis Foundation, suspected HCC cases (raised AFP or ultrasound abnormality) are referred to local secondary gastroenterologists who then refer to an MDT run by a tertiary center Liver Unit. The MDT provides diagnosis and management recommendations, start patients on treatment, and then refer them back to GPs to continue treatment.

A well-connected MDT may also give patients more confidence in decisions and avoid them seeking second opinions. Patients who can afford it will often go to the big cities to seek out 'better care'. Both Malaysia and South Korea mentioned this type of behavior. In Indonesia, one patient mentioned that his PCP (a general internist) called a colleague to discuss his case while he was with him; he heard everything that was said—this made him trust his doctor and the treatment recommended. Of course, this may not be perceived similarly by all patients. However, an MDT can, in this way, help patients tap into a wider pool of expertise.

An MDT can, in this way, help patients tap into a wider pool of expertise.

The range and state of MDTs varied country to country, and even city to city. New Zealand has a population of 5.1m²¹ and one nationwide MDT. They conduct weekly calls to discuss all cases which are coordinated by nurse specialists. Up and down the country, it was clear where referrals should go to, and diagnoses were made swiftly.

Malaysia has a population of 34.2m²² and there were two major MDTs that participants mentioned. One of these MDTs is run by The University of Malaya Medical Centre who collaborate with ECHO to reach rural HCPs. This Ministry of Education (MOE) led initiative runs a weekly session via Zoom and evolved from discussing Masters students' case studies in a forum format. It continues this successful approach where HCPs are invited to bring their cases for discussion, but also attend if they don't have cases; it's about the learning.

In Indonesia, MDTs that participants mentioned were usually within the same hospital between 3-4 specialists or between personal contacts in the field in an unofficial manner. There is no right or wrong way to run an MDT, and each country's settings will call for different setups. We presented examples from what we know runs well in certain countries, but regardless of the modality, we share these practical considerations that came out of the Malaysian KOL roundtable:

- HCPs need support in setting MDTs up. They have limited time to get the technical aspects of the collaboration going, for instance, the discussion forum platform, or to organize the online calls.
- Investigate what motivates HCPs in the area. For example, in Malaysia, there was an idea to have an online platform where cases can be presented and specialists could comment, but it did not receive a good response because it lacked rewarding interactions. This may resonate well in other countries depending on the context, but in Malaysia, acknowledgement of contributions, and an environment and culture of being open to learn as opposed to giving strict medical opinions was desired.

There is no right or wrong way to run an MDT, and each country's settings will call for different setups.

Theme 6: Stratification of high-risk patients is pivotal to a pragmatic strategy.

It's not about just screening or surveilling more; it's about doing so strategically. Better targeting of surveillance is needed. This can be achieved through stratification—sorting a population or patient group based on unique risk factors for effective targeting and management. In order to distinguish these subgroups of risk, appropriate diagnostic tools are required. However, there are concerns that the current gold standard ultrasound alone lacks the specificity and sensitivity that is required to detect early HCC, and is not technically useful in many patients due to obesity. This has driven South Korea and some other countries to use MRI (non-contrast or accelerated contrast sequences) but few countries in APAC would be able to provide this.

With the ultrasound bottleneck, inaccessibility, unaffordability in many lower income countries, and operator dependent inconsistencies leading to delays in diagnosis mentioned earlier, it is worth reviewing HCC surveillance protocols to determine how diagnostic resources are used to make wiser investment choices with limited healthcare budgets and bring better patient outcomes. These changes need not be complicated, for example, knowing that there is an ultrasound bottleneck and struggles with booking appointments, routine scheduling of the next ultrasound can be done during clinic visits when their latest ultrasound and blood results are being reviewed. Observing patient behaviors and barriers help us identify such solutions.

“When using ultrasound for diagnosis, it is difficult to find it [HCC] in the early stages, so in many cases, patients are diagnosed only when the disease has progressed. As a radiologist who runs ultrasound, I believe ultrasound is not enough for surveillance.” – HCP, South Korea

It's not about just screening or surveilling more; it's about doing it strategically.



