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Luminary Learnings

Gastrointestinal Disorders

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Definition and changes in nomenclature of hepatic encephalopathy

Chathur Acharya, Jasmohan S. Bajaj

Definition

The definition of hepatic encephalopathy (HE) according to the AASLD/EASL guidelines is "Brain dysfunction caused by liver insufficiency and/or PSS; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma" [1]. Hence, by definition the presence of a portosystemic shunt or end-stage liver disease is not necessary. This is further explained in the nomenclature of HE.

The International Society for Hepatic Encephalopathy and Nitrogen Metabolism (ISHEN) concurred with this definition in the last meeting in 2017 and no changes were advocated to it.

Current issues with nomenclature of HE

Broadly, HE is broken down into overt HE (OHE) which is Grade 2 and above on the West Haven scale/criteria (WHC) [2] and covert HE (CHE) per the ISHEN classification [3]. Table 1 explains the overlap in more details.

From a clinician's perspective the difference between minimal and Grade 1 HE is elusive often due to subjectivity. However, Grade 1 HE or CHE is easily differentiated from OHE by the presence of asterixis and hence the classification holds value. Grade 1 HE, given its subtle nature, can be differentiated from MHE with the help of the patient's caregivers and if the clinician has a long-standing relationship with the patient. MHE by definition has no clinical manifestation, just psychometric and neurophysiological abnormalities on specialized testing. From a clinical perspective MHE has a varied clinical course from Grade 1 OHE [4] so there is an ongoing debate as to whether the term CHE should be done away with and the old classification be adopted again.

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Table 1: Nomenclature guide for HE components for incorporation.

Based on underlying disease	Based on WHC severity scale	Based on ISHEN	Based on time course	Based on precipitating factors
A	MHE			
B	Grade 1	Covert	Episodic	Spontaneous
C	Grade 2			
	Grade 3	Overt	Recurrent	Precipitated
	Grade 4		Persistent	

From a researcher's standpoint clubbing Grade 1 HE and MHE for study purposes allows more study recruitment and helps to easily create groups.

This was formally tested using standardized simulated patient videos across seven centers across North America for both trainees and independent practitioners. There was a significant concordance for grades 2–4 (>90%), which dropped to <60% for patients who were normal or had Grade 1 HE. This justifies the need for a covert HE diagnosis until better user-friendly techniques are developed to diagnose Grade 1 HE [5].

Classification

The current approach to the nomenclature of HE relies on four main axes. This concept was first introduced in the world gastroenterology congress in 1998 [6] and has been followed since after minor changes by ISHEN in 2011 and formally being introduced in the last HE guidelines. The consensus is that this approach encompasses all the elements relevant to HE and can aid in appropriate treatment, continuity of care, and uniformity in research models if followed universally. Each axis in itself is a subtopic and hence taken as a whole the methodology provides all the pertinent information. Table 1 lists the nomenclature guide.

The four axes are as follows:

1. Underlying disease:

   As mentioned in the definition, the presence of HE does not require the presence of a portosystemic or chronic liver disease for that matter and this is reflected in this axis. Based on the underlying pathology there are three types of HE:

   a) Type A resultant of (A)cute liver failure
   b) Type B resultant of portosystemic (B)ypass/shunting from other non-liver-related pathology
   c) Type C resultant of (C)irrhosis

   Based on these subtypes we can see that Type C is the most common form that one will clinically encounter. Phenotypically Type C will have stigmata of cirrhosis as HE manifests on decompensation but the HE manifestations will be similar to Type B. Type A which has a separate pathophysiology due to acuity of disease process clinically appears different and has a different approach to management. Knowledge of etiology guides management.

Table 2: West Haven criteria as proposed by Conn *et al*. with comparison to ISHEN grading.

Grade of HE on WHC	Clinical manifestation	ISHEN Grade
Minimal	No clinical features	Covert hepatic encephalopathy
Grade 1	Trivial lack of awareness-Euphoria or anxiety Shortened attention span-Impairment of addition or subtraction Altered sleep rhythm	
Grade 2	Lethargy or apathy-Disorientation for time-Obvious personality change Inappropriate behavior-Dyspraxia **Asterixis**	Overt hepatic encephalopathy
Grade 3	Somnolence to semistupor Responsive to stimuli-Confused Gross disorientation Bizarre behavior	
Grade 4	Coma	

2. Severity of manifestation:
   This axis is the most contentious part of the classification. This is as per the current grading of severity scale (WHC), though universally accepted as a standard, not thought to be objective and is arguably more subjective. Table 2 describes this scale in detail. The second point of contention is the nomenclature of that of CHE as mentioned above. Again, though currently accepted as standard there is an ongoing debate as to the usefulness of this classification, i.e. creating an extra category of CHE and reverting to a more basic classification of minimal HE and OHE only. However, the concept of CHE was introduced to aid in attaining a more universal platform for enrolling for International clinical trials given the subjective nature of the WHC to begin with and further discussion will be done before the next consensus guidelines.

   Knowledge of the severity changes our approach of medication administration and also dose of the drug. The grade also determines the location of management and can prognosticate the course [7].
3. Time course of manifestations:
   The timing of HE adds to the appropriate classification as certain etiologies for precipitation are more associated with recurrent HE and some more so for episodic HE [1]. Since, these different timelines refer to obvious (overt) manifestations it is not applicable to the nomenclature of CHE. Having this information, i.e. non-HE time between episodes, helps the provider plan on long-term management strategies to alleviate the precipitating factor. Knowledge of time course also helps aid in treatment options (when to add rifaximin) and also need to recruit for HE clinical trials (if patient can be tried on second-line medications, etc.). Figure 1 explains the time course of OHE.
4. Existence of precipitating factors:
   There is an urgent need to look for precipitating events for OHE as correction of the underlying precipitator will help in earlier resolution of the episode. Apart from instituting

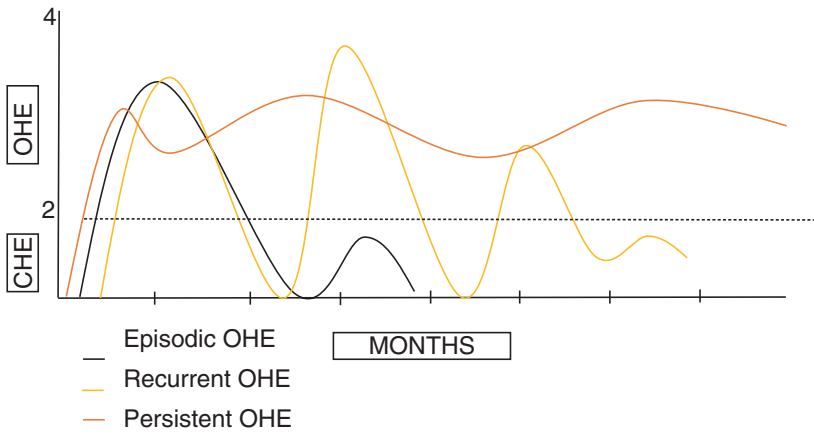


Fig. 1: Description of subtypes of OHE based on time course.

standard-of-care therapy for management of HE, correcting of underlying metabolic abnormalities, infections, etc. which are common precipitating factors helps. Sometimes despite extensive evaluation a precipitating factor is not found and then the episode is labeled as spontaneous.

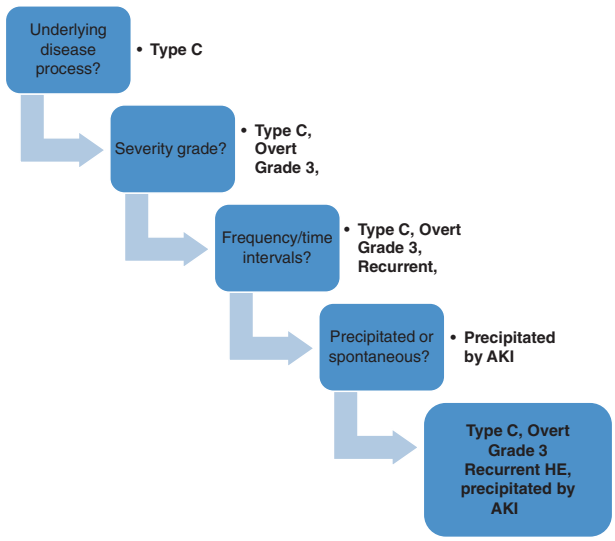
The importance of combining all these axes into a unified description of HE is imperative for continued care of patients and also for the current provider to recognize precipitants that can be remedied to prevent the long-term consequences of HE. Knowing a patient's entire HE-related course/information lends for a strong foundation for being proactive in care.

To help the reader put this nomenclature to practice and to emphasize the importance we will provide a variety of examples.

Case 1

A 60-year-old female with hepatitis C-related cirrhosis is admitted to your hospital for the third time in a 5-month period with an episode of acute confusions diagnosed as HE. On examination the patient is noncoherent, lethargic, and disoriented to time and place, and has no focal neurological deficits but does have asterixis. No ascites or edema was noted on exam and this was confirmed on radiological studies of the abdomen. Lab work including drug screen was only notable for an acute kidney injury and elevated ammonia levels. Previous admission urinalysis was significant for UTI. She is already on lactulose and rifaximin and takes step 1 diuretics. Per caregivers she has been complaining with three to four bowel movements a day. She was continued on home meds and given IV fluids and was discharged home with changes to her diuretic regimen.

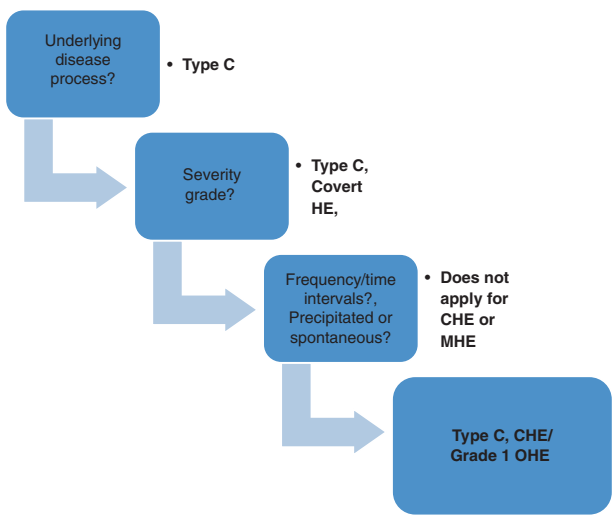
Based on the current recommendations let us examine the diagnosis.



Case 2

A 46-year-old man with chronic alcoholic cirrhosis with abstinence from alcohol for the past 2 years is seen in your clinic for complaints of episodes of confusion. The patient's daughter who is accompanying the patient states that "Dad has been acting weird" for the last couple of weeks. The patient does say that he did get a little confused while driving to the store a week back. On examination, there is no ascites or asterixis and the patient is oriented to time, place, and person. Investigation does not reveal any signs of infection and all laboratory workup including a drug screen is within normal limits. The patient is evaluated by the hospital's hepatic encephalopathy research team and is found to be impaired on psychometric and neurophysiological testings.

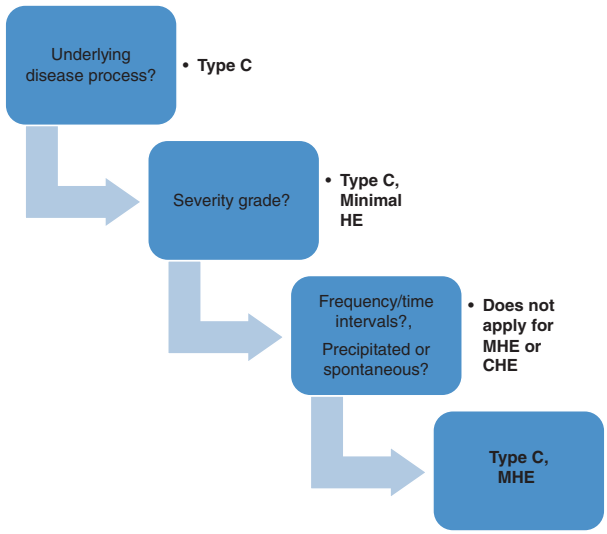
Based on the current recommendations let us examine the diagnosis.



Case 3

A 48-year-old woman with obesity and nonalcoholic steatohepatitis, with a new fibroscan diagnosis of cirrhosis, presents to your clinic for discussion of the plan of care. Review of lab work does show some hepatitis. She is employed as a ride-sharing taxi driver. On examination, there is no asterixis and she is oriented to time, place, and person. She says that she has been feeling well and does not really have any complaints. Given her job and potential for neurocognitive impairment she was referred to the hepatic encephalopathy research group for neurocognitive and psychometric testing. Results were abnormal and she was advised to start an empiric trial of lactulose.

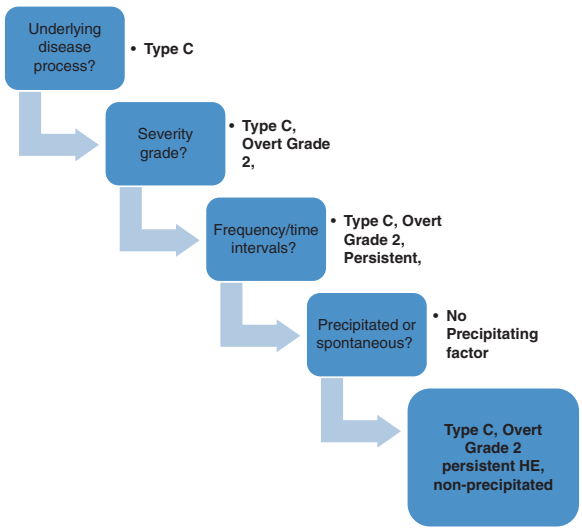
Based on the current recommendations let us examine the diagnosis.



Case 4

A 58-year-old female with primary biliary cirrhosis awaiting transplant presents to your hospital's emergency room for acute confusion. Her course of recent events has been complicated by refractory ascites requiring serial large-volume paracentesis and multiple episodes of encephalopathy requiring admission. Despite optimal therapy with lactulose and rifaximin for 7 months, step 3 diuretics, she has not improved much. On presentation she feels she is at her baseline. She appears to be slow, is oriented to place, and on exam has obvious jaundice, asterixis, ascites, and edema. Her partner and caregiver report that she is taking all her medications as prescribed but still has been confused for the most part over the last 6–7 months. Labs including comprehensive metabolic panel, urinalysis, and toxicology screen are all within normal. Patient is admitted for management of ascites and for hepatic encephalopathy.

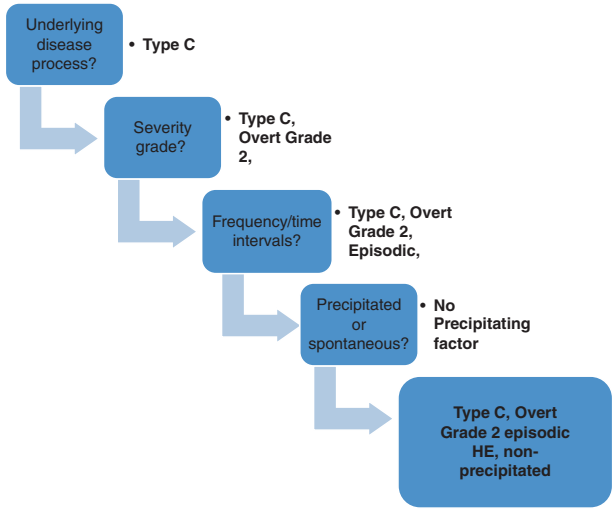
Based on the current recommendations let us examine the diagnosis.



Case 5

A 38-year-old female with alcoholic cirrhosis, now abstinent for 11 months, presents to your emergency room for confusion. She appears to be hemodynamically stable and laboratory work per ER is essentially normal except for mild elevation in her liver functions and for ammonia being elevated. She is oriented to place but appears drowsy while conversing. Examination is unremarkable except for asterixis. You order a drug screen which is negative. Urinalysis and chest X-ray are negative. You admit the patient for management of HE and start her on lactulose orally.

Based on the current recommendations let us examine the diagnosis.



Conclusion

The definition of HE has reached a consensus and one might not see much change there over the next decade. The nomenclature of HE, on the other hand, is more complex and has many aspects that need more research and debate on. The broad components may not see much change but as our data and research progress the subcategories may evolve. As we stand, the four axes for categorizing the HE provide the appropriate information to understand the current episode and help device strategies for treatment and prevention. The main goal to help improve the quality of care for this very sick population is well met with the current system of nomenclature but further research in this field will help us refine this further.

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2

Nutrition in patients with diseases of the liver and pancreas

Roman E. Perri

Key points

- Malnutrition is common in patients with cirrhosis. The assessment of this can be challenging but recognition and prompt treatment are essential to improving patient prognosis.
- Dietary protein intake of 1.2–1.5 g/kg/day is recommended for patients with advanced liver disease. Protein restriction should be avoided in cirrhotic patients, even those with hepatic encephalopathy.
- Severe acute pancreatitis can result in significant malnutrition and high rates of mortality. Nutritional support through enteral nutrition is the preferred method of maintaining adequate nutrition.
- Supplemental pancreatic enzymes are of central importance in managing the exocrine insufficiency associated with chronic pancreatitis.

Keywords: Protein-calorie malnutrition, Hepatic encephalopathy, Ascites, Pancreatic exocrine function, Steatorrhea

Patients with liver disease

The end-stage liver disease of cirrhosis is a serious medical condition with high rates of mortality. The average life expectancy of a patient when diagnosed with cirrhosis is 10 years. Complications of liver disease including ascites, hepatic encephalopathy, or gastroesophageal variceal hemorrhage portend a grim prognosis with a 2-year mortality rate of 50% without liver transplantation [1]. These complications herald the onset of significant portal venous hypertension, where the degree of fibrosis within the cirrhotic liver significantly disrupts blood flow through the

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splanchnic vasculature. There were 36,400 deaths due to cirrhosis and chronic liver disease in the United States in 2013, with a mortality rate of 11.5 per 100,000 population [2].

Malnutrition is commonly seen in patients with cirrhosis. The appropriate medical management of patients with cirrhosis must therefore include a focus on nutritional aspects of this disease. The liver's role in metabolic homeostasis has long been recognized and with significant compromise of the liver's function, derangements of metabolism will result. In fact, the prevalence of protein-calorie malnutrition (PCM) has been recognized in up to 90% of patients with cirrhosis [3]. Typically, patients with alcoholic liver disease exhibit the most severe degrees of PCM but other causes of liver disease, including cholestatic liver disease and viral liver disease (i.e., hepatitis) are also complicated by significant rates of PCM. The presence of malnutrition in patients with cirrhosis has been recognized to be a predictor of mortality [4, 5]. The recognition of malnutrition in the patient with cirrhosis, with both an assessment of degrees of malnutrition and interventions designed to lessen its severity, are therefore of paramount importance.

The causes of malnutrition in patients with cirrhosis are multifactorial and include poor appetite, early satiety, nausea, and alterations of metabolism. In addition, cholestasis and small intestinal bacterial overgrowth can result in malabsorption of ingested nutrients [3]. The assessment of nutritional risk must therefore take these factors into account.

The clinical appraisal of malnutrition in the setting of cirrhosis can be difficult. A clinical history can disclose important information about dietary intake although in patients with even preclinical encephalopathy, patient recall may be inaccurate. A physical examination plays an important role in the assessment of malnutrition in the cirrhotic patient although these assessments can also be challenging. Measurements such as body mass index or waist circumference can be skewed due to the presence of ascites and edema. Fluid retention can obscure the loss of adipose tissue in the viscera as well as extremities. Nonetheless, a physical examination can disclose the presence of temporal muscle wasting as well as loss of proximal musculature in the arms and legs; areas that may be less susceptible to fluid retention. Indeed, subjective descriptions of proximal muscle weakness are common in patients with cirrhosis, and body protein stores have been noted to be significantly decreased in patients with cirrhosis [6].

Biochemical evidence of malnutrition by measurements of proteins such as albumin and transthyretin (prealbumin) are imperfect measurements of nutritional status as these levels are affected by the presence of inflammation. Nonetheless, serum levels of albumin have been shown to predict survival in patients with decompensated cirrhosis as a component of the Child-Turcotte-Pugh score [1]. Due to the limitations of individual markers of nutritional status, it is imperative to utilize multiple clinical tools including clinical history, physical examination, and laboratory assessments to gain as thorough an understanding as possible regarding the presence of malnutrition in the cirrhotic patient.

Nutritional support in cirrhotic patients requires that attention be paid to multiple considerations. Recommendations regarding dietary intakes in these patients should consider dry weight of the patient, discounting ascites and edema; an assessment that can be challenging in the setting of significant fluid retention. The total calorie needs of patients should be assessed; it is recommended that an intake of 25–35 kcal/kg/day should be administered to patients with

well-compensated cirrhosis. Those patients with more severe illness, including decompensated liver disease and hospitalization, require higher daily caloric intake of up to 30–40 kcal/kg/day in order to combat the development of a catabolic state [7]. Protein intake is of paramount importance in the cirrhotic patient. Prior recommendations that patients with decompensated liver disease should restrict dietary protein intake in order to prevent complications of hepatic encephalopathy have not been supported by clinical studies, and have had the effect of exacerbating malnutrition in cirrhotic patients. Dietary protein intake for patients with cirrhosis should be in the range of 1.2–1.5 g/kg/day to minimize the muscle breakdown that is common in patients with decompensated liver disease [8]. Even in patients who are hospitalized with hepatic encephalopathy, immediate protein restriction has not been found to be clinically useful; a hospital diet that provides 1.2–1.5 g/kg/day of protein should continue to be administered [9].

In order to maintain an adequate daily calorie and protein intake, as well as to compensate for a poor appetite, early satiety, and hepatic synthetic dysfunction, some modifications to the daily diet often must be considered. Cirrhotic patients should eat more frequent (4–6), smaller meals daily, including a nocturnal snack that is enriched in protein to help maintain the recommended intake of both calories and protein in the setting of their physiological derangements [3].

An alteration of the ratios of aromatic and branched-chain amino acids may play a role in the pathogenesis of hepatic encephalopathy. Dietary supplementation with branched-chain amino acids (BCAA) is well tolerated by cirrhotic patients. BCAAs are a reasonable supplement, in lieu of other protein sources, in the patient with refractory hepatic encephalopathy. Supplementation with BCAAs may offer additional benefits to cirrhotic patients including improved prognosis [10]. The regular administration of these supplements in the form of "hepatic" enteral supplements has not been demonstrated to be beneficial in routine use.

Vitamin needs should be considered in patients with end-stage liver disease. Fat-soluble vitamins are commonly found to be deficient in cirrhotic patients due to both poor oral intake and malabsorption. Vitamin D deficiency should be assessed regularly with measurement of 25-OH vitamin D levels. Supplementation should be provided to prevent the development of osteomalacia. Vitamin A deficiency can lead to night blindness. Vitamin K deficiency can lead to increased risks of bleeding in the setting of a prolonged prothrombin time. Supplementation of these vitamins is commonly required in cirrhotic patients. A lack of improvement of prothrombin time despite the administration of supplemental vitamin K implies that decreased hepatic synthetic function is responsible for the observed coagulopathy. Thiamine deficiency is commonly seen in patients with alcoholic liver disease and can precipitate neurological consequences such as Wernicke's encephalopathy. Prompt administration of supplemental parenteral thiamine should be performed in patients hospitalized with complications of alcoholic liver disease and maintenance with oral thiamine supplements should be provided thereafter.

Overnutrition and obesity have emerged as among the leading causes of liver disease. Nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of insulin resistance. This condition is increasing in prevalence and is the leading cause of cryptogenic cirrhosis [11]. Paradoxically, the presence of protein-calorie malnutrition (PCM) can coexist with cirrhosis due to overnutrition. Clinically useful medications have not yet emerged for NAFLD although clinical

trials are ongoing. At present, the mainstay of therapy for NAFLD is gradual weight loss achieved through lifestyle modification. Various diets, including low-calorie diets as well as ketogenic low-carbohydrate diets, have been studied; an optimal diet for the treatment of NAFLD has not been defined. Some studies have suggested that restriction of simple carbohydrates, or modulating certain types of fatty acids in the diet may have an effect on improving hepatic histology but convincing evidence that would allow firm recommendations continues to be lacking [12].

Ascites is the most common of the major complications of cirrhosis and, as mentioned, heralds a 2-year mortality of 50%. The presence of ascites can result in decreased gastric accommodation and resultant early satiety leading to malnutrition. The etiology of ascites is retention of sodium, not water. The fluid that accumulates in ascites and edema is passively associated with retained sodium. The initial therapy of ascites is to decrease dietary sodium intake thereby inducing a negative sodium balance. This can often be accomplished with sodium restriction to 2000 mg/day, a level of intake that is still consistent with a palatable diet. When dietary interventions fail, diuretic therapy with spironolactone as well as furosemide may be required to increase urinary sodium excretion.

Nutritional support for patients who cannot utilize their intestines, either temporarily due to medical or surgical issues or permanently due to gut failure, is by total parenteral nutrition (TPN). While this intervention has been helpful in the maintenance of the patient's nutrition, well-defined hepatic complications of TPN include the development of cholestasis and even of end-stage liver disease in 15% of those receiving long-term TPN [13]. It is unclear what the best treatment options are for liver disease associated with TPN. Recent studies have focused on the potential use of omega-3 fatty acid infusions during TPN administration although a lack of high-quality data prevent firm recommendations from being made [14].

The utility of herbal supplements in patients with cirrhosis is poorly defined. Milk thistle (silymarin) has been used medicinally for centuries and purportedly has beneficial effects on the liver. Despite the fact that milk thistle has been tested in human trials and the general acceptance of the herb's safety, a clinical benefit for its use of has not been established. In the absence of evidence of utility of other herbal remedies, the use of herbal dietary supplements for the treatment of chronic liver disease is not recommended. The potential hepatoxicity of herbal remedies has been long recognized [15] and without clear evidence of safety, the use of these supplements is not recommended in patients with chronic liver disease.

Patients with pancreatic disease

Acute pancreatitis is characterized by marked abdominal pain with nausea and vomiting and associated elevations of serum levels of amylase and lipase. Abdominal imaging with computed tomography can also be used to secure a diagnosis. Typically, abdominal pain is exacerbated by eating which has been attributed to stimulation of the inflamed pancreas that occurs during the digestion process. Acute pancreatitis is characterized as mild when edema of the pancreas is noted on abdominal imaging. Discontinuation of eating is typically one of the first measures taken in a bout of acute pancreatitis along with administration of intravenous fluids and analgesics. In cases

of mild acute pancreatitis, abdominal pain typically abates over a few days. Upon improvement of pain, oral intake can be resumed. As oral intake is only delayed by a few days, it is not felt that bouts of mild acute pancreatitis pose a significant nutritional risk to patients.

Severe acute pancreatitis is associated with the development of the systemic inflammatory response system that can result in a high risk of morbidity and mortality. Pancreatic necrosis can result from organ failure; resultant infected pancreatic necrosis can entail mortality rates as high as 30% [16]. Mortality rates are high when adequate nutritional support is lacking because of the marked negative nitrogen balance, hypermetabolism, and catabolism that are characteristic of severe acute pancreatitis. The standard management of patients with severe acute pancreatitis was, for many years, to avoid oral intake so as to prevent further stimulation of the inflamed pancreas. When nutritional support was necessary, this was typically provided by TPN. This approach, however, was found to be associated with high rates of infectious complications due to bacterial overgrowth and translocation of bacteria via the intestines [17]. The use of enteral nutritional support has resulted in improved outcomes from severe acute pancreatitis. It is necessary to initiate nutritional support within 48 h of admission for pancreatitis in order to combat the metabolic distress of the condition [16]. Enteral nutrition improves the structural integrity of the intestinal mucosa, preventing bacterial translocation and infectious complications.

Nutritional support is best administered via a nasojejunal feeding tube, which has the advantage of delivering nutrition distal to the pancreas thereby avoiding further stimulation of the pancreas. Interestingly, studies have demonstrated that there is no significant difference in outcomes between nasojejunal and nasogastric feedings [18]. Therefore, enteral nutrition should not be delayed if deep intestinal intubation is not obtained with a feeding tube. There is no convincing evidence that any particular type of enteral tube feeding is superior [19]. There is no evidence that the administration of probiotics yields any improvement in clinical outcomes and clinical trials have actually yielded contradictory data as to whether mortality rates may be affected by the administration of probiotics [19]. Until clear evidence emerges, no recommendations about specific enteral formulations can be made, other than that enteral nutritional support is superior to parenteral nutrition, as well as superior to no nutrition at all.

Chronic pancreatitis is the condition where progressive inflammatory changes in the pancreas result in structural changes of the pancreatic duct as well as fibrosis and calcification of the pancreatic body. Over time, both endocrine and exocrine functions of the pancreas become compromised. The most common cause of chronic pancreatitis is long-standing abuse of alcohol, which may be accompanied by nutritional deficits irrespective of associated pancreatic disease. Chronic pancreatitis is a cause of pain that can lead to anorexia and resultant malnutrition. Maldigestion of food results from deficient pancreatic exocrine function. When the functional mass of the pancreas declines to the point that pancreatic enzymes including lipase and trypsin are reduced to less than 10% of baseline, steatorrhea indicative of poor fat digestion can occur [20].

Maintaining adequate caloric intake is the nutritional goal of patients with chronic pancreatitis but can be limited by chronic pain. Multiple modalities often need to be utilized to treat the chronic pain. There is some evidence that elemental diets, fat avoidance, supplemental pancreatic

enzymes, and lifestyle modification including alcohol avoidance and tobacco cessation may improve symptoms of pain in chronic pancreatitis [21]. In addition to conservative measures to improve the pain, the judicious use of analgesics, as well as surgical and endoscopic therapies may improve pain and anorexia in selected patients [21].

While avoidance of dietary fat will result in improvement of steatorrhea, this intervention can result in an inadequate intake of fat-soluble vitamins. Therefore, the use of supplemental pancreatic enzymes (SPE) along with a normal fat diet is the preferred means of treatment of steatorrhea [22]. The administration of 25,000–75,000 IU of pancreatic lipase ingested concurrently with meals allows for the proper digestion of dietary fat and amelioration of steatorrhea [20]. As the effect is greatest if the enzymes properly mix with ingested food, it is therefore important that the SPE be taken during the meal and not before or after it. SPE should be taken with all ingested foods though the amount taken can be reduced for snacks. Some types of SPE are susceptible to inactivation by gastric acid; medical control of gastric acidity may therefore be required for full effectiveness. Fat-soluble vitamin supplementation (A, D, E, and K) should be offered to all patients with chronic pancreatitis in whom maldigestion or steatorrhea is seen.

In the rare patient in whom weight loss and steatorrhea persist despite the use of SPE, mediumchain triglycerides can be used as a dietary supplement [20]. They are absorbed by the intestine in a lipase-independent manner and can provide adequate fat-derived calories despite the lack of sufficient pancreatic function. The use of TPN is generally not required in patients with chronic pancreatitis though rare indications may be discovered.

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Suggested Further Reading

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3

Oral branch chain amino acids and encephalopathy

Lise Lotte Gluud, Gitte Dam, Niels Kristian Aagaard, Hendrik Vilstrup

Key Points

- Hepatic encephalopathy is a serious complication to severe liver disease.
- Interventions to prevent episodes of hepatic encephalopathy and improve manifestations of the disease are essential considering the high morbidity and mortality.
- Although a number of high-quality randomized controlled trials on BCAA for hepatic encephalopathy are available, none of the individual trials are able to provide definite evidence to support treatment recommendations.
- A Cochrane systematic review on nutritional interventions for patients with liver disease found no definite evidence to support or refute the use of BCAA based on meta-analyses including some of the available trials.
- Meta-analyses of BCAA for hepatic encephalopathy found that enteral administration may be more beneficial than intravenously administered BCAA.
- A systematic review found a clear beneficial effect of oral BCAA on manifestations of chronic recurrent hepatic encephalopathy based on analyses of outcomes recalculated based on individual patient data.
- Oral BCAA should be considered in the treatment of patients with hepatic encephalopathy.
- The role of BCAA in relation to other interventions for hepatic encephalopathy (in particular rifaximin and nonabsorbable disaccharides) should be assessed.

Keywords: Branched chain amino acids, Hepatic encephalopathy, Cirrhosis, Portal-systemic encephalopathy, Systematic reviews, Meta-analysis, Randomized controlled trials

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Abbreviations

BCAA	Branched chain amino acids
CI	Confidence intervals

Introduction

Hepatic encephalopathy is a metabolic neuro-psychiatric syndrome of cerebral dysfunctions due to severe chronic or acute liver disease. The condition can occur in the clinical course of liver failure and is often precipitated by clinical events such as infection, gastrointestinal bleeding, electrolyte derangements, or insertion of a transjugular intrahepatic portal-systemic shunt (TIPS). The manifestations of hepatic encephalopathy range from minor symptoms with personality changes and altered sleep patterns to deep coma. Characteristic signs include shortened attention span and asterixis (flapping tremor). The clinically evident stages of hepatic encephalopathy are classed as overt whereas subtle stages identified through specific tests are classed as minimal [1]. Diagnosing hepatic encephalopathy is paramount because it has deleterious effects on the patient's and the caregivers' lives and is in most cases treatable [2]. Prevention of hepatic encephalopathy as well as correct and early administration of evidence-based interventions is essential.

How the intervention might work

The branched chain amino acids (BCAAs) consist of the three essential amino acids valine, leucine, and isoleucine. Patients with cirrhosis have a low plasma concentration of BCAA so that the ratio between the aromatic amino acids and the BCAA is increased. The *relatively* higher concentration of the aromatic amino acids is reported to lead to cerebral neurotransmitter synthesis disturbances. Therefore, treatment with nutritional supplements containing BCAA was initially developed to normalize the ratio between aromatic amino acids and BCAA in cirrhosis patients with hepatic encephalopathy. The results of subsequent experimental and clinical studies showed that the role of BCAA supplements in cirrhosis was much more complex involving several organs including a beneficial effect on the building of muscles that assist the liver in ammonia removal. Several clinical trials have evaluated the effects of BCAA supplements in patients with cirrhosis and hepatic encephalopathy [3–8]. The results of individual trials vary considerably with the trial setting and design and the patients' inclusion criteria. None of the individual trials were able to provide a definite conclusion regarding the potential effects of BCAA for hepatic encephalopathy. Due to the differences between trials, combined analyses that allow for the differences and adjust for the variation between different trials are necessary to assess the role of BCAA for the treatment of hepatic encephalopathy.

Oral or intravenous BCAA supplements

Branched chain amino acid and other nutritional interventions for patients with liver disease

In a recent comprehensive Cochrane review Koretz and colleagues included randomized clinical trials on any type of nutritional support for any type of liver disease [9]. A meta-analysis from the systematic review included 18 randomized controlled trials on the effect of nutritional therapy versus no nutritional therapy for liver disease in a medical (nonsurgical) setting. The meta-analysis found no effects on mortality (parenteral supplements risk ratio 0.67; 95% CI 0.28–1.62 and enteral supplements risk ratio 0.81; 95% CI 0.50–1.33). Meta-analyses of randomized controlled trials on the effects of nutritional supplements on the prevention of hepatic encephalopathy found no detrimental or beneficial effects when analyzing medical trials or trials on patients undergoing surgery. A subgroup analysis of trials on nutritional supplements containing a high concentration of BCAA found no difference between the intervention and control group regarding the risk of developing hepatic encephalopathy (risk ratio 0.82; 95% CI 0.63–1.09). A fixed effect meta-analysis of six small trials including a total of 119 participants found that nutritional supplements have a beneficial effect on resolution of hepatic encephalopathy (risk ratio 2.10; 95% CI 1.18–3.72). The effect was more pronounced in the two trials on BCAA-enriched nutritional interventions (risk ratio 7.48; 95% CI 1.87– 29.94) than in the remaining trials that evaluated "standard" amino acid nutritional supplements (risk ratio 1.13; 95% CI 0.62–2.07). The subgroup analysis on the effect of BCAA-enriched interventions for the resolution of hepatic encephalopathy included two trials with a total of 33 patients randomized to the BCAA-enriched supplements and 29 patients to the control groups [10, 11]. One of the trials by Calvey and colleagues [11] was published in 1985 and included patients with acute alcoholic hepatitis. The trial compared BCAA versus "conventional" protein supplements administered orally, nasogastrically, or intravenously depending on the severity of the underlying disease. The trial found no differences between the BCAA and control groups regarding mortality, hepatic encephalopathy, or nutritional parameters. The second trial by Hayashi and colleagues [10] was published in 1991 and included 67 patients with cirrhosis who were randomized to a BCAA versus a control diet. The BCAA-enriched supplement and the control supplements were administered orally or via an enteral feeding tube. The trial found a clear beneficial effect of BCAA on improvement of clinically overt hepatic encephalopathy (relative risk 6.40; 95% CI 1.58–26.00). Potential bias was identified in both trials including selection, ascertainment, and attrition bias [9]. Therefore, the result of the meta-analysis based on the two trials may also be biased. Considering the limited number of patients included and limitations related to the trial design and available data, Koretz and colleagues did not find the evidence strong enough to recommend BCAA-enriched supplements or any other type of nutritional intervention for patients with hepatic encephalopathy or for prevention of hepatic encephalopathy [9]. However, it may be argued that the evidence is promising. Furthermore, the Cochrane review only included two of the available trials on BCAA. The exclusion of larger high-quality trials, published after the two trials that were included in the Cochrane Systematic Review, may provide additional

essential information on the influence of oral or intravenous BCAA on manifestations of hepatic encephalopathy. To evaluate the potential effects of BCAA-enriched interventions, separate analyses of intravenous and orally administered supplements are needed to determine the potential beneficial and harmful effect in different settings.