Image by @HENADZY

Additionally, with the shifting etiology, current imaging is ineffective for accurate staging of fatty liver disease and NASH. FibroScan can support cirrhosis staging, but its accuracy is limited for high BMI and is seen as unable to diagnose NASH²³; it is also not widely available. Biopsy is still seen as the ‘gold standard’ to diagnose NASH although has increased patient risks and higher costs; it is also prone to sampling errors²⁴. These are problems because in most countries, GPs do not refer for fatty liver disease and lack the tools to accurately identify cirrhosis. Progression continues to happen under their care and cirrhosis and early-stage tumors can go undetected.

Biomarkers complement AFP in providing better sensitivity and specificity for early HCC detection

Many KOLs are investigating the potential of biomarkers to address ultrasound access barriers. The current Standard of Care (SOC) is to use Alpha-fetoprotein (AFP) followed by ultrasound for the detection of early-stage HCC. However, AFP has limitations in diagnosis accuracy especially for early-stage HCC²⁵. Prothrombin induced by vitamin K deficiency or antagonist- II (PIVKA-II) is a serum marker for HCC²⁶ which used in combination with AFP is showing improved sensitivity and specificity for early HCC detection²⁷.

As biomarkers only require a simple blood test, there is potential to bring first line surveillance into the local clinic setting and more effectively triage high-risk patients for ultrasound. Through this ability to stratify risk more effectively, the scanning bottleneck could be reduced with the benefit of less false negatives and more true positives. More clinical research is needed in this space to determine how to best position this biomarker in workflows and clinical guidelines—the reason for many KOLs conducting pilots to explore the possibilities to really shift the prognostic curve using diagnostic tools available today.

As biomarkers only involve a simple blood test, there is potential to bring first line surveillance into the local clinic setting and more effectively triage those high-risk patients that need to proceed to ultrasound.

Aside from clinical practice, the bottom line comes down to cost. To give an idea, the cost of AFP in Thailand is around 8 USD, PIVKA-II is around 10 USD, whereas ultrasound is estimated to be in the order of 100 USD. In Malaysia – the cost of PIVKA-II is around 4-5x more than AFP, but only currently used in a few private centers—the sentiment is that if tests are done more widely, costs could come down due to economies of scale.

The question of payers is ‘how do we value a surveillance program at a population level’? It presents the situation where a smaller number of high-risk patients need more frequent monitoring; a small group benefits, but the whole population bears the cost of these tests. The flip side to this equation are the costs brought on by the total burden to the healthcare system. Costs are high when patients enter secondary care directly as it is more expensive to treat those who are already sick. Early diagnosis allows early intervention which reduces the number of hospital admissions and more extensive treatments that tend to progress to palliative care in the case of liver cancer.

“It’s a no brainer that we should be identifying patients early. That’s the beauty of a surveillance program, you already have identified high-risk, they’re already targeted so you can just focus on them. This [potential for higher sensitivity] would make a huge improvement and case to justify a surveillance program. Even just conceptually and logically that would make sense.” – Healthcare economist, New Zealand

While pilots and lobbying for and policy change take place in many countries across APAC, we can look to South Korea as an indicator of considerations for what could come next. There, PIVKA-II is already funded and in clinical guidelines, albeit only as a comment instead of a recommendation. There is work to be done to improve awareness amongst HCPs about its clinical utility. Currently, it’s used for monitoring treatment, but it’s underutilized as a tool for HCC surveillance. Not only do HCPs need to be informed, but patients need to be aware that they can request this test from their HCPs. This would help patients understand how their disease is progressing which is a current unmet need and desire of South Korean patients we spoke to.

APAC in action: Malaysia and Thailand – Comparing PIVKA-II biomarker against the current SOC

Prof. Dr. Yeong Yeh Lee, Consultant Hepatologist, Universiti Sains Malaysia Hospital

Unresectable HCC is the major challenge of late presentation as it limits options for cure. AFP lacks sensitivity and leads to frustration and disappointment because it prevents the inability to detect HCC early. In response, Prof. Dr. Yeong Yeh Lee and his colleagues conducted a study to determine normative levels of PIVKA-II and AFP in patients with unresectable HCC and healthy participants. In addition, PIVKA-II and AFP responses were correlated with radiological responses post-locregional intervention. Of those screened, 54/125 patients with unresectable HCC (mean age 58.9 years, 49 males) and 40/50 controls (mean age 33.5 years, 26 males) were recruited. This study is currently unpublished, but submitted and currently under peer review.

The results of their study are encouraging. The ability to detect and differentiate HCC from the healthy control group is very distinctive with the use of PIVKA-II compared to AFP. With PIVKA-II, the median serum levels were 988 mAU/ml compared to 24 mAU/ml in healthy controls. For AFP, the difference was 13.6 ng/ml compared to 1.7 ng/ml in healthy controls.

Their second finding was that the combination of PIVKA-II and AFP, in comparison to AFP alone, did result in higher diagnostic sensitivity. Cut off levels found for PIVKA-II was 41.4 mAU/ml and for AFP 4.8 ng/ml. Note: these absolute numbers will vary depending on the provider of the diagnostic tool, but the difference in diagnostic efficiency is clear.

Thirdly, their study showed that using PIVKA-II as a marker to determine treatment response did correlate with radiological responses, while AFP did not.

These results are in line with Dr. Passakorn's preliminary findings from his pilot in East Thailand that also showed using PIVKA-II in combination with AFP or ultrasound improves sensitivity. This study was called the EZ Liver project and involved 300,000 high-risk patients; it is the starting point for Thailand to be able to run a mass surveillance program. **What will it take to cross the chasm to adopt this nationally?**

“Access to tests, reimbursement and awareness are key areas to consider for a broader adoption.” – Prof. Dr. Yeong Yeh Lee, Consultant Hepatologist



Image by @angellodeco

Theme 7: Unaffordable HCC treatments are still the reality for most.

We have talked a lot about the desire for early detection, although currently, patients invariably present late. This means the outstanding unmet need is for targeted therapies which offer superior treatment for late-stage HCC. The reality, however, is patients are left with conventional chemotherapy due to the cost. A Malaysian oncologist told us they tell patients that they can try for a special application to get a treatment reimbursed, but they should come up with enough money themselves to cover any shortfall. Sometimes these special fundings only cover patients for a limited time, like a month, after which funding is stopped and patients may not be able to afford to continue if they require more cycles of treatment.

The outstanding unmet need is for targeted therapies.

“At the end most of the patient—chemo, then progressed—chemo again, progressed—chemo again. This is our treatment.” – Oncologist, Malaysia

“Up until advanced stage there is no issue with reimbursement, however, targeted therapy is not reimbursed, thus chemo is used instead even though it is less efficacious.” – Hepatologist, Thailand

“Doctors often recommend the best course of treatment given the patient’s budget.” – Hepatologist, Thailand

Patient story – I had to stop taking lifesaving medications because of the cost



Image by @airdone

Alya is a 47-year-old patient with Stage 2 HCC. She has a 3-year-old and a 17-year-old but had to stop treatment because of the cost. She wishes that medicines were not made too expensive. One medication is 50,000 IDR (3.35 USD) per pill, another 400,000 IDR (27 USD) per pill, and a combo medicine with 3 drugs in it was 1.8 million IDR (121 USD). Because of the prices, she doesn’t take them. - Patient, HCC, Indonesia

Upstream, patients often need to pay (at least in part) for their own screening and surveillance. In Thailand, until they receive a diagnosis, many tests are not covered. This is nonsensical with the goal of early detection. Incentives need to be reviewed across the board. For example, in South Korea the reimbursement process takes an extremely long time, often years. An HCP mentioned the National Health Insurance Service (NHIS) communicated a reimbursement cut from 5 years ago to them, but he couldn’t recall the decisions made since it was so long ago, so he couldn’t object. They called it “overtreatment”, which is when a treatment decision or

requested tests don't seem necessary according to guidelines resulting in denied reimbursement. This leaves the bill for providers, hospitals, or clinics. Disincentives like this must be addressed. MDTs also face financial challenges—a policy maker commented “The upcoming trend of MDT is good in terms of providing better clinical care to patients, but this is not something that hospitals can make a profit from”.

Funding requires epidemiological data

Costs need to be reduced for patients at high-risk, but epidemiological data is missing to identify them. PCPs struggle to manage their populations without integrated and comprehensive electronic health record databases. This creates a vicious cycle of insufficient and inaccurate epidemiological data to support funding and prioritize action. In New Zealand, incidence of HCC is thought to be around 20% higher than what is recorded, this was a shared issue across the countries. Funding is not only insufficient for diagnostics and medicines, but also resources. A policy maker in Indonesia mentioned funds could not be allocated to improve resourcing in rural areas because it was not clear where the gaps in care were occurring across the country; they needed to know how many specialists were available compared to what the demand was.

Costs need to be reduced for patients at high-risk, but epidemiological data is missing to identify them.