Intravenous BCAA

A number of trials have evaluated the effect of intravenous BCAA supplements [12–15]. Three of the earliest trials were published in 1985 [13–15]. One of the trials was conducted by Fiaccadori and colleagues [14]. The trial included 48 patients with cirrhosis and overt acute or chronic intermittent hepatic encephalopathy. Included patients were randomized to one of two BCAA-enriched solutions that were depleted in aromatic amino acids versus isocaloric glucose. All intervention groups received lactulose. Based on clinical assessments, the number of patients who survived and had complete recovery from hepatic encephalopathy was higher in the BCAA than the control groups (relative risk 1.55; 95% CI 1.06–2.28). Michel and colleagues found less encouraging results in a similar randomized controlled trial comparing BCAA-enriched versus "standard" amino acid infusion for 70 patients with cirrhosis and acute hepatic encephalopathy [13]. The trial found no difference between the allocation groups regarding any of the clinical outcome measures assessed. In particular, the proportion of patients with improved manifestations of hepatic encephalopathy was similar in the BCAA and control group (relative risk 1.13; 95% CI 0.56–2.27). No difference in survival was detected. In the third trial from 1985 [13], Michel and colleagues reached a similar result. The trial included 70 patients with cirrhosis and acute hepatic encephalopathy. Included patients were randomized to 5 days of treatment with a BCAA-enriched solution or an isonitrogenous, isocaloric control. None of the patients received nonabsorbable disaccharides. No differences were seen between the intervention and control group regarding improvement of hepatic encephalopathy manifestations, mortality at the end of follow-up, or mortality 1 month after the end of treatment. Vilstrup and colleagues reached a similar result in a trial from 1990 [12]. The trial compared infusion of a BCAA versus glucose for acute hepatic encephalopathy in patients with cirrhosis. Included patients were randomized to an amino acid mixture (1 g per kg of body weight per day) with 40% BCAA or isocaloric glucose for a maximum of 16 days. Both intervention groups received lactulose. The number of patients who died and the number of patients with improved hepatic encephalopathy were similar in the two groups. However, the negative nitrogen balance at baseline reversed in the amino acid, but not in the glucose group.

Three trials published from 1986 to 1998 evaluated the effects of BCAA, lactulose, and antibiotics [16–18]. Rossi-Fanelli and colleagues included 40 patients with cirrhosis severe (at least grade 3) acute HE and found that BCAA was more effective than lactulose in the improvement of hepatic encephalopathy manifestations. Mortality was similar in the two groups. Strauss and colleagues [18] compared the effect of BCAA versus neomycin administered orally or as enemas in 29 patients with cirrhosis and acute hepatic encephalopathy. Some of the patients were included more than once. Irrespective of whether each patient was included only once in the analysis or whether the analysis was based on the number of episodes of hepatic encephalopathy (i.e.,

patient were included more than once), no differences were identified between allocation groups regarding improvement of hepatic encephalopathy manifestations or mortality. A similar result was reached by Hwang and colleagues who evaluated the effect of neomycin and lactulose alone or with a BCAA-enriched solution in 55 patients (60 episodes of hepatic encephalopathy) with acute hepatic encephalopathy associated with acute liver failure [16].

In conclusion, only two of seven trials found a potential benefit of intravenous BCAA on clinical outcome measures and one trial found a potential benefit on nutritional parameters. The individual trials provide little evidence to support the use of intravenous BCAA-enriched solutions for acute episodes of hepatic encephalopathy in clinical practice. On the other hand, the trials were small and the statistical power was weak, which could mean that clinically relevant intervention effects may be overlooked. Furthermore, the trials were published several decades ago, which means that the collateral interventions and supportive care for the underlying liver disease did not follow current recommendations. The prognosis for patients with cirrhosis and acute hepatic encephalopathy is considerably improved, which means that the benefit of intravenous BCAA-enriched solutions may still need to be assessed in relation to current practice.

Oral BCAA supplements

Eight trials have evaluated the effect of orally administered BCAA for hepatic encephalopathy [3, 4, 7, 8, 19–21]. The definitions and assessments used in the diagnosis of hepatic encephalopathy varied between trials (Table 1). All trials included patients with cirrhosis. The first two trials were published as early as 1984 [21] and 1985 [19]. Both trials included a control group randomized to

Table 1: Table of diagnostic criteria and methods used in included trials.

Hayashi [10]	Portal-systemic encephalopathy index, Trail Making Test Part A, serial sevens test, and plasma ammonia
Horst [21]	Asterixis, Portal-systemic encephalopathy index, Trail Making Test Part A, electroencephalography, and ammonia
Marchesini [3]	Portal-systemic encephalopathy index, a complete neuropsychological examination, Trail Making Test Part A, electroencephalography, and fasting venous ammonia
Marchesini 2003 [4]	Encephalopathy score and Trail Making Test Part A
Muto [7]	West-Haven criteria grade 1–4
Plauth 1993 [20]	The digit symbol test, Trail Making Test Part A, number revision test, motor performance test battery, and the Vienna Reaction Time Apparatus
Egberts [19]	Culture Fair intelligence test, Wechsler Adult intelligence test, Digit Symbols, Multiple Choice Vocabulary Test, The visual retention test, Number Revision Test, Attention Stress Test, Attention Diagnostic Method, Motor Performance Test Battery, and Vienna Reaction Time Apparatus
Les [8]	Trail Making Test part A, Symbol Digit Test (oral version), Grooved Pegboard Test (dominant hand), and Barthel's autonomy index

an isonitrogenous control. Egberts and colleagues included 22 patients with alcoholic liver disease (86%) or viral hepatitis (14%) [19]. Horst and colleagues [21] included a total of 37 patients (38% with alcoholic liver disease and 8% with viral hepatitis). None of the trials found a beneficial effect of BCAA on improvement of hepatic encephalopathy manifestations or mortality at the end of treatment. In a larger randomized controlled trial from 1990, Marchesini and colleagues included patients with cirrhosis and chronic latent hepatic encephalopathy [3]. The trial compared BCAA (30 patients) versus an isonitrogenous control diet containing casein (34 patients). Only three patients were lost to follow-up. The trial found a clear beneficial effect of BCAA on improvement of hepatic encephalopathy manifestations after 3 months of follow-up (relative risk 2.27; 95% CI 1.39–3.70), but no difference in mortality between allocation groups. Hayashi and colleagues performed a similar trial that was published in abstract form in 1991 [10]. The trial included a total of 67 patients and found that BCAA increased the proportion of patients with improved manifestations of hepatic encephalopathy at the end of treatment compared with an isonitrogenous control group (relative risk 6.40; 95% CI 1.58– 26.00). The effect of BCAA on mortality was not described.

Three trials have evaluated the effect of oral BCAA for patients with cirrhosis and an increased risk of developing clinically overt hepatic encephalopathy [4, 7, 8]. The trials were published between 2003 and 2011. The first trial by Marchesini and colleagues [4] compared 12 months of treatment with BCAA (n = 33) versus isonitrogenous and isocaloric supplements (n = 79). The proportion of patients with minimal hepatic encephalopathy at inclusion was 74%. The trial found a beneficial effect of BCAA on a composite outcome measure that included mortality and clinical deterioration. When analyzing patients with minimal hepatic encephalopathy at baseline, no benefit of BCAA was detected (relative risk 1.31; 95% CI 0.74–2.32). In a subsequent trial, Muto and colleagues reached a similar result [7]. The trial included 646 patients who were randomized to a standard diet with or without BCAA. In agreement with Marchesini and colleagues, Muto and colleagues found that the BCAA supplement had a beneficial effect on a composite outcome measure that included mortality and deterioration of the underlying liver disease. When analyzing patients with clinically overt hepatic encephalopathy at baseline (n = 39), BCAA had no beneficial effect on hepatic encephalopathy manifestations (relative risk 1.08; 95% CI 0.62–1.89). Les and colleagues performed a randomized controlled trial on 116 patients with cirrhosis and at least one previous episode of clinically overt hepatic encephalopathy [8]. Included patients were randomized to a standard diet alone or with a BCAA supplement. The duration of follow-up was 56 weeks. The number of patients who developed clinically overt hepatic encephalopathy and the number of patients who survived were similar in the BCAA and control group. Among patients with minimal hepatic encephalopathy at baseline, no improvements in hepatic encephalopathy manifestations were identified.

The results of individual trials on oral BCAA supplements vary considerably. Some trials found a potential benefit of oral BCAA on hepatic encephalopathy manifestations. Other trials found the opposite result. None of the trials found a benefit on mortality, but a potential benefit cannot be excluded when evaluating the result of composite clinical outcome measures. Based on the differences between trials and trial outcomes, systematic reviews with meta-analyses of available trials are needed.

Cochrane systematic reviews

In a Cochrane Review from 2003, the results of individual randomized clinical trials on BCAA were evaluated [22]. The review included eleven randomized trials on BCAA versus placebo, no intervention, control diets, or other interventions (including lactulose or antibiotics) for hepatic encephalopathy. Due to the inclusion criteria, the trials by Marchesini and colleagues was excluded from the review [4]. Trials were included regardless of blinding, language, or publication status. The maximum duration of follow-up was 30 days. Nine of the trials reported data on improvement of manifestations of hepatic encephalopathy. The remaining trials did not report data that allowed an assessment of this outcome measure. A random effects meta-analysis of the nine trials (Fig. 1) showed that BCAA had a beneficial effect on hepatic encephalopathy compared with control interventions (risk ratio 1.34; 95% CI 1.12–1.61). The result was confirmed in fixed effect meta-analysis (Fig. 2). There was no difference between trials in which the control group received an isonitrogenous diet or a nonisonitrogenous diet (test for subgroup differences $P = 0.19$). No differences were seen between trials using a high or low dose of BCAA (test for subgroup differences $P = 0.50$) or trials with a duration of follow-up that was less than 3 months or at least 3 months BCAA (test for subgroup differences $P = 0.37$).

There were no beneficial or detrimental effects on mortality, quality of life, or adverse events. A subgroup analysis was performed to evaluate the potential influence of the mode of administration on the estimated intervention benefit. The subgroup analysis found some evidence of a beneficial effect of intravenous BCAA in random effects model meta-analysis (risk ratio random effects model 1.17; 95% CI 1.00–1.36; Fig. 1. The fixed effect model meta-analysis confirmed the findings (risk ratio 1.21; 95% CI 1.02–1.43; Fig. 2). There was no difference between trials

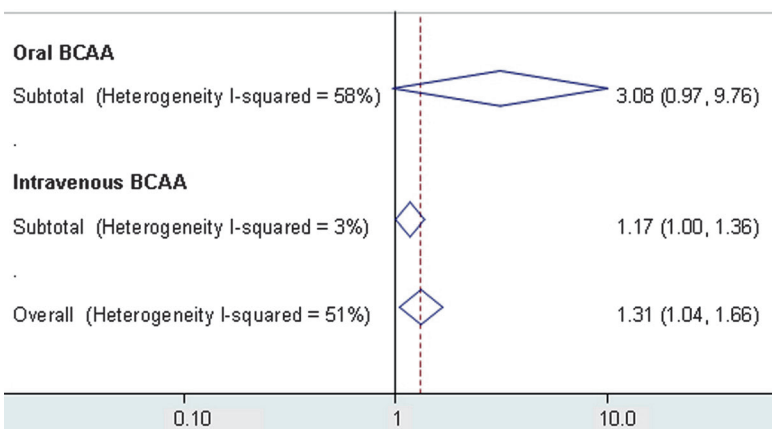

Fig. 1: Random effects meta-analysis on branched chain amino acids for patients with hepatic encephalopathy. Random effects model meta-analysis of randomized controlled trials on branched chain amino acids (BCAA) versus placebo, no intervention, control diets, or other interventions for hepatic encephalopathy. The outcome measure is improvement of manifestations of hepatic encephalopathy. The analyses are stratified for subgroups of trials on intravenous or orally administered BCAA. The results of the meta-analyses are presented as risk ratios (RR) with 95% confidence intervals (CI).

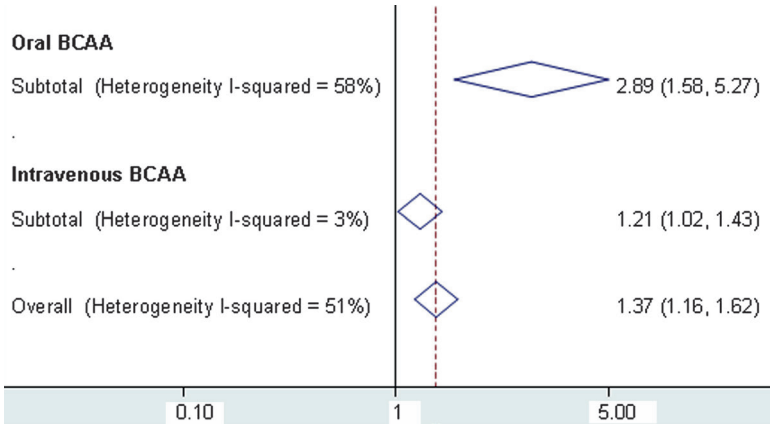

Fig. 2: Fixed effect meta-analysis on branched chain amino acids for patients with hepatic encephalopathy. Fixed effect model meta-analysis of randomized controlled trials on branched chain amino acids (BCAA) versus placebo, no intervention, control diets, or other interventions for hepatic encephalopathy. The outcome measure is improvement of manifestations of hepatic encephalopathy. The analyses are stratified for subgroups of trials on intravenous or orally administered BCAA. The results of the meta-analyses are presented as risk ratios with 95% confidence intervals (CI).

in which patients in the control groups received standard diets, neomycin, or lactulose (test for subgroup differences $P = 0.79$). When analyzing trials on oral BCAA there was a potential benefit on manifestations of hepatic encephalopathy when the meta-analysis was performed using a fixed effect model (relative risk 2.89; 95% CI 1.58–5.27). The beneficial effect was not confirmed in random effects meta-analysis (relative risk 3.08; 95% CI 0.97–9.76). However, the analysis of oral BCAA supplements only included two trials with a total of 41 patients [3, 10]. Considering that the Cochrane review did not include the large high-quality trials by Marchesini and colleagues [4] or the more recent trials on oral BCAA supplements (Muto and colleagues and Les and colleagues [7, 8]), an updated meta-analysis is needed to determine the strength of the overall evidence.

Updated meta-analysis on oral BCAA supplements

Updated meta-analyses were performed in order to include the evidence from all available randomized controlled trials [5, 6]. One meta-analysis included trials on oral or intravenous BCAA [5] whereas the second meta-analysis focused on oral BCAA and excluded trials in which intravenously administered BCAA solutions were used [6]. Based on extensive searches, the meta-analysis in the Cochrane Review [22] was updated with inclusion of data from the three randomized controlled trials on oral BCAA [5]. The updated meta-analysis on intravenous or oral BCAA included data from a total of fourteen trials. Seven trials assessed the effect of intravenous BCAA formulations for patients with acute episodes of overt hepatic encephalopathy and seven trials assessed the effect of oral BCAA supplements for recurrent/minimal hepatic encephalopathy. Data on the outcome measures that were assessed were recalculated based on individual patient data for four of the included trials [3, 4, 7, 8]. The included trials were small (Fig. 3). In most

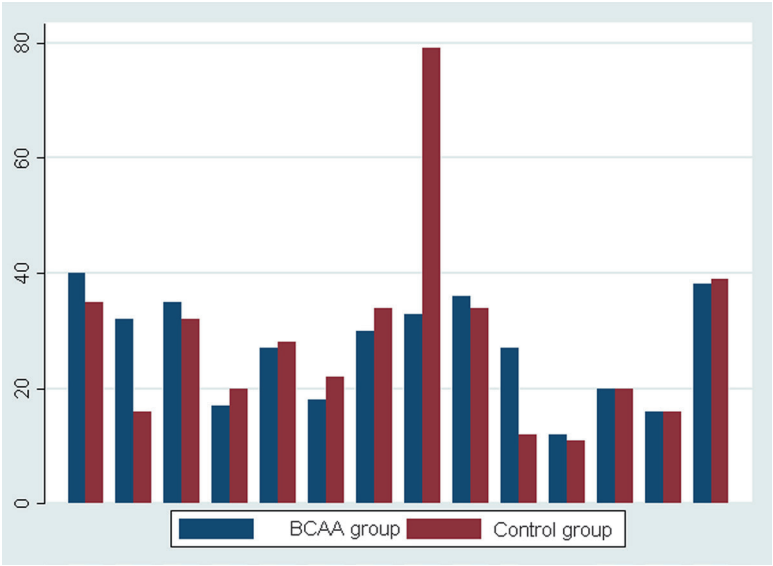

Fig. 3: Included patients in randomized controlled trials on branched chain amino acids for hepatic encephalopathy. Sample size in randomized controlled trials on branched chain amino acids (BCAA) versus placebo, no intervention, control diets, or other interventions for the treatment of hepatic encephalopathy. The figure shows the number of patients with hepatic encephalopathy in the allocation groups at the time of randomization.