Image by @AzmanL

Spotlight: Malaysia—collecting data to build the national registry

In Malaysia, data from pathologists is particularly good, but usually only from patients who have undergone resection. What's difficult in collecting data from specialists is when staff go on rotation. To make it easier, a simple template was developed to capture the data which is now used in 3 hospitals. This template includes noting etiology which wasn't captured before and has been introduced to the National Cancer Registry; it is thought that this will take time to be adopted due to the format change, but is a necessary start.

In addition, the National Cancer Society in Malaysia is rolling out a cancer preventative registry, which is an open access electronic platform where patients can access their individual health records and screening tests. This allows patients to keep their own data and share it with institutions if they choose to. The government will have access to the data as the MOH is a project partner. Currently, Malaysia only has a disease registry, so this screening data is important. The database will help produce better insights into prevalence from fatty liver disease as well.

Theme 8: Navigating the healthcare system is confusing for patients.

As we have seen, the end-to-end journey for a patient navigating liver disease involves interactions with multiple parts of the healthcare system. As the disease progresses, treatments change, doctors change, patient living conditions and situations change, and their stage of life changes. Arriving at a diagnosis was a convoluted process for many patients often involving trips between their PCP and a range of specialists and departments for tests. The disease continuum also encompasses a variety of terms like hepatitis, fatty liver disease, cirrhosis, and the multiple stages of HCC, all of which can become confusing for patients who sometimes don't realize that one can lead to the next. A large problem with liver disease is to keep patients engaged; complicated systems don't help. Patient navigation is needed.

As disease progresses, treatments change, doctors change, patient living conditions and situations change, and their stage of life changes.

Referrals and reimbursements were frequently mentioned as areas of confusion that consequentially led to patients dropping out, delays, and paying out-of-pocket because they just couldn't figure it out. In extreme but not uncommon cases, patients had to refuse tests or treatments because of the cost. An example of complicated reimbursement can be taken from Indonesia. Their national insurance payer policy specifies the use of cheaper, less specific tests first, and a cap on reimbursement per visit. For patients without private insurance, this policy can add months to their diagnosis, compared to private care which can be achieved in a week.

“So, it is like step, by step, by step, to do the test. Because every time the patient comes to the outpatient department, they [Badan Penyelenggara Jaminan Sosial Kesehatan (BPJS), Indonesia's social security agency] only pay a certain amount of funds, let's say, we'll just say it is \$10. They don't care if the \$10 is enough for treatment, for the doctor, for the lab examination. So, if you want to do all the examinations at once, you can do it, but they only pay you the same amount.” – Pathologist, Indonesia

Patient story—Did the tumor grow during the reimbursement process?



Image by @ryanking999

Sunti is 65 years old, a retired schoolteacher, he likes to garden and walk his dog alongside the river in East Thailand where he lives. He had a blood test during his annual check and found it to be abnormal, so the doctor sent him for an ultrasound at the small hospital 2-3 weeks after detecting the abnormal results. A suspicious 1cm lump was found and Sunti was sent for a CT scan to confirm the diagnosis.

Luckily, the provincial hospital not too far from where Sunti lives has a CT scanner, however, since Sunti is now retired, he went through the proper registration with the hospital to make sure he wouldn't need to pay out of pocket. That took almost 6 weeks. By the time he could register for a slot with the CT, he was told he had to wait 2 months.

2 months later Sunti completed his scan and he met with a surgeon, "we found a 2cm lump, it's too big, you're not eligible for resection." The entire process took him 4 months, Sunti wonders if his tumor potentially grew from 1cm to 2cm during the wait. – Patient, HCC, Thailand

Patient navigator programs

HCPs mentioned the need for patient navigator programs in this demotivating and uncertain journey. Patient engagement strategies will need tailoring though, especially considering who the messaging comes from. In New Zealand, there is a wide distrust in the government's healthcare system by indigenous Māori who form part of the high-risk population. It was recommended to tackle awareness from within the Māori community itself. In Singapore, there was thinking that "community care is inferior" so messaging from specialists would likely hold more weight. In Indonesia, patients tend to have higher trust in their PCPs and happily take their advice. In Malaysia, patients often "shopped around for care" and got second opinions. In South Korea, patients often want to go under the radar. And in Thailand the Subdistrict Administrative Organization (SAO) was identified as a logical communication avenue since they were thought to "have close relations to locals within their areas".