trials, less than 40 patients were randomized to BCAA versus control groups. Accordingly, the effect of BCAA versus control interventions on hepatic encephalopathy manifestations was not statistically significant in individual trials. However, BCAA had a clear beneficial effect on hepatic encephalopathy manifestations when the results of the trials were combined in a meta-analysis, regardless of whether a random effects model (risk ratio 1.35; 95% CI 1.11–1.64; Fig. 4) or fixed effect model was used (relative risk 1.41; 95% CI 122–1.63; Fig. 5). The updated meta-analysis revealed a clear difference between subgroups of trials on oral or intravenous formulations of BCAA (test for subgroup differences $P = 0.023$). The beneficial effect or oral BCAA was confirmed in meta-analyses using a random or fixed effect model (random effects relative risk 1.41; 95% CI 1.22–1.63 and fixed effect relative risk 1.84; 95% CI 1.41–2.39, respectively). Additional subgroup analyses of the trials on oral BCAA found no difference between subgroups of trials stratified by the control intervention (test for subgroup differences $P = 0.13$). All patients in the trials on oral BCAA had cirrhosis and most used the standard dose of BCAA. Accordingly, there was very little intertrial heterogeneity (Fig. 4). No evidence of bias was identified and the results were robust for multiple comparisons [23]. No beneficial or detrimental effects were identified when assessing mortality (Fig. 6). The analysis of losses to follow-up showed some evidence that the proportion of patients who were withdrawn or dropped out after randomization was higher in the BCAA than the control group (Fig. 6). However, the difference in losses to follow-up was only statistically significant in the fixed effect meta-analysis (relative risk 0.46; 95% CI 0.22–0.95) and not when a random effects model was used (relative risk 0.49; 95% CI 0.23–1.02). The combined evidence suggests that BCAA should be considered in the treatment of patients with cirrhosis and hepatic

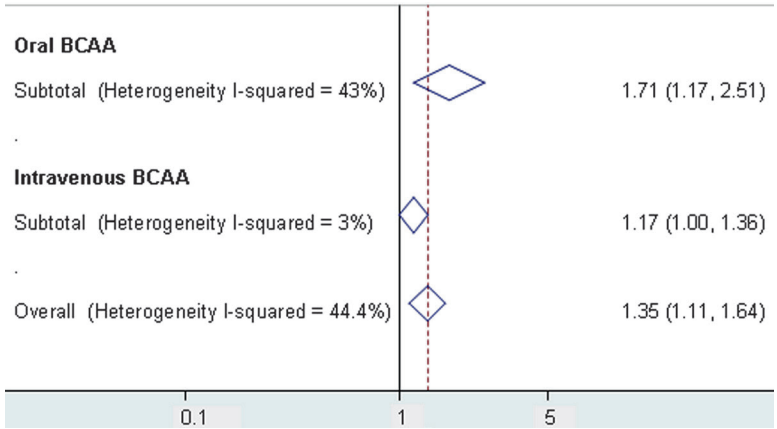

Fig. 4: Updated random effects subgroup meta-analysis of oral or intravenous branched chain amino acids for improvement of manifestations of hepatic encephalopathy. Updated random effects meta-analysis of randomized controlled trials on branched chain amino acids (BCAA) versus placebo, no intervention, standard diets, or other active interventions for improvement of manifestations of hepatic encephalopathy. The analyses are stratified for subgroups of trials on orally administered BCAA versus placebo or control diets and trials on intravenous BCAA versus placebo, no intervention, control diets or other interventions. The results of the meta-analysis are presented as risk ratios with 95% confidence intervals (CI).

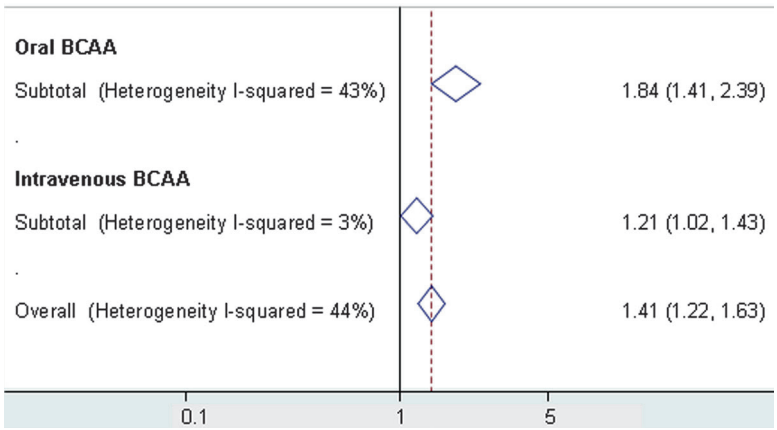

Fig. 5: Updated fixed effect subgroup meta-analysis of oral or intravenous branched chain amino acids for improvement of manifestations of hepatic encephalopathy. Updated fixed effect meta-analysis of randomized controlled trials on branched chain amino acids (BCAA) versus placebo, no intervention, standard diets, or other active interventions for improvement of manifestations of hepatic encephalopathy. The analyses are stratified for subgroups of trials on orally administered BCAA versus placebo or control diets and trials on intravenous BCAA versus placebo, no intervention, control diets, or other interventions. The results of the meta-analysis are presented as risk ratios with 95% confidence intervals (CI).

encephalopathy. The evidence on oral BCAA is more promising than intravenous BCAA solutions. In a meta-analysis that focused on oral BCAA, a similar overall result was achieved [6]. The meta-analysis was based on outcomes recalculated based on individual patients' data from four trials (n = 255 patients) and data extracted from published trial reports from four trials (n = 127

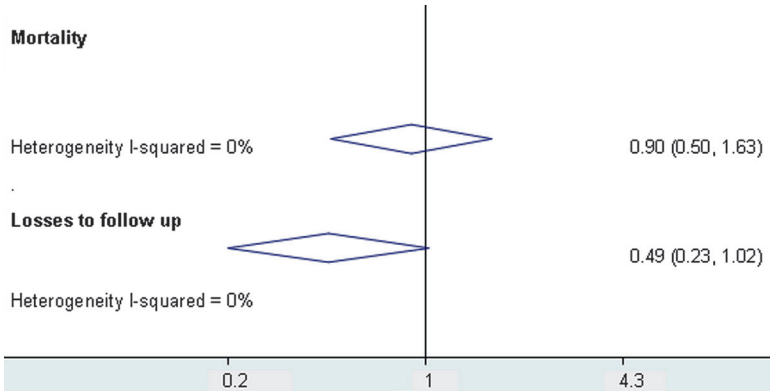

Fig. 6: Random effects subgroup meta-analysis on mortality and losses to follow-up in randomized controlled trials on oral branched chain amino acids. Updated random effects meta-analyses of randomized controlled trials on oral branched chain amino acids (BCAA) versus placebo or standard diets for patients with hepatic encephalopathy. The outcomes measures are mortality (all-cause) and losses to follow-up (including all withdrawals and dropouts). The results of the meta-analyses are presented as risk ratios with 95% confidence intervals (CI).

patients). Included patients had cirrhosis and recurrent clinically overt hepatic encephalopathy or minimal hepatic encephalopathy. Seven trials reported the proportion of patients with improved manifestations of hepatic encephalopathy (all trials with individual patient data and three trials with published data). Improved manifestations of hepatic encephalopathy were seen in 87 of 172 patients in the BCAA group and 56 of 210 patients in the control (random effects model relative risk 1.71; 95% CI 1.17–2.51). The corresponding number needed to treat was 5 patients. The effect of BCAA was associated with the type of hepatic encephalopathy (minimal or clinically overt) at baseline (test for subgroup differences $P = 0.04$). In random effects meta-analysis the relative effect of BCAA was different in patients with clinically overt hepatic encephalopathy (relative risk 3.26; 95% CI 1.47–7.22) and patients with minimal hepatic encephalopathy (relative risk 1.32; 95% CI 0.97–1.79). A similar result was seen when a fixed effect model was used (clinically overt hepatic encephalopathy relative risk 3.11; 95% CI 1.93–5.01 and minimal hepatic encephalopathy relative risk 1.30; 95% CI 0.95–1.79). No evidence of bias was identified. No beneficial or harmful effects on remaining clinical outcome measures (including mortality) were identified.

The dose of BCAA

The evidence concerning the optimal dose of BCAA supplements in liver disease is weak. Dose finding studies are based on measurements in healthy controls and pathophysiological assessments or plasma concentrations of BCAA and aromatic amino acids in patients with liver disease. In a randomized controlled trial from 1993 [24], thirty patients with cirrhosis and severe hepatic encephalopathy (coma) were randomized to a standardized BCAA-enriched solution with or without additional valine. The results of the trial showed no added benefit of valine when evaluating the course of the disease or mortality. The updated meta-analysis included trials on several

different doses of oral BCAA supplements. At present the recommended dose of oral BCAA is 0.25 g per kg of bodyweight per day. Several trials included in the meta-analysis evaluated this recommended dose [3, 19]. For a patient with a body weight of 70 kg, this corresponds to 17.5 g of BCAA per day. Three of the included trials used a relatively low dose of BCAA, 7.2 g to 12 g [4, 10]. In other trials [8, 21], the daily dose of BCAA was set higher than recommended to 20 or 29 g. In subgroup analyses, the beneficial effect of BCAA was confirmed in all three subgroups of trials. BCAA had a beneficial effect on hepatic encephalopathy when administered at a dose of 20–29 g per day (relative risk 2.15; 95% CI 1.33– 3.49), 0.25 mg per day (relative risk 2.15; 95% CI 1.33–3.49), or 7.2–12 g per day (relative risk 1.65; 95% CI 1.11–2.45). The difference between subgroups was not statistically significant (test for subgroup differences $P = 0.69$). Considering that the beneficial effect of oral BCAA on hepatic encephalopathy is established, future trials should consider the assessment of the optimal dose.

The effect of BCAA in relation to other interventions

At present, the nonabsorbable disaccharides lactulose and lactitol are recommended as the first-line intervention in hepatic encephalopathy. A systematic review and meta-analysis from 2004 evaluated the effect of the disaccharides [25]. The review included 22 randomized controlled trials. The primary outcome measure was "lack of improvement of hepatic encephalopathy." The overall analyses showed a potential beneficial effect of the disaccharides (lactulose and lactitol) compared with placebo or no intervention. The findings were not confirmed in subgroup analyses of trials with a low risk of bias (relative risk 0.92; 95% CI 0.42–2.04). Several randomized controlled trials have evaluated the effect of lactulose after the systematic review was published [26–30]. One of the trials compared the effect of lactulose versus no intervention. The trial also included intervention groups receiving probiotics or L-ornithine-L-aspartate. The included patients had cirrhosis and minimal hepatic encephalopathy. The results showed that all interventions improved manifestations of hepatic encephalopathy compared with no intervention. Other randomized trials have evaluated the preventive effect of lactulose. One trial included patients with cirrhosis and no previous episodes of hepatic encephalopathy [31]. The results showed that lactulose reduced the proportion of patients who developed hepatic encephalopathy episodes (lactulose 11% versus no intervention 28%; $P = 0.02$). A similar trial on secondary prevention of hepatic encephalopathy episodes in cirrhosis reached a similar result [30]. In a recent trial on patients with cirrhosis and gastrointestinal bleeding [26], lactulose also prevented hepatic encephalopathy. When updating the meta-analysis from 2004 with recent trials [5], the disaccharides have a beneficial effect on hepatic encephalopathy manifestations (improvement of manifestations) in both random effects (relative risk 1.99; 95% CI 1.14–3.48) and fixed effect meta-analysis (relative risk 2.21, 95% CI 1.60–3.05). The benefit of nonabsorbable disaccharides for prevention of hepatic encephalopathy was also established (random effects model relative risk 1.27; 95% CI 1.17–1.39 and fixed effect model relative risk 1.23; 95% CI 1.05–1.44).

A large high-quality randomized controlled trial evaluated the effect of the addition of rifaximin to lactulose in patients who did not respond to lactulose alone [32]. The trial found that

rifaximin reduced the risk of developing hepatic encephalopathy compared with placebo (hazard ratio 0.42; 95% CI 0.28–0.64). A meta-analysis of trials on rifaximin versus lactulose showed a clear benefit of rifaximin. The benefit was confirmed in a trial on minimal hepatic encephalopathy [33]. When comparing rifaximin versus lactulose for clinically overt HE, rifaximin increases the proportion of patients with improved manifestations (relative risk 1.57; 95% CI 1.03–2.39).

Unlike nonabsorbable disaccharides and rifaximin, there is no evidence to support the use of BCAA for prevention of hepatic encephalopathy. Based on the results of individual meta-analyses, the size of the effect of the three interventions is similar. Only one trial on patients with overt hepatic encephalopathy has compared the effect of BCAA versus lactulose [17]. The trial found no statistically significant difference between the two intervention groups (71% vs. 47%; $P > 0.05$). The trial was small, the duration of follow-up was short and the design entailed a considerable risk of bias. The benefit of BCAA compared with other interventions for hepatic encephalopathy is not established. Additional trials comparing these interventions may be considered. However, the potential benefit of combining interventions is equally or maybe even more important. In a recent randomized trial on 5–6 months of treatment with BCAA versus BCAA and zinc supplements for patients with liver cirrhosis [34]; the trial included 40 patients with blood albumin levels of ≤3.5 g/dL and zinc levels of ≤70 μg/dL. The trial found that the addition of zinc to BCAA improved nitrogen metabolism. No effects on clinical outcome measures were identified.

Suggestions for future research

Additional evidence is still needed to determine the effects of BCAA for both clinically overt and minimal hepatic encephalopathy. Future trials should use a randomized design and evaluate the effect of interventions on symptoms and manifestations as well as the prevention of hepatic encephalopathy episodes. The dose of BCAA should be established to optimize the management of patients with hepatic encephalopathy.

Conclusions

The combined evidence supports the use of oral BCAA as treatment for patients with hepatic encephalopathy. The evidence supporting the use of oral BCAA includes several large, high-quality randomized controlled trials. There is no convincing evidence on the use of intravenous BCAA for acute or chronic hepatic encephalopathy. The value of combining BCAA with other recommended interventions focusing on lactulose and rifaximin remains unresolved albeit promising.

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Mobile health

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Abstract

Rapid innovations in digital communications technologies have fueled the use of mobile phones for delivering health services and information—a phenomenon termed mobile health (mHealth). Current mHealth strategies for health service delivery range from the implementation of simple text message reminders to complex clinical decision support algorithms, and extending in recent years to connect mobile phones to sensors and other portable devices for diagnosis at the point-of-care. This chapter summarizes the current state of mHealth, important strides that have been made in strengthening the global mHealth evidence base, and key 'best practices' in scaling mHealth for achieving universal health care.

Keywords: Mobile health, mHealth, Digital health, 12 common mHealth and ICT applications, Universal health care

Introduction

No other technological innovation has diffused through human society as rapidly as mobile phones. Mobile-cellular network infrastructure has seen an exponential growth in the last decade,

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reaching almost 95% of the world's population in 2016 (International Telecommunications Union 2016). Some of the most rapidly growing regions of mobile phone ownership and use are in the developing world, including countries in the Asian and sub-Saharan African continents. In concert with this growth in infrastructure, ownership, and use, the rapid evolution of mobile devices has fostered new opportunities to address information and communication challenges that previously did not exist (Qiang *et al*. 2012). While phone calls and short messaging service (SMS) continue to remain the most common modes of communication, mobile phones present a novel modality for internet access not previously possible in rural, hard to reach areas or for individuals without a means of accessing traditional fixed broadband connections. Currently, close to 3.6 billion people are anticipated to be reached by mobile internet services (International Telecommunications Union 2016). Massive infrastructural investments by mobile network operators in extending the reach of mobile network coverage, along with the accessibility, portability, and connectivity-on-the-go offered by mobile phones make them a widely-appealing communication medium for the delivery of information and services (World Health Organization 2009). Not surprisingly, several areas of innovation leveraging mobile phones have emerged in the last decade, including mHealth, mAgriculture, mGovernance and mFinance (Kelly *et al*. 2012). Increasingly, the power of mobile network connectivity is being harnessed within these mDomains to improve service delivery, user experience, and coverage, supplementing the basic phone call and text messaging services utilized by individuals in their daily lives (Kelly *et al*. 2012).

One area where the utilization of mobile phones has garnered much attention is health care. The use of mobile phones to optimize the delivery and receipt of health information and services, also referred to as mobile health or mHealth, is innovative for several reasons. First, the ubiquity of mobile phones makes the concept of remote health care a viable and scalable reality. No longer is health care tethered to facilities as mHealth pushes these bounds further to the communities, and in many cases to the individual themselves. Unlike prior generations of digital innovation such as telemedicine and eHealth, there has been little to no investment by the Public Health community to build this global infrastructure. Second, the fact that most mobile phone owners carry the device with them where they go, we now have the unprecedented ability to deliver health services and information to individuals where they are and when they want or need it. Third, mobile phones have allowed users of health care to seek information and connect to providers with ease. In many developing countries, people are using mobile phones as the preferred medium to access the internet. Consequently, their ability to seek health information-on-demand is very high, even in the absence of formalized mHealth programs. As phones incorporate increasing computational power, while becoming cheaper and sleeker, the opportunities for health service delivery via these devices are tremendous. Current mHealth strategies for health service delivery range from the implementation of simple text message reminders to complex clinical decision support algorithms, and extending in recent years to connect to sensors and other portable devices to aid diagnosis at the point-of-care (Labrique *et al*. 2013a).