Better movement through the healthcare system involves synchrony across different care providers. In the example below, we see how KOL Prof. Dr. Irsan Hasan in Indonesia is working to unify all health services, including insurance, to deliver a more seamless patient experience.

APAC in Action: Indonesia—Expanding surveillance guidelines for all health services including insurance providers

Prof. Dr. Irsan Hasan, Consultant Hepatologist, Cipto Mangunkusumo, Jakarta

Liver cancer is the 4th top cancer for males in Indonesia with more than 20,000 cases a year, with many more believed to be undiagnosed. Most cases are picked up late stage like most other countries, resulting in the survival rates being exceptionally low, usually not more than 158 days. Alarmingly, in the 15 years between 1998 to 2013 there have been no improvements. Part of the cause for the low survival is poor surveillance coupled with a lack of funding for systemic therapy.

Prof. Dr. Irsan Hasan and his team at Cipto Mangunkusumo Hospital led the progress to publish national guidelines for HCC treatment in 2017, and national guidelines for systemic therapy in 2021. These guidelines, however, only applied to hepatologists. To address the wider ecosystem influencers, they pushed the MOH to build national guidelines for all health services. This expanded reach to all physicians, insurance bodies, and all healthcare centers.

Following Japan who has some of the best HCC survival rates in APAC due to their good surveillance, they also put PIVKA-II into their guidelines. While there is still a lot of work to be done with primary care and insurance, this is Indonesia's first step towards national surveillance. Recognizing that all the actors in the system are needed to create a seamless patient experience, too often only HCPs are targeted in these interventions. **How might we achieve better consistency of clinical guideline implementation?**

"Indonesia's challenge is inconsistent implementation of guidelines, improving this is not just on HCPs, it requires the support from every person involved in delivering this healthcare service." – Prof. Dr. Irsan Hasan, Consultant Hepatologist

Theme 9: Consider human life when designing interventions.

From patient navigation to public awareness, we are designing in the context of human life which doesn't just revolve around healthcare. Equity does not only mean making things accessible, but also acceptable. Different countries and people have cultures and ways of living that need to be acknowledged. It is one thing to tell patients to change their diet, but when this is intertwined with social belonging, or lifelong habits, it is not so easy. We need to see human barriers and design appropriate solutions. We need to acknowledge that people define quality of life as a life free from frequent hospital visits. One oncologist from East Malaysia mentioned many of their patients refused treatments because they would rather live a shorter life than to be burdened and entangled with medications, treatments, and checkups. We need to support human life, not just patient life—there is a gap.

We need to support human life, not just patient life—there is a gap.

Closing the care gap involves action across the full journey, and surrounding moments. A solution needs to consider work, kids, transport, confidence, family, self-esteem and more. Given the chronic nature of liver disease, we need to remember that patients will be at various stages in their journey—some coming out of a fresh diagnosis, to those who have been regularly going back for tests wondering if the hassle is even worth it.

Uncertainty drives people to the ER

Not knowing what to expect creates anxiety. Patients often wondered 'is this normal?'. This has knock-on effects to the healthcare system when patients turn up to ER for symptoms they have questions or concerns about. Much strain on secondary care can be avoided by simply communicating better with patients.

People need support in changing lifestyle habits

Lifestyle changes are the only interventions for fatty liver disease and preventing cirrhosis. It is critical to begin as early as possible because reversal becomes more difficult after the liver becomes cirrhotic. Diet and exercise are critical, but without a roadmap and support, patients are unable to do so successfully. Physicians set weight loss goals for NAFLD/NASH patients without guidance, leaving patients to wonder 'how do I implement this?'. It's not that people don't know they need to lose weight; it's that whatever efforts they are doing don't seem to be enough.

“Fatty liver is the only reversible etiology. There's a fool proof way to reverse it, but patients can't do it.”
– Oncologist, Singapore

It's not that people don't know they need to lose weight; it's that whatever efforts they are doing don't seem to be enough.

A disease doesn't just impact patients, it impacts families

There were two main groups of patients we spoke to: those in their 40's with young children, the other in their 50's and 60's with adult children as their caregivers. Many also said they were not able to work anymore due to fatigue which creates single income families; more males develop HCC than females as well. The toll on the family only escalates at the end-of-life.