In this chapter, we will describe the 12 key applications of mHealth that have categorized how this technology has been used in mitigating the key constraints to health systems. We will

use real-world implementations of mHealth to illustrate how these technologies function across the three layers of health care, namely at the patient, provider and health system-levels. We will briefly review the current evidence base and highlight areas where more rigorous evaluations are warranted to establish the impact of mHealth. Finally, we will close with recommendations for researchers new to mHealth on currently available resources to help plan research and implementation of these technologies.

mHealth and its public health appeal

Numerous constraints and barriers exist to providing high quality, accessible, and timely health services, especially in low-resource settings (Labrique *et al*. 2013a; Mehl and Labrique 2014; Agarwal *et al*. 2015). These health constraints impede optimal health promotion, diagnosis, and care, and can be described as barriers to: (1) information, (2) availability, (3) quality, (4) acceptability, (5) utilization, (6) efficiency, or (7) cost related to health or health services (Mehl and Labrique 2014; Mehl *et al*. 2015). The "bottom billion", representing the world's poorest populations, receives health care predominantly from low trained, non-facility based front-line health workers (Agarwal *et al*. 2015; Kallander *et al*. 2013). Equipping these frontline health workers with mHealth solutions helps bring these clients under the umbrella of the traditional health system, allowing them to be counted and enumerated, which builds accountability for frontline health workers to their supervisors. mHealth interventions capitalize on key features inherent in mobile technologies to bridge these constraints. In settings where women frequently give birth at home, the decision to seek medical help during delivery can be a difficult one (Kim *et al*. 2012; Kruk *et al*. 2016; Sikder *et al*. 2011). In many cases, women require family approval and input before such a decision is made. Even without the need for co-decision making, the choice to move to a health facility is complicated, weighing the potential financial costs and/or difficulty of reaching the facility in light of the woman's obstetric risks during childbirth (Sikder *et al*. 2014). mHealth interventions may act in several ways to reduce these barriers. In a more robust system, where frontline health workers have registered every pregnancy and are aware of impending births, they can be held accountable for attending these births, advocating for women, and helping the family make the decision when it is time to go to a health facility. Several mHealth interventions aim to compress this delay, using methods ranging from digital population registries to SMS-based labor and birth notification (Kruk *et al*. 2016; McNabb *et al*. 2015). In the event an extensive registry system like this is not available, provision of one simple thing-the emergency contact number of the designated frontline health worker to the woman and her family-enables the family to connect with a supportive decision-maker. Leveraging simple SMS-based delivery of health information leading up to childbirth about reasons for delays/danger signs can also help women and other key members of her family make a decision to seek medical attention in a timely manner (Lund *et al*. 2012).

The 12 Common mHealth and ICT Applications

The 12 common mHealth and ICT applications are currently the most widely adopted categorization of the ways in which mobile technologies are used for the delivery of health services and information (Fig. 1) (Labrique *et al.* 2013a).

The 12 applications are cross-cutting—extending across the three layers of the health care system—patient, provider and broader system. At the client level, there are extensive examples for the use of mHealth as a medium to deliver behavior change communication in a variety of health domains. Current implementations focus on leveraging simple communication modalities such as phone calls and text messaging to reach a broad audience—especially for those without access to smart-phone technologies and 'apps'. Examples include the use of text messaging services or interactive voice response systems for the delivery of health information related to family planning, pregnancy and newborn care, immunizations, and management of chronic illnesses. In South Africa, the National Ministry of Health has capitalized on high mobile phone ownership among pregnant women to register them and provide age and stage-appropriate messages related to their health and the health of their babies (Department of Health, Republic of South Africa 2014; Johnson and Johnson 2014). Similarly, the Mobile 4 Reproductive Health (m4RH) program provided family planning information on demand in Kenya and Tanzania. In a randomized control trial in Kenya, individuals accessing m4RH had 13% higher family planning knowledge compared to control individuals (FHI360 2017; L'Engle *et al.* 2013; Willoughby and L'Engle 2015). Other examples include the provision of mobile phone-based reminders, either for upcoming clinical visits or for adherence to medication regimens. The mTika project in Bangladesh was successful in improving timely vaccination coverage in rural areas as well as urban slums in Dhaka through text message reminders to mothers about upcoming vaccination appointments (Uddin *et al.* 2016). In rural Kenya, mobile phone text messaging promoted adherence to antiretroviral therapy in HIV patients (Chang *et al.* 2012). At their very core, mHealth deployments facilitate communication between patients and providers as well as within peer groups (Rotheram-Borus *et al.* 2012). This

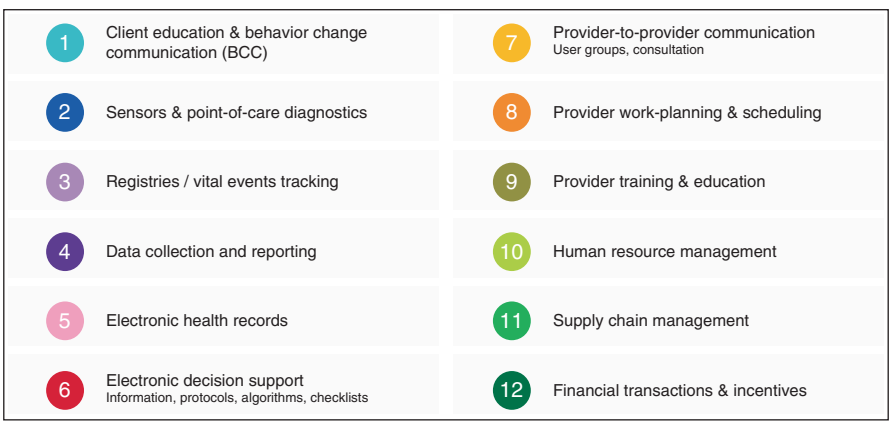

Fig. 1: Twelve common mHealth and ICT applications (Labrique *et al.* 2013a).

improved access to a clinical or non-clinical support network alone may impact the ability of individuals to monitor their own health.

In contrast to the simple modes of communication on client-focused mHealth deployments, implementations of mHealth for streamlining health service delivery by providers may be more complex, often leveraging smartphone technology. This means providers using mobile phones have the ability to collect, manage, and longitudinally track patient data on mobile phones. The Open Smart Register Platform (OpenSRP) is a tablet-based data management system for frontline health workers to register and track their community-based clients longitudinally (THRiVE consortium 2017). OpenSRP includes several features such as automated scheduling to prioritize services to clients, risk profiling to prioritize clients in need for immediate attention, dynamic patient look ups that facilitate the ability to pull up relevant patient records, and automated reporting to improve timeliness of data use and reduce the reporting burden for the frontline health worker. Finally, multimedia integration abilities support provider-initiated counseling using OpenSRP. Advanced clinical decision-support algorithms may be programmed into the phone such that health providers may be guided in clinical decision-making. For instance, D-Tree's electronic integrated management of childhood illness (eIMCI) application promoted higher adherence to the IMCI protocol by health providers compared to a paper version of the protocol (Mitchell *et al*. 2012; Derenzi *et al*. 2008). Mobile phones also enable providers to connect to each other, enhancing the ability to seek expert support for complex cases, make referrals, and coordinate care. Closed user groups such as that managed by Switchboard in Ghana allow trained healthworkers to call within their network at no cost (Kaonga *et al*. 2013a; b). This encourages peer-problem solving and communication. Several portable point-of-care diagnostic devices such as ultrasounds, heart monitors, and glucometers now come with the ability to connect wirelessly to mobile devices such that readings are automatically processed, captured, and displayed in meaningful ways. The portability of these devices implies that preventive screening and diagnostics can be conducted at the point-of-care or in community-based settings such that the coverage of preventive programs is maximized. Examples include AliveCor Heart Monitor, MobiUS SP1 ultrasound and the Pocket Colposcope (Lam *et al*. 2015; MobiSante 2016; AliveCor 2016).

At the health system-level, mHealth-facilitated data collection ensures that health management information is available in a reliable and timely manner to support decision-making and resource allocation. Web-based dashboards and analytics support meaningful visualization of health determinants, health status, and human resources, making it easier for the district or national-level health managers to make informed decisions and prioritize areas of need. The District Health Information System (DHIS 2) is currently used in over 40 countries to monitor health and human resource performance at the district and national levels (Health Information Systems Programme, University of Oslo, 2017). Platforms such as iHRIS are customized for tracking and managing health worker performance and training (Intrahealth 2017). mHealth deployments can be used to track and manage the supply chain for essential commodities and medicines, reducing incidences of stock-outs. SMS for Life used text message-based check-ins with hospital pharmacies about essential commodity levels to reduce stock-outs of antimalarials (Barrington *et al*. 2010). Other supply tracking systems such as cStock include performance planning for

district product availability teams, thereby building capacity while supporting logistics management (Dimagi 2016). Health management systems also allow surveillance of diseases and can be used to pre-empt outbreaks, thereby reducing delays in response (Vasudevan *et al.* 2016).

Complex health systems require multiple solutions to address equally complex constraints. With the recent establishment of new global health targets under the sustainable development goals, universal health care (UHC) has emerged as a key area of focus. UHC encompasses three key concepts—equitable access, quality health care, and protection from financial risk (World Health Organization 2017). In this context, the domain of mHealth has seen a renewed interest based on recognition by global stakeholders that it represents a comprehensive strategy addressing these key concepts—the use of mHealth for client enumeration, development of registries to track patient care, and coverage of essential interventions can be leveraged to facilitate and monitor achievement of UHC (Mehl and Labrique 2014; Labrique *et al.* 2012). Digital patient records using systems such as OpenMRS promote continuity in care and informed clinical decision-making that was previously challenging in the era of fragmented paper-based record-keeping systems (Regenstrief Institute 2017). In parallel, mHealth interventions that take advantage of mobile financial transactions to promote savings, health insurance payments or provide reimbursements for health services can make health care costs more affordable, reducing the financial burden on clients (Wakadha *et al.* 2013).

Evidence for mHealth Impact

The term, mHealth, was first coined by Istepanian in 2004. With the emergence of smartphone technologies from 2006–2010, the field of mHealth entered a phase of rapid innovation and, in parallel, unfettered proliferation. The rampant duplication of mHealth projects led to the coining of the term, "pilotitis", highlighting the frequent failure of mHealth projects to translate beyond small-scale (i.e., pilot) implementations (Labrique *et al.* 2013b). The 2011 Bellagio eHealth declaration warned that mHealth implementation must be guided by evidence, going as far as stating that 'if used improperly, (e)Health may divert valuable resources and even cause harm' (Fraser *et al.* 2011). Tomlinson and others offered strategies to streamline efforts in mHealth—encouraging innovative research designs, interoperability, and a focus on the scalability and sustainability (Tomlinson *et al.* 2013). During this time, we reported that mHealth evidence was emerging and that there were ongoing research studies that would enrich our understanding of the impact these technologies have on health and service delivery. Currently, there are several systematic reviews that describe the growing evidence base for strategies of mHealth. (Agarwal *et al.* 2015; Free *et al.* 2013a, b; Beratarrechea *et al.* 2014; Bloomfield *et al.* 2014; Watterson *et al.* 2015; L'Engle *et al.* 2016).

There is also a growing recognition that mHealth projects have a unique project maturity pathway. As mHealth projects evolve from pilot to scale, evaluations must be tailored to ask relevant questions at different time points—ranging from feasibility and usability at earlier time points to efficacy and cost-effectiveness at later stages. A recent 2017 WHO toolkit reviews the

Box 1: Useful Resources and Tools for mHealth Researchers.

1. ASH compendia	http://www.africanstrategies4health.Org/Mhealth-database.Html
2. mHealthknowledge	http://www.Mhealthknowledge.Org/Resources/Mhealth-Compendium-Database
3. K4Health mHealth planning guide	https://www.k4health.Org/toolkits/mhealth-planning-guide
4. mFHW report	https://media.Wix.Com/ugd/f85b85_cc8c132e31014d91b108f8dba524fb86.Pdf
5. MAPS toolkit—readiness for scale	http://www.Who.Int/reproductivehealth/topics/mhealth/maps-toolkit/en/
6. mERA guidelines for reporting	http://www.Who.Int/reproductivehealth/topics/mhealth/mERA-checklist/en/
7. Monitoring and evaluating digital health interventions: A practical guide to conducting research and assessment	http://www.Who.Int/reproductivehealth/publications/mhealth/digital-healthinterventions/en/
8. PMNCH country readiness for ICT/RMNCH	http://www.Who.Int/pmnch/knowledge/publications/ict_mhealth.Pdf
9. eHealth strategy—enabling environment (WHO-ITU toolkit)	http://www.Itu.Int/pub/D-STR-E_HEALTH.05-2012
10. A practical guide for engaging with mobile operators in mHealth for RMNCH	http://www.Who.Int/reproductivehealth/publications/mhealth/mobile-operatorsmhealth/en/

range of stage-appropriate methods of evaluation and program monitoring from observational studies to randomized trials (see Box 1).

New Frontiers in mHealth

Important, across the examples presented in this chapter, is the recognition of inherent diversity in the emergent field of mHealth. Digital solutions, or strategies, align to the need or problem being addressed. The importance of clarity in describing the form and function of specific mHealth solutions cannot be undervalued, and forms a key point of the 2016 mHealth Evaluation Reporting and Assessment (mERA) guidelines (Agarwal *et al*. 2016). Disambiguation is critical to promotion the sharing of experiences and to reducing redundancy and re-invention in this field.

Over the past 5 years, important strides have been made in recognizing the existence of key 'best practices' in this space, enshrined in the ICT4D principles (Fig. 2).

Many are also acknowledging the importance of donor and government investments in the ecosystem and information systems architecture to promote more robust and scalable innovations, reducing the risk of "pilotitis". Most importantly, it is critical to keep in mind the importance of a systems approach to health problem solving, where mHealth strategies are one facet of a complex solution addressing the multidimensional root causes of the problem. mHealth strategies, derived

[AU6]

Fig. 2: The ICT4D (Information Communication Technologies for Development) principles endorsed by many development organizations, including USAID, World Bank, DFID, UNICEF and others (http://digitalimpactalliance.org/why-the-world-bank-endorses-the-principles-for-digitaldevelopment/).

from the information and communications revolution, solve problems which are inherently information and communications obstacles. Improved information and communications in the hands of the patient, the provider and the health system policy makers can help catalyze programs with known efficacy and impact potential. In thinking about the role of mHealth as part of a complex solution, it is best to view it as a catalyst, or digital "adjuvant", helping to improve the coverage, quality or demand for public health interventions we know can save or improve lives. Whether these are vaccine programs or nutritional interventions, mHealth strategies might be, in some cases, the missing ingredient to achieve the levels of effective or universal coverage so sought after in global health.

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5

Redesigning healthcare systems to provide better and faster care at a lower cost

J.P. van der Heijden, L. Witkamp

Abstract

The use of information and communication technologies in the health care industry has been referred to as "telemedicine" or "e-health." Our health care systems are facing big increases in demand due to growing elderly populations, rising chronic diseases, and the rapid development of new treatments; thus, the use of telemedicine is believed to be a part of the solution in restructuring and redesigning our health care systems. Despite often positive results, many telemedicine services remain stuck in a pilot or experimental phase and never make it to a larger implementation. The most important obstacle is the lack of structural financial reimbursement and available budget. In The Netherlands, we have developed and successfully applied our Health Management Practice (HMP) Model on a large number of telemedicine services using the "start small, think big" approach, leading to fully integrated telemedicine services. Results show a 70–96% reduction in hospital visits in dermatology and ophthalmology, which translates into an immediate cost reduction of 18%. Response times of 4–5 working hours and the learning effect have a high impact on the quality of care delivered. Telemonitoring programs in mental health have shown that involving the patient as an active actor can result in more motivation and ownership of their own health. Telemedicine also allows hospitals to remain focused on delivering high-quality specialized care. In many peripheral centers in residential areas, more routine care services will be delivered close to the patient by paramedics, caregivers, and patients themselves under the direction and supervision of a general practitioner and medical specialist at a distance.

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Fundamentals of telemedicine

Health care systems worldwide are under stress mainly due to the expanding elderly population. The World Health Organization states that the percentage of people over 60 years old will double to 22% by 2050. This effect is a result of improved sanitation and medical services as well as breakthroughs in medical technologies and pharmaceuticals. Furthermore, low- and middle-income countries often lack adequate health care infrastructure and their populations have little access to health care services (Mills *et al.* 2014). Finally, the rise of chronic diseases, such as diabetes, cancer, and dementia, increase demand for long-term health care plans (World Health Organization 2015). These problems can only be addressed by restructuring and redesigning our health care systems. One of the technologies that is believed to be a big driver and also part of the solution is the Internet in its broadest sense. "Broadest" here means the three primary characteristics of the Internet that in the last decade have changed how many industries work (e.g., travel, finance, retail): (1) its ability to have people efficiently share and access information from and to almost anywhere and anyone, (2) it provides communication (real-time, store, and forward) between actors (human and machine) anywhere in the world, closing the gaps of physical distance and time, and (3) it provides a platform for creating networks and communities. The use of these attributes in the health care industry has been referred to as "telemedicine" or "E-health".

The term "telemedicine" has been around since the 1960s and 1970s, when pioneers used telephone and telegraph networks to deliver care to remote locations (Preston *et al.* 1992). However, by the end of the twentieth century and as the Internet was emerging, its popularity grew and the term telemedicine was heard and read frequently within the health care domain. The term covers a spectrum of novel interventions that leverage the capabilities of the Internet. Medical domains dealing with imaging and visual based diagnostics (e.g., radiology, dermatology, pathology) were among the first to start embracing this new technology (Grigsby *et al.* 1995). The potential for more efficient and cost-effective delivery of health care has driven the development of numerous telemedicine services like teleconsultation, telediagnostics, telemonitoring, and telecare in almost all medical fields throughout the world over the next decade with various outcomes in effectiveness and in different implementations and business models (Ekeland *et al.* 2010; Mistry 2012; Chen *et al.* 2013). To give some indication of the scope of the field, at the time of writing, MEDLINE had indexed 23,367 articles when searched for "telemedicine" or "e-health."

The terminology used to describe telemedicine services has also exploded the last 10 years. Other associated terms include e-health, telehealth, health 2.0, smart-health, m-health, digital health, blended care, and connected health, which makes it difficult to reach a common understanding of what is being discussed or described. E-health is the term most commonly used and mostly in a broad context, including everything having to do with some electronic/digital

function in the domains of wellness, health, and health care both in the professional, but even more so in the consumer sphere.

E-health instruments in the consumer sphere range from wearables, self-measurement, self-diagnostics via demotic products such as step counters, smart scales, and anti-depression lighting solutions to a wide range of medical/health apps on mobile devices. "Dr. Google" and websites offering vast libraries of information in these domains exist both with and without validation or medical certification.

In the professional sphere, e-health instruments include, for example, electronic health record (EHR) systems and interoperability systems connecting the EHRs, certified and approved medical devices, prosthetics and robotics, decision support and predictive big data systems, and, finally, what we understand to be telemedicine services:

A care process or the whole of several care processes that meets both of the following two characteristics:

1. *A distance (physical or temporal) is bridged by using both information technology and telecommunications, and.*
2. *There are at least two actors involved in the care process, of which at least one is a registered health care professional or under the supervision of a registered health care professional.*

Two important notes should be made here. First, using this definition, telemedicine is positioned in the professional domain as a registered health care provides has to be involved. A comparison can be made with pharmaceuticals, where self-medication drugs which can be acquired without prescription are counterpart to all consumer sphere e-health instruments freely available to the public and prescription drugs, where a prescription by a health care professional is needed, are the counter-part to telemedicine care processes. Just as there are different rule sets in place for over-the-counter and prescription drugs, this comparison immediately outlines an idea on how we could and maybe even should deal with the evaluation, validation and certification, admission, and reimbursement of these telemedicine services. This is elaborated later in this chapter.