Palliative care for HCC patients is not good, neither through primary care nor palliative services. Patient symptoms are not well understood by HCPs or patients and their families. For example, hepatic encephalopathy specifically can't be reversed with laxatives like other encephalopathy. Patients don't realize

how confused they are and sometimes act out in aggression; families struggle and are unaware of what's going on. When we design solutions, we need to design for multiple actors in the system, families especially.

Shame and stigma can prevent patients from getting treatment

There is stigma that liver disease is caused by drinking. This impacts some cultures more than others. In Indonesia where the drinking culture is low and people tend to catch acute viral hepatitis A and E from contaminated foods, stigma is less of an issue; it was more evident in New Zealand and South Korea where the drinking culture was problematic. Chronic viral hepatitis B and C which is spread by blood, or body fluids led to additional shame and stigma, but more so in communities where drug needle sharing or unprotected sexual contact was a suspected cause, opposed to maternal transmission.



Image by @BrianScantlebury

In New Zealand we heard a story where two sisters were seeing the same nurse for hepatitis treatment without each other knowing. In South Korea, we heard experiences where patients felt isolated due to self-blame and stigma and didn't want their disease to be known to others or "go viral". Mental health and social isolation are often forgotten when thinking about liver disease care, although this is a vital component of how the disease impacts people.

Other times, the shame of alcoholic relapse was enough to make patients feel embarrassed enough to not go back to their doctors for treatments or check-ups.

"...one thing I always encourage them to do is, whichever part of their journey with alcohol they're in, please still come back and see me. If you have gone back to drinking. That's part of the disease, it is the way it is." – Hepatologist, New Zealand

Tailor interventions for the behaviors seen locally

There are universal human needs such as certainty, belonging, and financial security. Other human needs are heavily influenced by culture. Awareness of societal influence is needed. Remember, the goal is to improve holistic wellbeing and be mindful that liver cancer outcomes are driven by determinants that are not always obvious.

Conclusion

The etiology of liver cancer is steadily yet silently changing, and our protocols are out of date. A new approach is needed. The ecosystem perspective provides an awareness of logical places to intervene. We have pinpointed breakpoints, connections, drivers, and influencers. Key areas that can benefit from immediate action include empowering and supporting primary care to play a more active role in early detection, improving patient navigation, addressing the unmet need of lifestyle behavior change, funding treatments for the existing late presenters, and addressing the ultrasound bottleneck.

The significance and centrality of the radiology issue justifies investigation to use biomarkers such as PIVKA-II to compliment AFP for HCC surveillance. This can improve sensitivity and specificity and presents promising improvements to access. Better accuracy in diagnostics will help the task of stratification. Fine tuning risk algorithms help adjust the frequency at which patients are surveilled reducing undue burden from over-testing and preventing high-risk cases from progressing between appointments.

The moments between appointments remind us that intervention design goes well beyond a test or treatment. An immersion into the human-centric perspective of the liver disease journey revealed to us how people make decisions. The key insight was how people struggle to fathom 'risk'. Additionally, that risk behavior is relative to perceived benefit. Currently, the burden of going for testing, including logistics and costs are unattractive for an array of reasons we have presented. If we can improve the patient experience of screening and surveillance by creating a path of less resistance, we can start to tip the cost-benefit analysis that goes on in their heads and improve early detection. We are encouraged to see KOLs in APAC already taking action.

We encourage each country to consider how culture and healthcare systems influence how patients navigate chronic uncertainty in local settings. Such nuances help tailor interventions like surveillance program pilots. After breaking down the complexity of the problem, we can see opportunities which render an optimistic future for liver care. Technology and medical advances available to us today can tackle inequities and access issues in substantial ways. Together we can truly shift the story from palliative care to cure.

Recommendations—immediate actions to improve the state of liver care

The challenges mentioned in this paper will not resolve themselves. Without proactive and united action, the mortality trend will worsen. Below are our recommendations for practical starting points.

Recommendations towards the goal of early detection	
Actor(s)	Recommendation
Patient Advocacy Groups (PAGs) and HCPs	<p>Advocate for national screening and surveillance programs for early detection of HCC risk factors.</p> <ul style="list-style-type: none"> To detect hepatitis B: a national screening program amongst those born before neonatal hepatitis B vaccination programs To detect NAFLD: routine screening for NAFLD amongst those with Type 2 diabetes To detect early HCC: a surveillance program based on HCC risk stratification in existing liver disease patients
HCPs	Consider the use of hepatitis B surface antigen (HBsAg) tests as a first pass screening tool.
	Collaborate with PAGs to help educate patients about their disease, possible side effects, and risk factors.
	Consider digital technology to improve communication, access, and the ability to scale efforts nationally.
Specialists	Take part in education to empower PCPs to identify risk factors.
	Support MDTs and open access to PCPs.
	Initiate the simplification and clarification of referral pathways.
Primary Care Providers (PCPs)	Check, and where necessary clarify, the understanding of your patients about their perceived risk.
Private Insurers	Raise awareness in at-risk populations of their eligibility of liver function tests.

Table 3: Recommendations – early detection

Recommendations towards the goal of more effective stratification of public and patient risk	
Actor(s)	Recommendation
Policy Makers	Update clinical guidelines to reflect the change in etiology ensuring cases from fatty liver disease are not being missed. Leverage existing touchpoints with metabolic patients to combine appointments and tests with liver function tests.
HCPs	Stratify your high-risk populations according to the latest etiology and update protocols for surveillance frequency accordingly.
Specialists	Investigate the use of alternative diagnostics to achieve better sensitivity and specificity to segment your population. Kick-start a pilot; they are easy to stop when they do not work compared to removing a treatment that has been funded.
PCPs	Learn about the latest risk factors affecting your population and conduct opportunistic screening. Collaborate within your clinic to agree responsibilities for educating patients.

Table 4: Recommendations – risk stratification

Conclusion

Recommendations towards the goal of improved patient care:	
Actor(s)	Recommendation
PAGs	Initiate education and patient navigation efforts in collaboration with HCPs and government.
HCPs	Remember patients will be at different life stages, don't assume the length of time they have had the disease correlates with their understanding. Ask what they understand to be happening to them and what their concerns are as a starting point to steer the conversation more efficiently; involve their caregivers as well.
	Advocate for support to make lifestyle support available to patients. Consider digital therapeutics when prescribing.
Collaborate	Agree on a fair model for shared care between primary and secondary care, and public and private care.

Table 5: Recommendations – patient care

Recommendations towards improving patient access to care:	
Actor(s)	Recommendation
HCPs	Support efforts to collect better epidemiological data for payers by recording your patient cases with details of etiology into digital national databases.
Payers	Review reimbursement policy to ensure high-risk populations and patients are not disincentivized to go for tests or treatments; nor that policy delays diagnosis for these groups.
	Note up- and down-stream interventions that can support and maximize outcomes of already funded programs.
Collaborate	Discuss as a wider group, how to combat physical access barriers to care. Consider technology, novel diagnostics, and partnerships that leverage the resources of the country. Ensure incentives are acceptable for a sustainable approach.

Table 6: Recommendations – patient access

Considerations for an ecosystem and human-centric approach

Remember the chronic journey of liver disease through to liver cancer is an ecosystem problem heavily influenced by nuanced human behavior. To channel efforts strategically, we recommend considering the following:

- **Breakpoints:** Consider the most critical breaks in your system. For example, tackling viral hepatitis or improving HCC surveillance.
- **Key influencers:** Look upstream and downstream for opportunities to support initiatives. For example, how to increase the number of patients that will go through a new screening program.
- **Opportunities and threats:** Look for macro dynamics that may provide threats or opportunities for a given intervention. For example, healthcare system structures that may beneficially support the opportunity for public-private-partnerships to combat access issues.
- **Human centricity:** Remember people at the heart of any intervention design. For example, HCP constraints, patient motivation, caregiver fears, peer pressure, and other actors or factors in the system that influence behaviors.

The strategy to tackle ecosystem challenges is not to wait for a perfect solution, but to take small actions, then iterate. In all this, we are guided by the people we are designing for.

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Figure 2: Example of types of actors and connections within the liver care ecosystem by author

Figure 3: Example of up-stream and down-stream considerations surrounding an intervention by author

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Figure 4: Model of Integration Liver Clinic System by Roche Liver Ecosystem Advancement Program core team Thailand

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Participants

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Roche Project Team

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Veranex Research and Strategy Team

This research was commissioned by Roche, conducted by Veranex. Veranex combines design, engineering, quality, clinical, regulatory, and commercialization expertise to drive concepts to commercialization. Their research team specialize in uncovering human-centered insights that fuel meaningful innovation and tangible improvements to patient care.

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