The second argument is that most, if not all, telemedicine services (should) represent a redesign of care processes that already exist, using innovative technologies (the internet and new soft- and hardware). Following this logic, telemedicine is *medicine* (and e-health is *health*); thus, it is to be expected that the prefixes "tele" and "e" in the health care domain will disappear when these new services become the industry standard, similar to how nobody talks about e-booking, e-tickets, and e-banking anymore. To get to that industry standard, however, there are some obstacles to overcome in the implementation and upscaling of telemedicine.

Implementing and upscaling: The Dutch HMP model and use case

The most commonly heard problem with embedding telemedicine services in regular health care systems is that a large proportion of these services remain at a pilot or experimental phase, despite often positive results, and never make it to a larger implementation (Broens 2007). The reasons for this vary and can be found in any of the following categories: technology, acceptance, financing, organization or policy, and legislation. However, the most critical and perennial obstacle to

implementation has been the lack of structural financial reimbursement for telemedicine services. Often, it is not a case that the local system of reimbursement cannot handle these redesigned health care processes—rather, it is the lack of an appropriated budget.

There are many frameworks and models described in the literature aimed at providing implementation roadmaps for telemedicine services that convey advice on how to avoid or handle these obstacles [e.g., the Health Readiness Instrument for Developing Countries, the Layered Telemedicine Implementation Model, the PACS Maturity Model, the Telemedicine Process Model, and the NHS Maturity model (Broens 2007; Khoja *et al*. 2007; Haris 2010; Van de Wetering and Batenburg 2009; Wynchank and Van Dyk 2011)]. Although these models differ in their approach on some levels, they are united on two accords: (1) they follow the "*start small, think big*" approach and (2) they prioritize their change management strategy.

In The Netherlands, we have developed and successfully applied our own model—the Health Management Practice (HMP) model—on a large number of telemedicine services using the "start small, think big" approach (Witkamp and van der Heijden 2012). Additionally, the change management strategy was ensured by a dedicated telemedicine provider (KSYOS Tele Medical Center) commissioned to drive and oversee the implementation. Results of these implementations will be given later in this chapter. The HMP model encompasses a four-phase approach that enables private and public parties to jointly develop, research, and implement new telemedicine services (see Table 1).

The phases are executed in a consecutive manner and are non-overlapping. The completion of all phases for a service takes between 2 and 4 years, however the telemedicine service is already running in real practice after 2 months.

The following sections describe how development of the service, evidence of effectives, healthy reimbursement and successful implementation can be achieved in concordance with the HMP phases.

Health management development

Telemedicine stakeholders—manufacturers, service providers, end-users (patients, caregivers, health care practitioners), policy makers, and health insurers—should all be actively involved in

Table 1: Health management practice phases.

Phase 1	A specific telemedicine service is developed and is tested internally by the development team for usability and safety for a period of 1–2 months
Phase 2	10–20 future users (health providers and patients) test this telemedicine service for usability and feasibility in regular practice for a period of 3–6 months
Phase 3	50–100 future users (health providers and patients) test for a period of 6–12 months whether the telemedicine service actually contributes to improved efficiency in the health care process, a higher production volume, and/or better quality at lower or the same cost
Phase 4	Many users (between 100 and 1000) in a full implementation of the telemedicine service generate data in real life settings for a period of 1–2 years. These are used to investigate large scale cost efficiency. Results can be used in developing sustainable business cases

the redesign of the health care process to ensure a solid support platform. In phase 1 of the HMP it is important to always start with a clear understanding of the current health care pathways, i.e., what technologies are used, in which care process(es), in which health care sector, and what actors (primary and secondary) are involved. The new telemedicine service should not be on top of the old care processes, but should aim to replace parts or the whole process by redesigning the old care process using innovative technologies. Technology combined with redesigned health care processes should lead to an integrated telemedicine service, including a description on how to address the following issues: software used, hardware used, infrastructure interoperability, hosting and education that meet (national) requirements of safety, security, certification, connectivity, and user friendliness.

Health management research

Independent research should be performed during HMP phase 2, 3 and 4 to evaluate different outcomes, depending on the implementation phase. Ultimately, the aim is to collect effectiveness evidence on the telemedicine service resulting in increased efficiency and better quality of care at equal or lower cost. To determine quality aspects of the telemedicine service, the questions on the elements described in Table 2 can be a starting point (Ossenbaard and Duivenbode n.d.). These questions were derived from a think tank of experts organized by the Dutch National Institute for ICT in Health care.

The evaluation of telemedicine services has proven difficult through classic randomized controlled trial designs, mostly because such studies tend to be long and drawn out and, therefore, unable to keep up with the fast pace of technology development; that is, the object of the research is like a "moving target" (Ossenbaard and Duivenbode n.d.). Moreover, telemedicine services are often complex interventions with multiple actors and, as such, unsuitable for the RCT models that work so well for pharmaceuticals research (Ossenbaard and Duivenbode n.d.).

New methodologies for evaluation research are being developed specifically to manage these characteristics of telemedicine services, such as the Trials of Intervention Principles (TIP) method

Table 2: Telemedicine quality elements.

Safety	Are the risks or unintended effects of the telemedicine service on the health of the patient known and restricted to an acceptable minimum?
Effectiveness	Is the telemedicine service based on scientific evidence and does it realize the desired effect in terms of process of care or outcomes (cheaper, better, faster)?
Patient centeredness	Does the telemedicine service have a central focus on the needs and preferences of the patient (self-management, ease of use, accessibility, reliability, privacy, etc.)?
Timeliness	Is the telemedicine service available and accessible when required?
Expediency	Does the telemedicine service contribute to reducing overtreatment, under treatment, non-adherence, lack of transparency, or poor care coordination?
Justness	Is the telemedicine service equally useful for everyone, regardless of personal or social characteristics?

(Ossenbaard and Duivenbode n.d.), Multiphase Optimization Strategy Trials (MOST) (Ossenbaard and Duivenbode n.d.), Sequential Multiple Assignment Randomized Trial (SMART) (Ossenbaard and Duivenbode n.d.), Continuous Evaluation of Evolving Behavioral Intervention Technologies (CEEBIT) (Ossenbaard and Duivenbode n.d.), and the Health Technology Assessment-based Model for Assessment of Telemedicine Applications (MAST) (Ossenbaard and Duivenbode n.d.).

The debate on the best methodology is ongoing; however, for those who are implementing telemedicine, the important goal should be to obtain appropriate evidence. There is no one-size-fits-all method and one should choose the method that best fits the enquiry.

Health management business models

Telemedicine stakeholders should all be actively involved in the development of the reimbursement models. When significant effectiveness results on a macro level have been proven in phase 3 of the HMP, the next step is to create a healthy business case to support the full implementation of the telemedicine service. The interested parties together establish a price for the use of the telemedicine service and predefine the performance indicators required for reimbursement. These performance indicators may entail health outcomes as well as logistic outcomes. To assure successful full scale implementation in regular care, active support and marketing from all stakeholders should take place.

The biggest barrier, as mentioned earlier, is the availability of a working budget and for reimbursement. It is up to government, insurers, and relevant parties to work toward the contracting of innovative health care services. Indeed, provided that sufficient funds are available, the following six topics may facilitate the safe and expeditious introduction and implementation of telemedicine services and should already be taken into consideration when starting phase 1 of the HMP (Witkamp 2016).

Societal business case

Providers of telemedicine have demonstrated that their services lead to better, faster care, closer to the patient and at lower cost in phase 1, 2 and 3 of the HMP. Health insurers should not hesitate to compensate promising services, even if the effect in the long-term is likely, but not certain.

Business case stakeholders

Telemedicine providers should ensure that all stakeholders of the telemedicine service experience benefits. Examples of such benefits are the patient receiving very fast feedback through teleconsultation instead of waiting and travel time, the general practitioner experiencing a learning effect that improves the quality of health care they provide, the medical specialist strengthening professional relations with local GPs in the region and having higher job satisfaction, and the hospital benefiting through improved adherence (Witkamp 2016).

Low-hanging fruit

Parties should scale telemedicine services for simple routine care processes that have already been proven and already have been implemented in exemplar regions in phase 3 of the HMP. These services so far have the largest proven social benefit when scaled up, because routine care processes tend to deal with large numbers of patients resulting in high impact.

Current reimbursement system

Parties should stop identifying existing compensation system as an obstacle to telemedicine implementation. Telemedicine services are a redesign of existing care processes. Thus, within existing laws and regulations, all telemedicine services can and will be reimbursed.

High-quality care in the second line

Parties should reduce benefits for simple routine professional care and increase fees for the care of complex, and serious problems. This allows simple routine care to be redesigned and transferred to primary care under the supervision of medical specialists who, in part, have the ability to free up time to deliver care for which they are trained.

Admission

A system is needed where a central body evaluates new telemedicine services and approves them for admission, which, in turn, compels the health insurer to reimburse.

Health management implementation

Challenges and barriers on the road to a successful telemedicine service implementation can be overcome when a care institution, department within a care institution, or a commercial company acts as a dedicated telemedicine provider, thus offering a single organization that lobbies for telemedicine services, manages the complete telemedicine service implementation, acts as the point of contact for patients, care professionals, and other actors such as government and supervisory bodies. The responsibilities and tasks that a telemedicine provider should incorporate during phase 3 and 4 of the HMP to set up a telemedicine service are:

- Administration, registration, and storage of clinical records.
- Negotiating sustainable reimbursement with health care insurers.
- Handle claiming and crediting incorrect claims.
- Imbursement of involved actors (e.g., specialist, general practitioner, telemedicine provider staff).
- Providing clinical liability insurance specifically tailored to telemedicine procedures.

- Providing a telemedicine software platform and keeping it up-to-date in concordance with the latest security standards, legislation, and regulations.
- Providing suitable hardware for telemedicine procedures (e.g., smartphones, diagnostic equipment).
- Acquiring or enforcing the required certifications on quality and safety (e.g., ISO, CE).
- Providing continued medical education-accredited training programs for medical staff.
- Providing project management for telemedicine implementation in a region.
- Providing a helpdesk service for technical and administrative issues.
- Providing yearly reports on performance indicators (e.g., per clinic).
- Providing integration with electronic health records (EHRs) from all involved parties.
- Negotiating and developing communications standards together with EHR providers and other (governmental) actors.

Best practices from The Netherlands

In The Netherlands, the largest telemedicine provider is the KSYOS Tele Medical Center. Founded in 2005 as a health care organization, KSYOS contracts with more than 11,000 health care professionals—6000 general practitioners, 2500 medical specialists, and 2500 paramedics—and delivers care to over a 1000 patients every day: it is the largest health care organization in The Netherlands that solely delivers health care by intelligent internet: i.e., telemedicine. KSYOS has implemented various somatic and mental health telemedicine services using the HMP model, e.g., teledermatology in 2005, teleophthalmology in 2007, telecardiology and telepulmonology in 2009, and eMentalhealth in 2014.

In the following sections, we discuss the KSYOS general telemedicine processes in patient care and several telemedicine service implementation results of teledermatology, teleophthalmology and telemental health.

General KSYOS workflow

Most of the telemedicine processes implemented follow a standardized workflow that is divided into sub-processes, e.g., teleorder, tele-examination, telemonitoring, teleconsultation, and telereferral. Note that not all sub-processes are used in every field and a new patient can start at any of the sub-processes (Fig. 1). A health care provider (often a GP) orders an examination (e.g., ECG, spirometry, bloodwork, retina photo) through the teleorder system. Examination-specific inclusion criteria can be added. The patient then goes to the location where the examination is performed by a biometrist. This can be at the GP practice, but also in a local shopping mall at an optometrist store or at a medical diagnostic center. All biometry is stored and can be accessed online through the secured online KSYOS electronic patient record as PDF, video, or image files accompanied with examination-specific findings. These examinations are assessed by a grader, who can be the same actor as the biometrist but can also be at a different place and time; thus, the patient does not need to be present for the grading. The grader can be a specialist or a paramedic

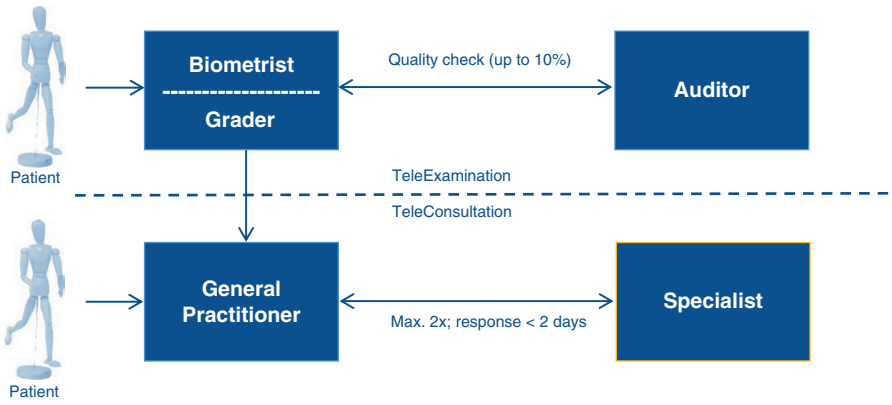

Fig. 1: KSYOS workflow for tele-examination and teleconsultation.

analyst trained specifically for this task. The results (biometry and grading) are presented to the GP who ordered the tele-examination. If an abnormality is found, then the GP can decide to refer the patient physically using a telereferral or to send a teleconsultation request to the regional specialist along with all the data received from the tele-examination, all from within the KSYOS Electronic Patient Record. Additionally, the system selects about 10% of the tele-examinations at random for anonymous auditing, where a specialist reviews the quality of the biometry and grading anonymously. The biometrist and grader thus receive feedback on their work.

Teledermatology

Teledermatology does not utilize a tele-examination process and only uses teleconsultation between the GP and dermatologist. Since 2006, the use of teledermatology has increased every year. By mid-2016, over 3600 general practitioners had performed one or more teleconsultations. Since its introduction in 2005, over 135,000 teledermatology consultations have been performed (Van der Heijden *et al.* 2011).

Of the 14,897 teledermatology consultations in 2015, 2 evaluation questions posed to the GPs were completed for 10,305 teleconsultations (Van der Heijden *et al.* 2011). The first question (Q1), "Would you have referred this patient if a teledermatology consultation were not available?" was asked before starting the teleconsultation. The second question (Q2) "Are you referring this patient to the dermatologist?" was asked when the teleconsultation was closed by the GP. Comparing the responses (both questions were answered with YES or NO) to these two questions showed for each teleconsultation if a physical referral was prevented (a prevented referral was counted when the answer to Q1 was YES and to Q2 was NO). The responses showed that 69% of teledermatology consultations were performed to prevent a physical referral (Q1 = YES, N = 7150) and, in this group, ultimately, 70% of the referrals to the specialist were prevented (N = 5021). In addition, 31% of the teleconsultations was performed to obtain specialist advice (Q1 = NO, N = 3155). Within this group, 20% were referred to the dermatologist through a

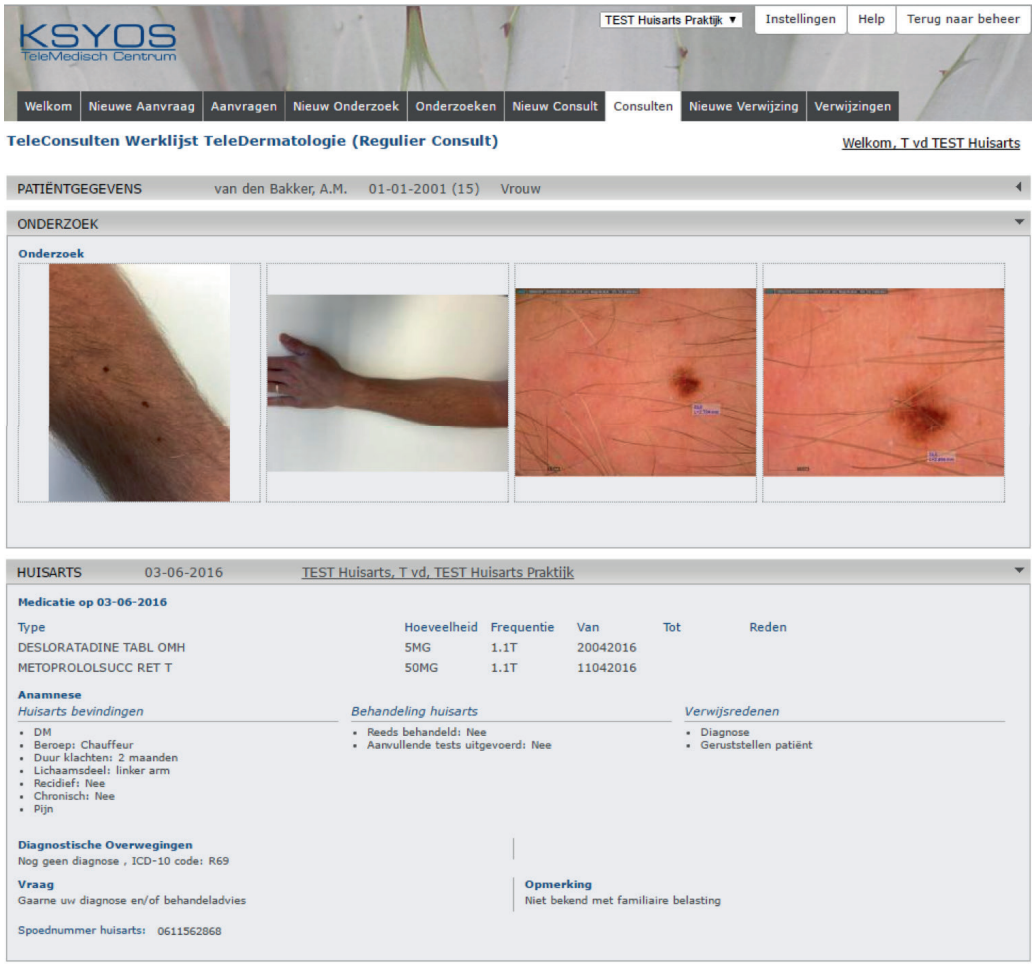

Fig. 2: Screenshot of a KSYOS teledermatology consultation.

fast-track process, which improved the quality of care for these patients (Fig. 2). The average response time for the dermatologists was 5.4 working hours. These results are consistent in all evaluations over the last years and hold true for all 135,000 teledermatology consultations (Van der Heijden *et al.* 2011).

Apart from preventing unnecessary hospital visits, teledermatology has a significant learning effect on the GP due to the immediate answers received. This leads to better care by the GP over time. After five years of active teledermatology, the GP performs 60% fewer teleconsultations compared with their first year due to the learning effect (Van der Heijden *et al.* 2011). Moreover, these GPs refer 30% fewer patients to the hospital compared with colleagues who have never done teledermatology, also due to the learning effect. By avoiding immediate referrals, teledermatology has realized a cost saving effect of 18% (Van der Heijden *et al.* 2011). However, the

savings attributed to prevented referrals to secondary care by the learning effect over the years vary between 40% and 60% (Van der Heijden *et al.* 2011).

Teleophthalmology

There are several teleophthalmology examination processes. The telefundus screening (TFS) process, which refers to the screening of type 2 diabetes patients for diabetic retinopathy. The other teleophthalmology examination processes are focused on other eye diseases such as cataract, macular degeneration, and glaucoma. The optometrist performs eye examinations on own indication or after an order by a GP. The eye examination includes medical history, refraction, tonometry, and fundus photography. The GP can send tele-examination results to a regional ophthalmologist for teleconsultation (Fig. 3). Around 50,000 TFS are performed annually through the

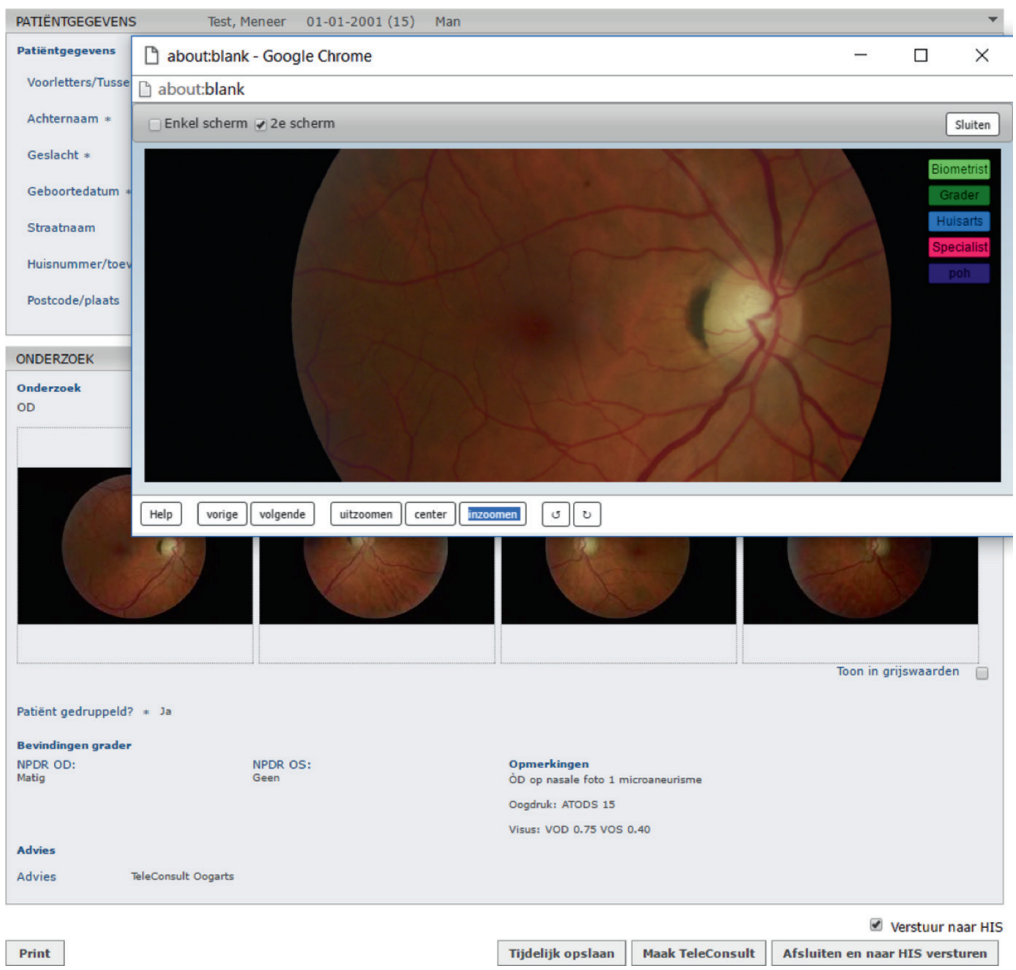

Fig. 3: Images from a KSYOS teleophthalmology examination.

KSYOS Tele Medical Center, which, to date, has performed 204,037 screenings (Van der Heijden *et al*. 2011). These patients have their retina photographed at local shopping centers in optometrist stores, at GP practices, or medical diagnostic centers instead of going to an ophthalmologist at a regional hospital. Twelve percent of TFS are converted into a teleophthalmology consultation with a regional ophthalmologist due to a positive grading for retinopathy. After teleconsultation, only 40% of patients are actually referred to the hospital (Van der Heijden *et al*. 2011). Because of teleophthalmology, only 4% (instead of 100%) of type 2 diabetes patients visit an ophthalmologist (Van der Heijden *et al*. 2011).

Telecardiology

Telecardiology consists of two types of tele-examinations (telecardiology rest ECG, or TCER, and telecardiology event ECG, or TCEE). Both examinations can be converted to a telecardiology consultation (TCC) with the regional cardiologist. Depending on the clinical context, a GP can give patients a TCER on the spot or the GP can record the cardiac rhythm continuously for 24, 48, or 72 h (even up to 7 or 14 days in a TCEE). Unlike conventional event diagnostics, the advantage of continuous recording is that asymptomatic clinically relevant arrhythmias are indeed registered (for example, paroxysmal atrial fibrillation). Since 2009, there have been 56,803 TCERs performed and, since 2013, 12,137 TCEEs have been performed. Respectively, 65% and 7% of TCERs and TCEEs were converted to a telecardiology consultation (Van der Heijden *et al*. 2011). Looking at efficiency improvement indicators, in 46% of all TCER consultations and 86% of all TCEE consultations, the GP intended to refer the patient physically to the cardiologist if teleconsultations were not available (Van der Heijden *et al*. 2011). In these groups, 59% and 49%, respectively, of these referrals were prevented following a teleconsultation. The groups were teleconsultation was used to obtain advice (TCER: 54%, TCEE: 14%) there was a physical referral in 20 and 30% of the cases, respectively. This led to quality improvement as these patients now received advice from the cardiologist and were physically referred on the request of the cardiologist. The average response time by cardiologists was 5.4 working hours (Van der Heijden *et al*. 2011).

TeleMental health

This telemedicine service consists of four components: (1) a psychometric tele-examination delivered to the patient as an online questionnaire. The answers are put through an algorithm to analyze the severity of the mental health complaint and to provide advice as to what echelon of care the patient should receive; (2) a blended-care telemonitoring tool, offering 30 programs to treat mild cases of mental disorders (e.g., depression, burn out, stress, insomnia) through online courses utilizing videos, animations, and exercises while also providing online contact with the health care provider; (3) teleconsultation services for GPs to gain advice on treatment and medication from, e.g., child psychologists, psychiatrists, and addiction physicians; and (4) a telereferral system to secondary mental health care facilities.

Since its implementation in early 2015, around 1300 GPs have used this service, over 8500 patients have completed the online psychometric tele-examination, and over 17,500 patients have followed an online blended-care program (mostly the burn-out, stress, panic, and mindfulness programs) (KSYOS Research 2016). In both services, the patient is an active actor in the telemedicine process and has logged into a telemedicine system at least once. On average, patients logged into the system nine times per blended care treatment, scored their treatment through a blended care program with an average of 7.7 out of 10 points, and 61% of patients reported a decrease in or even complete disappearance of their symptoms. The health providers using the blended-care programs in their treatment reported that in 20% of cases they needed fewer physical consultations compared with standard treatment and in 26% of the cases they used the same number of physical consultations but felt they provided a higher quality of care (KSYOS Research 2016). In 8% of cases, physicians reported using more physical consultations, whereas the other 46% of cases were reported as "I don't have this knowledge" (KSYOS Research 2016).

Concluding remarks

We are faced with a big challenge to make our health care systems ready for the surge of patients and demands in the coming years. Redesigning our health care processes using new and innovative technologies can help us prepare for that. We should also be aware that when doing so, it is best to aim for those processes that have a routine and simple character, but high turnaround rate, the so-called "low-hanging fruit."

Based on the outcomes of the Dutch telemedicine services introduced by KSYOS, focusing on redesigning these sorts of processes can yield positive results in efficiency, quality, and cost. They have already treated 450,000 patients through their teleorder, tele-examination, teleconsultation, and telemonitoring services in the last 10 years. As far as we know, this is the largest implementation of fully reimbursed telemedicine services in a regular health care system in the world. Results show a 70–96% reduction in hospital visits in dermatology and ophthalmology, which translates into an immediate cost reduction of 18%. The response time of 4–5 working hours and the learning effect also have a significant impact on the quality of care delivered. Telemonitoring programs in mental health have demonstrated that the patient as an active actor can result in motivation and ownership of their own health. These results pave the way to similar positive psychology-based blended-care programs in somatic care, especially for lifestyle adjustment in patients suffering from diabetes, chronic obstructive pulmonary diseases, and cardiovascular diseases.

Telemedicine will make it possible for hospitals to concentrate on high-quality specialized care. In many peripheral centers in residential areas, e.g., general practitioner centers, pharmacies, optician stores, physiotherapy centers, and others, more routine care services will be delivered close to the patient by paramedics, caregivers, and the patients themselves under the direction and supervision of the general practitioner and medical specialist at a distance—and at a fraction of the price. This process is not only irreversible in health care, but also necessary to continue to meet the changing and increasing demand. Telemedicine services (and e-health instruments in

a broader sense) are promising and proven telemedicine services are widely embraced by health care providers and patients. The only barrier to scaling up these services is the availability of a budget within regular compensation systems. That obstacle must be removed as soon as possible.

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6

Patient-centric strategies in digital health

Larry F. Chu, Ashish G. Shah, Dara Rouholiman, Sara Riggare, Jamison G. Gamble

Abstract

It is important to consider that the goal of digital health is to improve the experience of the patient as they traverse the health care system and to ultimately improve their health outcomes. In today's fully connected and digitally integrated world, patients, not providers are the rising stars in digital health innovation. Working from their own experiences and expertise, patients are leading the way in design innovation of novel digital health technologies. As patients become more and more connected, providers must keep up with their patients by utilizing the same technology as their patients. By doing so, providers create a foundation for participatory medicine, levelling power hierarchies and making patients feel comfortable and welcome throughout the process of their care. This chapter explores patient centric strategies in digital health and outlines the foundation of the Everyone Included™ initiative.

Keywords: Precision medicine, Physician-patient relations, Patient-centered care, Patient outcome assessment, Diffusion of innovation, Connected doctor, Everyone included, Participatory medicine, Shared decision making, Digital health

"Nothing about us without us": The value of patients in digital health design

The success of digital health tools and solutions depends on patient participation and engagement. By failing to recognize the value of patient engagement, a number of digital health tools have seen low sale rates, loss of product traction, and a low rates of product adoption by intended users. By

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directly engaging patients and incorporating them into the design process of digital health tools, valuable insight can be gained by developers. Taking the time to understand the needs of digital health tool end users, better digital health tools can be developed that more precisely address the needs of intended users.

The concept of "nothing about us without us" was first brought to light by disability rights activists in the late 1990s who believed that policy involving the disabled community should be co-created with input from the very community it was designed to impact (Delbanco *et al.* 2001). Recently, the expression "nothing about us without us" has been adopted by patient communities seeking broader involvement with the health care system (Paul 2016; Schiavo 2014). This concept has moved into almost every corner of health care, from shared decision making in health care to medical conferences (Chu *et al.* 2016). "Nothing about us without us" also applies to the design of digital health tools which are intended to improve both patient experience and health outcomes.

The creation of novel digital health tools can be thought of in three pathways of patient involvement (Fig. 1). In the first pathway, a digital health tool is designed, implemented and validated without any patient involvement. The patient provides input once the device has been released into the market. In the second pathway, patient thoughts, opinions and needs are assessed during the design phase of the digital health tool through focus groups. In this pathway, the digital health tool is developed based on the current needs of the population it is trying to impact. In the third pathway, the patient is brought in as a member of the team and co-creates the digital health tool. By utilizing the third pathway, patient expertise and knowledge surrounding their specific needs can be incorporated into the design process leading to more innovative and creative solutions. Many patients are now taking this process into their own hands, creating digital health tools to meet the specific needs of their particular community.

Digital health is thought to spark innovation in health care by providing better tools and solutions which empowers the end-users, patients and providers. Development of any new innovative solution and tool goes through the iterative design process. Iterative design is a methodology based on a cyclic process of ideation, implementation, and validation.

Iterative design begins the innovation process with ideation, working with your community to uncover problems and design solutions to address them. The process continues by implementing the solution in an organization or a targeted population. Validation comes in the innovation

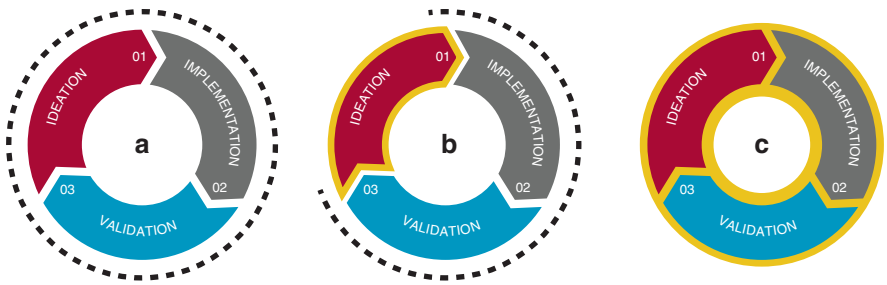

Fig. 1: Three pathways of patient-centric digital health innovation. (**a**) The patient is not involved in any phase of design. (**b**) Patient thoughts, opinions and needs are assessed during the ideation phase. (**c**) The patient co-creates as a member of the design team.

process after implementation to test the efficacy of the solution and measure the strengths and shortcomings of the solution.

By turning issues inside out, and bringing all stakeholders to the table at the beginning, we have created a targeted, innovation-focused approach that embraces and expands the contributions of all, that brings elite entrepreneurs and researchers together with empowered patients to create solutions that solve problems, rather than generating solutions in a search of problems. The infinite loop of refinement helps to generate digital health solutions that are effective and efficient and in which all stakeholders are invested. From designing a wearable device to designing a mobile application, including patients in the design process of digital health tools can be manifested in various ways.

How patients are leading the way in digital health

After passing out on a train platform and receiving a diagnosis of hypertrophic cardiomyopathy, Hugo Campos's life was forever changed. Campos was considered at high risk for sudden cardiac arrest and was fitted with an implantable cardioverter-defibrillator (ICD). As his condition slowly took over his life, he realized that he needed to learn as much as he could about his condition so that he could have educated conversations with his care team. What he really wanted was access to the data that was being collected by his ICD to help guide his interactions and better empower his decisions.

The story of Hugo Campos perfectly illustrates the concept of an empowered patient (ePatient) defined as a patient who is engaged and actively participates in their own treatment and health. The term ePatient was first used by Dr. Tom Ferguson to describe individuals who are equipped, enabled, empowered and engaged with their health care (Ferguson 2007). The ePatient journey begins with the search to truly understand themselves and their own health. Hugo Campos is one of the many ePatients who are redefining health care and redefining our thinking of how technology can be used to redefine the doctor-patient relationship. Digital health is increasingly being advertised as a means to facilitate patient empowerment, engagement and innovation (Frist 2014; Birnbaum *et al.* 2015; Steven and Steinhubl 2013).

In 2016, 15% of consumers in the United States utilized wearable technology and 46% of consumers were active digital health adopters, a 27% increase from 2015 (Terry 2016; Piwek *et al.* 2016). Pathway C, patient-co-created innovation illustrates a radical transformation in the digital health development sector. Movements like The Quantified Self (QS) and #WeAreNotWaiting are examples of such transformation. The Quantified Self movement promotes individual engagement in self-tracking and analyzing of self-data, with the goal of improving individuals understanding of their bodies and needs to make more informed decisions. The frustration of the type 1 diabetes community stemming from a seeming lack of urgency by the health care industry to utilize digital health tools in monitoring and treating their condition led to the #WeAreNotWaiting movement. The message of the #WeAreNotWaiting movement as described by ePatient Dana Lewis states "we can't wait years and years for better tools and solutions, so we will do everything we can to make today easier." Dana Lewis, who has had type 1 diabetes for over 15 years, started using open-source code to get access to her continuous glucose monitor (CGM) data and make louder

alarms for herself. She then utilized other open-source code and commercially available hardware to create a do-it-your-self "artificial pancreas", which was not commercially available for several years after that. In 2015, Lewis launched #OpenAPS, an Open Source Artificial Pancreas System movement for improving access and availability of a hybrid closed loop artificial pancreas system for people with type 1 diabetes (Lewis and Leibrand 2016). Existing digital health tools often fail to address some of the most important and immediate needs of patients and doctors.

Michael Seres experienced this first hand after undergoing only the eleventh small bowel transplant in the United Kingdom. As he recovered, he was required to wear an ostomy bag allowing his bowel to heal. The bag, which is used to collect waste from the intestine, must be changed and monitored manually, a significant burden to patients with a stoma. While still recovering in the hospital, Seres used a Nintendo Wii™ sensor, a battery, and a motherboard to build his very own sensor that would alarm to warn him when his bag was filling up. Today, Michael Seres has turned his sensor into a viable product with FDA approval to improve the lives of ostomy patients such as himself.

Sara Riggare, a Swedish engineer, experienced her first symptoms of Juvenile Onset Parkinson's disease when she was 13 years old. Today, Riggare is pushing the inclusion of patients on all levels of health care and research while pursuing a doctorate in health informatics at Karolinska Institutet in Stockholm. Riggare's research is centered around what she calls "digital selfcare", which includes the way she uses self-tracking to manage her disease and communicate with her physician but also making use of the knowledge that can be found online (Riggare and Unruh. 2015, Riggare *et al*. 2017).

Campos, Lewis, Seres, and Riggare all have one important thing in common, they don't accept the status quo, they engage, learn, and create what they need to improve their health.

There is a power shift happening in health care which Eric Topol, a cardiologist, geneticist and digital health researcher calls the "Democratization of Medicine", a grassroots movement where patients are developing solutions to their own health problems instead of waiting for the slow moving scientific and medical community (Topol 2015). Patients understand their needs, their own bodies, and have a vested interest in their own health care. Digital health technologies must give patients direct access to personal data that can contribute to their understanding of their health and facilitate preventive care.

Participatory medicine: A successful collaboration of patients and providers through digital health

At the heart of patient-provider communication is the concept of participatory medicine or shared decision making (SDM) which is centered around an open dialogue between patients and providers, where patient's thoughts, opinions and personal expertise are taken into consideration when making clinical decisions. As of 2011, the concept of SDM was supported by 86 randomized clinical trials which suggest SDM increases patient involvement in their health care, increases knowledge gained by patients, increases patient's confidence in decisions and suggests that when SDM is utilized patients often opt for more conservative treatment options (Stacey

et al. 2011). Participatory medicine is naturally supported and promoted through digital health technologies such as electronic health (eHealth) and more specifically mobile health technologies (mHealth) which promote ease of communication and sharing of information between providers and patients via portable diagnostic devices. mHealth technologies can be classified into five categories: smartphone-connected devices, smartphone health applications (apps), handheld imaging devices, wearable and wireless devices and miniature sensor technologies (Bhavani *et al*. 2016).

mHealth technologies are the vital link between the digital patient and the digital clinician and provide a foundation for participatory medicine. From the patient perspective, mHealth technologies facilitate patient self-measures which generate patient specific data and promote behavior modification and patient engagement and participation. Data collected by mHealth technologies from engaged patients can then be transmitted in real-time to providers or stored in the cloud to generate a big-picture of health parameters or to identify individual health concerns. Examples of such technologies include the Withings™ Blood Pressure Monitor, the Sanofi iBGStar® Blood Glucose Monitor, and the AliveCor® Mobile ECG. Data collected by these devices can be stored on the patient's smartphone for later review by a clinician or can be transmitted in real time directly to a clinician for immediate review or to be stored in the patient's electronic health record (EHR). Use of these devices promotes participatory medicine by allowing the patient to collect their own personal health care data and share it with the clinician and have also been shown to improve behavioral health outcomes in motivated patients.

While the majority of mHealth devices are aimed at general health outcomes, a number have been designed to address specific health concerns or specific patient populations. An example of such a device is the Ostom-i™ alert sensor developed by 11 Health and Technologies Limited. The Ostom-i™ alert sensor is a smartphone linked device which attaches to an Ostomy bag and alerts the user to the fullness of the bag. Data collected by the Ostom-i™ alert sensor is uploaded onto the user's smartphone which can then be sent directly to providers for their reference. These devices directly engage patients and act as a tool to promote and facilitate patient engagement with their own health care. Furthermore, digital health technologies provide patients with data and knowledge surrounding their specific condition or general health which allows them to act as an informed participant while interacting with care providers.

The future of participatory medicine facilitated by digital health technology will need to incorporate patient input and participation with providers across multiple disciplines. Future technologies such as the "GoalKeeper" system are already being formulated to meet these needs (Amir *et al*. 2014). The proposed function of the GoalKeeper system is to facilitate communication and implementation of care plans between providers and parents of pediatric patients with complex conditions. The GoalKeeper system will allow parents of children with complex conditions to participate in the design of care plans and relies on status updates provided by parents. This system will directly engage parents of pediatric patients and allow them to directly participate in the care of their child. The GoalKeeper system will use artificial intelligence (AI) to decide how changes in one providers care plan will affect the care plan of other providers. The AI decides which providers will be affected by changes in care plans and choses when and to whom these changes will be reported to. While the GoalKeeper system will only used for parents of children

with complex conditions, the technology has potential to be used across multiple patient populations to directly engage patients and allow them to participate in collection of health care data as well as to participate in decision making.

Social media and online communities of patients and providers

Social media and its role in the dissemination of ideas and information has impacted not only the health care system, but a myriad of other industries. Today, ePatients use Twitter, Facebook, YouTube and countless other social media networks rather than the peer-reviewed journals and academic conferences to learn and disseminate new ideas and information. Social media is defined as a computer-mediated tool that enables users to disseminate, collect and share information, ideas, pictures, and videos instantly in virtual communities (Thompson 2015). It provides an inclusive podium where both clinicians and patients benefit from each other's expertise and perspective by disseminating, collecting, and reacting to information that can instantaneously reach and affect millions of people worldwide.

Despite the fact that clinicians remain the top information source in health care, about twenty-five percent of adults in the United States turn to their peers with similar health condition for information and advice (Fox 2011; Landro 2016). A study among people with Parkinson's disease in Sweden showed that even in a generally older community (median age = 68 years) as many as 36% found their knowledge about Parkinson's online (Riggare *et al*. 2017). Social media gives patients and providers access not only to information and data, but to one another as well. In other words, social media provides a communication platform which broadens our social networks. Today, there are 137 recurring weekly tweet chats, 17,862 chat participants and 66,560 chat tweets pertaining to health care (Audun Utengen n.d.). The dispersion of medical information and advice is no longer limited to the traditional boundaries of doctors' offices and hospitals but has now expanded to incorporate the ePatient community.

Social media fosters engagement between clinicians and patients in real time. Today, Hugo Campos still does not have access to the data collected by the device implanted in his chest; however, he can use a single lead ECG attached to his smartphone to share his electrocardiogram with his social network in near real-time. This is exactly what he did when he began to feel a fluttering sensation in his chest. Minutes after sharing his ECG results on Twitter, the cardiologists in his social network helped him understand his ECG reading within the context of the symptoms that he was experiencing. This illustrates the power of social media, instant access to information and data needed to make an informed decision. Social media has empowered patients by leveling the traditional information hierarchy, placing patients and physicians on level ground and connecting providers directly to patients in real time.

The connected doctor

In today's world of hyperconnectivity, the field of medicine must stay on the cutting edge of the communication revolution. How is a connected doctor defined in our dynamic world of

communication technology? At its foundation, a connected doctor may simply be defined as one who utilizes EHRs to write notes and enter data. EHRs were first introduced to the medical community in the 1960s and 1970s and became commonplace around the start of the new millennium (Atherton 2011). In 2011, 57% of physicians reported utilizing EHRs, a 39% increase from 2001 (Analisys Group 2014). As communication technology grows, so to must the connected doctor. Today, simple use of an EHR is not enough to define a connected doctor. Instead, the connected doctor is defined within three parameters: (1) what they are connected to (EHR, online portals, mobile health applications), (2) who they are connected to (patients, the online community, hospitals, peers, consultants), and (3) how they are connected (internet, smartphones, messaging, mobile health platforms).

While the connected doctor may be thought of as an inevitable happening bringing about great improvements in shared decision making and the ePatient community, it may increase physician burnout rates. In 2011, 45.5% of physicians were found to have symptoms of burnout which increased to 54.5% by 2014. These rates of burnout are higher than are seen in other non-medical occupations (Shanafelt *et al.* 2015). During this period of increased physician burnout, the use of EHRs increased significantly leading to more time spent on the EHR by physicians (2 h of EHR reporting for every 1 h spent with a patient) (Villares 2016). Physicians are then expected to complete an additional one to two hours of patient-related clerical or EHR work. Furthermore, it has been suggested that physicians are dissatisfied with EHRs which in turn promotes physician burnout (Shanafelt 2016).

While EHRs facilitate improved documentation, order entry, patient safety and improve the billing and reimbursement process, they do not facilitate communication between patients and providers but rather between physicians and the hospital administrative system. Physicians primarily connect to their patients via online portal systems where patients can communicate directly with their providers and have direct access to lab results and other metrics. With the recent advent of mHealth devices and mobile health platforms, providers have direct access to a massive quantity of outpatient health data such as blood pressure, temperature, exercise and diet. Providers may join online patient communities and provide disease-specific or general health related information to an entire community of patients. Provider-to-provider communication is facilitated by secure, encrypted messaging allowing for easy consults or second opinions. While peer-to-peer interactions are incredibly important for provider communication and decision making the use of artificial intelligence (AI) is becoming a stronger presence in clinical decision support. As the field of precision medicine continues to grow, AI will begin to play a larger role in health outcome predictions allowing providers to treat patients in a preventative manner.

Imagine now the future of the connected doctor. Before a doctor sits down with their patient in person, AI will browse the patients EHR extracting information on allergies, medications, previous hospitalizations and other pertinent health information. The AI system will then incorporate the most current health data such as vital signs and information from health-related questionnaires directly into the EHR for the day's visit. As the doctor has been communicating with the patient via the online portal the reason for the visit is already understood. Once the patient-provider visit begins, information learned during the session is automatically incorporated into the

EHR by the AI system instead of the provider. As the provider begins the physical examination, images from connected smart glasses worn by the provider are automatically entered into the EHR and processed by the AI. Medical devices such as the stethoscope are fully connected and integrated into the system and can provide data directly to the providers' handheld smart tablet aiding in their diagnoses. The AI system will evaluate this new information and incorporate it into the EHR with previous data offering a differential diagnosis and providing recommendations for labs and other tests, to be verified by the provider.

As mHealth devices and AI become more prevalent, inpatient medicine will likely change as well. Imagine a patient suffering from congestive heart failure who has been in and out of the hospital due to fluid build-up in the lungs. With an appropriate sensor, a warning can be sent to the medical team alerting them to the fluid buildup. Patients with chronic conditions requiring an indwelling catheter to drain urine often suffer from urinary tract infections. Future sensors may be incorporated into catheter systems with the purpose of detecting bacterial buildup. If bacteria is detected within certain limits, an alert can be sent to the medical team recommending they prescribe a course of antibiotics. Both of these scenarios may prevent extended hospital stays and improve longitudinal health outcomes.

There is no doubt that physicians are becoming increasingly connected. It is important to define the connected doctor as more than just an active use of the EHR. A doctor is truly connected when the EHR provides information back to the physician, when they are constantly connected to their patients through data sharing and a direct line of communication, and when they can send digital information to experts around the world for second opinions. It is also important to recognize that there may be unintended consequences to becoming a fully connected provider. As physicians become more connected, the applications and platforms must be designed to improve work flow and efficiency. With these factors in mind, the future of the connected doctor looks very promising.

The Everyone Included™ initiative

In the short time patient-centered care has been recognized as a key element in providing a high level of quality care, there has been a coordinated effort to expand patients' role in their health care. A leading example of this concerted effort has come from the Everyone Included™ initiative. Everyone Included™ is a living framework for health care innovation, implementation and transformation based on principles of mutual respect and inclusivity.

> "*The first step is to identify the ultimate stakeholder–the patient–and then reach out and talk to them. Patients and families are eager to partner. We want to help. We want to be part of the process and we want to be there every step of the way. We want to help set strategic priorities, we want to co-design and co-produce studies, we want our expertise and insight to be valued as the essential part of the team that it is–and we also want our unique offerings to be harnessed to make health care better for us and everyone*"
>
> – Emily Kramer-Golinkoff, ePatient

Digital health like other medical innovations sectors requires validation in the form of empirical research. Everyone Included™ provides a framework for medical research that shatters the silos between researchers, diseases, and stakeholders. Emily's Entourage (EE) is an organization that has been utilizing the Everyone Included™ model to fast track research for new treatments and cures for rare nonsense mutations associated with cystic fibrosis. To achieve a breakthrough in time to save Emily Kramer-Golinkoff, a CF patient who founded Emily's Entourage, and others with nonsense mutations of CF, close collaboration between scientists, patients, clinicians, venture capitalists, and many more is required. Emily's Entourage is an example of an organization that brings successful innovation to health care utilizing the principles of Everyone Included™.

Everyone Included™ is the result of collaboration between patients, caregivers, providers, technologists, and researchers which has led to the formation of design and leadership principles intended to drive health care innovation efforts. It formulates a culture in which individuals are trusted and respected for the expertise they bring, openness and experimentation is the norm, people have personal ownership of health, individual stories have global impact, and the voice and choice of patients is a part of all stakeholder decisions. The value propositions of Everyone Included™ can be applied towards digital health innovation and include five elements: build trust and respect, create a shared mindset for change, produce more innovative and creative solutions, create a shared culture of health and identify problems that matter most (Fig. 2). The creation of digital health solutions requires a collaborative input from all major stakeholders, especially patients. There must be a mutual trust between providers, developers, users and patients to identify the core problems and produce creative solutions.

To accomplish this, the Everyone Included™ initiative has identified six leadership principles which can be implemented into a variety of patient centric design modules. The first leadership principle is "believe in respect, not power hierarchies", this leadership principle aims to break down the walls of traditional power hierarchies which limit creativity and fail to incorporate unique, individual expertise which patients and other stakeholders bring to the table. This is not

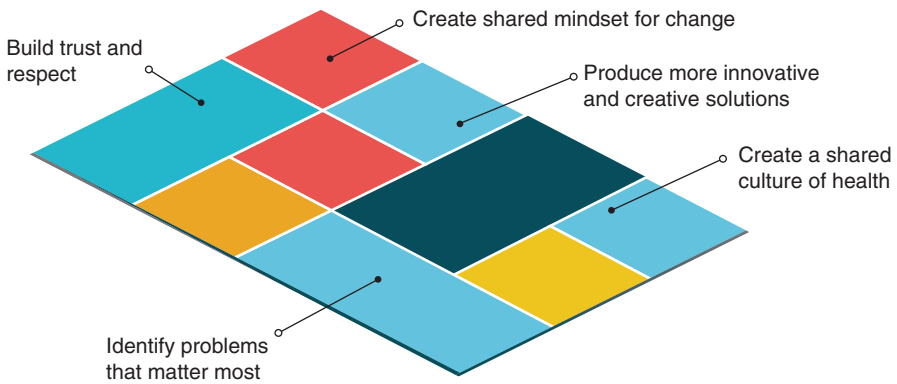

Fig. 2: Everyone Included™ value propositions.

to imply that hierarchies should be eliminated completely, but rather the power that comes along with hierarchies should be equalized amongst all participants. Second, "leadership can be flexible", this means that leaders respect and incorporate opinions and input from a variety of within team sources while simultaneously remaining true to the vision of their organization. Furthermore, leaders should consider themselves as the center point of a wheel instead of the top of a pyramid. Third, "diverse teams lead to more creative solutions", by creating a team of diverse individuals with different backgrounds and areas of expertise, we believe that more innovative and creative solutions can be reached than if a traditional pyramidal power hierarchy is utilized. Fourth, "diversity requires considerate leadership", a considerate leader within a diverse team keeps the collective "we" in mind while simultaneously recognizing the value, expertise and creativity that diverse teams bring to the table. A considerate leader will also mitigate misconceptions that arise around power and respect, motivating individuals to contribute to their fullest potential by distributing power equally and displaying mutual respect for all team members. Fifth, "create a culture of empathy and consideration", misconceptions and misperceptions inherently accompany diverse teams, however, a considerate leader will create an environment which values taking the time to understand the perspectives and opinions that each team member brings to the table. A considerate leader will foster an environment which addresses the physical and emotional well-being of each team member within a diverse team. The sixth and final leadership principle of Everyone Included™ is "recognize the value of conflict, but reduce its risk". Task conflict is a natural part of team work and if managed properly can lead to more creative solutions by taking alternate viewpoints into consideration.

With careful consideration of the Everyone Included™ initiative, digital health design should follow the third pathway (pathway C) model of ideation, implementation and validation, partnering with ePatients throughout all three steps. The three design steps are further defined as: Ideation; begin the innovation process by working with your community of health care stakeholders, designers, technologists and researchers to uncover problems matter most in your domain or problem area. Focus on designing for problems that matter most through co-design with relevant health care stakeholders using the Everyone Included™ co-creation and leadership principles. Rapidly iterate to optimize your design plans with a diverse team.

Implementation; the best design plan can fail without proper implementation strategies. Work with your team to optimize your plans for implementing change within your organization to avoid pitfalls using Everyone Included™ to anticipate and plan for challenges. Validation; the most important part of any innovation is the measurement of success that tests the effectiveness of the solution.

Conclusion

By placing an emphasis on patient centrism in digital health, power is put back into the hands of patients and traditional power hierarchies are lowered allowing patients to feel like a participant in their personal health care experience. Through patient involvement in the design of digital health tools, to facilitating shared decision making, collaboration with patients can spark creativity,

innovation and the creation of novel digital health tools which more precisely address the issues patients are experiencing. By utilizing Everyone Included™ as a framework for patient inclusion, providers, designers and researchers alike can elevate patient voices to ensure that patients are heard as a valuable and equal member of the health care team.

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Notes:

Notes:

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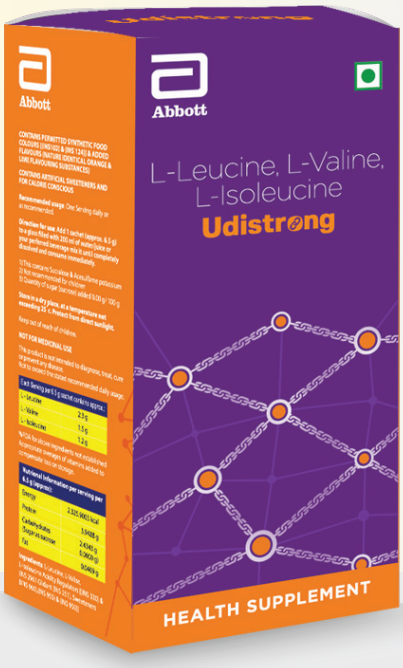
For registered use of medical practitioner, hospital or laboratory only

Support the treatment in your HE patients.

Udistrong

L-Leucine, L-Valine, L-Isoleucine

Recharge Life



BCAA support recommended by

AASLD[1] EASL[2] ESPEN[3] ISHEN[4]

- Helps restore BCAA:AAA ratio[5,6]
- Helps improve Hepatic Encephalopathy[6,7]
- Helps prevent progression of hepatic failure[6]
- Helps improve muscle mass[6]

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AASLD: American Association for the Study of Liver Diseases, **EASL:** The European Association for the Study of the Liver, **ESPEN:** European Society for Clinical Nutrition and Metabolism, **ISHEN:** International Society for HE and Nitrogen Metabolism.

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